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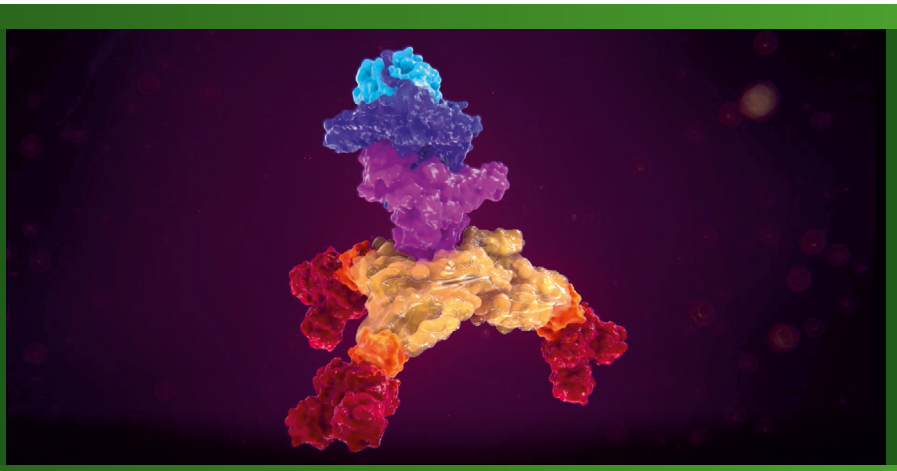

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Cover photo: The molecule of the neurotoxin A complex. Image provided courtesy of Allergan company.

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BOTOX®
Toksyna botulinowa typu A

Zaufaj doświadczeniu[1,2]
BOTOX® jest tylko jeden[3-8]

Allergan
an AbbVie company

Piśmiennictwo: 1. Allergan Dane w dokumentacji. INT/0721/2017 Wrzesień 2017. **2.** Allergan Dane w dokumentacji. DOF0663 wrzesień 2016 r. **3.** (KAR08) Karseuty G, i wsp. *Eur Uro* 2008; 53:275-287.**4.** (SmPC) Botox Charakterystyka Produktu leczniczego. **5.** (MAR05) Marchetti A et al. *Move Dis* 2005; 20: 937-944. **6.** (FER12) Fernandez-Salas E i wsp. PLoS ONE 2012; 7(11): e49516. **7.** (DYS) Dysport Charakterystyka produktu leczniczego. **9.** (XEO) Xeomin Charakterystyka produktu leczniczego Xeomin

PL-BTX-2150057

Skrócona informacja o leku: NAZWA PRODUKTU LECZNICZEGO: BOTOX, 100 jednostek Allergan, proszek do sporządzenia roztworu do wstrzykiwań. Toksyna botulinowa typu A do wstrzykiwań. **SKŁAD JAKOŚCIOWY I ILOŚCIOWY**: 1 fiolka zawiera: kompleks neurotoksyny Clostridium botulinum typu A (900 kD), 100 jednostek Allergan. Jedna jednostka odpowiada średniej dawce śmiertelnej (LD_{50}), po podaniu dootrzewnowo rozpuszczonej toksyny myszom w określonych warunkach. Jednostki są specyficzne dla preparatu BOTOX i nie są porównywalne z innymi preparatami toksyny botulinowej. **POSTAĆ FARMACEUTYCZNA**: Proszek do sporządzania roztworu do wstrzykiwań. Biały proszek. Produkt leczniczy BOTOX ma wygląd białego osadu, który może być trudny do zaobserwowania na dnie fiolki. **WSKAZANIA DO STOSOWANIA**: **Zaburzenia neurologiczne**: **BOTOX jest wskazany do objawowego leczenia: - Ogniskowej spastyczności** stawu skokowego i stopy u dzieci z **mózgowym porażeniem dziecięcym**, w wieku dwóch lat i starszych jako uzupełnienie terapii rehabilitacyjnej. - **Ogniskowej spastyczności** nadgarstka i dłoni u **pacjentów dorosłych po udarze**. - **Ogniskowej spastyczności** stawu skokowego i stopy u **pacjentów dorosłych po udarze**. - **Kurczu powiek (blefarospazm), połowiczego kurczu twarzy** i związane z nim ogniskowe dystonie. - **Idiopatycznego kręczu karku** (dystonia szyjna). Profilaktyki bólów głowy u pacjentów dorosłych cierpiących na **przewlekłą migrenę** (bóle głowy występujące 15 dni w miesiącu lub częściej). **Zaburzenia czynności pęcherza moczowego**: - **Idiopatyczna nadreaktywność pęcherza moczowego** z objawami nietrzymania moczu, parciem naglącym lub częstomoczem, u pacjentów dorosłych, z niewystarczającą odpowiedzią lub z nadwrażliwością na leki antycholinergiczne. - **Nietrzymanie moczu u pacjentów dorosłych z nadreaktywnością mięśnia wypieracza pęcherza moczowego** o podłożu neurogennym po stabilnych urazach rdzenia kręgowego poniżej odcinka szyjnego oraz u pacjentów ze stwardnieniem rozsianym. **Zaburzenia skóry i jej przydatków**: - **Uporczywa, ciężka, pierwotna nadpotliwość pach**, przeszkadzająca w codziennych czynnościach i oporna na leczenie miejscowe. **Przejściowa poprawa wyglądu następujących zmarszczek**: -**zmarszczki pionowe między brwiami o nasileniu umiarkowanym lub ciężkim** widoczne przy maksymalnym zmarszczeniu brwi (tzw. zmarszczki gładziny czoła) i (lub), - **zmarszczki w okolicy bocznego kąta oka** o nasileniu umiarkowanym lub ciężkim widoczne przy pełnym uśmiechu (zmarszczki typu „kurze łapki") i (lub), **zmarszczki poziome czoła** o nasileniu umiarkowanym lub ciężkim widoczne przy maksymalnym uniesieniu brwi, u dorosłych osób, gdy ich nasilenie ma psychologiczny wpływ na pacjenta. **DAWKOWANIE I SPOSÓB PODAWANIA**: **Zalecane jednostki Allergan odnoszą się do produktu BOTOX i nie są porównywalne z jednostkami innych produktów toksyny botulinowej**. *Pacjenci w podeszłym wieku*: Dawkowanie u pacjentów w podeszłym wieku jest takie samo, jak u młodszych, dorosłych pacjentów. Należy stosować najmniejszą zalecaną dawkę w danym wskazaniu. W przypadku wstrzykiwania kolejnych dawek zaleca się stosowanie najmniejszej skutecznej dawki produktu leczniczego, zachowując w oparciu o wskazania kliniczne możliwie najdłuższe odstępy między kolejnymi wstrzyknięciami. Ostrożność należy zachować w przypadku pacjentów o nietypowej historii w wywiadzie oraz przyjmujących jednocześnie inne leki. Istnieją ograniczone dane kliniczne dotyczące pacjentów w wieku powyżej 65 lat po udarze przyjmujących produkt leczniczy BOTOX z powodu leczenia spastyczności stawu skokowego i stopy. *Dzieci i młodzież*: Nie ustalono bezpieczeństwa i skuteczności produktu leczniczego BOTOX w innych wskazaniach niż opisane dla populacji pediatrycznej. Nie można podać zaleceń dotyczących dawkowania w przypadku wskazań innych niż spastyczność ogniskowa u dzieci związana z porażeniem mózgowym. Obecnie dostępne dane odnośnie wskazań pokazano w poniższej tabeli. BOTOX powinien być podawany wyłącznie przez lekarzy z doświadczeniem w ocenie i leczeniu ogniskowej spastyczności u dzieci oraz w ramach zorganizowanego programu rehabilitacji. *Blefarospazm, połowiczy kurcz twarzy:* 12 lat. *Dystonia szyjna:* 12 lat. *Ogniskowa spastyczność u dzieci:* 2 lat *Nadpotliwość pach:* 12 lat (ograniczone dane u młodzieży w wieku między 12 i 17 lat). **Poniższe informacje są istotne podczas rekonstytucji: Jeśli podczas jednego zabiegu używane są różne wielkości fiolek produktu leczniczego BOTOX należy zwrócić uwagę, aby użyć właściwej ilości rozcieńczalnika, w celu uzyskania odpowiedniej liczby jednostek w 0,1 ml. Ilość rozcieńczalnika niezbędna do rekonstytucji produktu jest różna dla poszczególnych mocy. Każda strzykawka powinna być odpowiednio oznakowana**. Produkt leczniczy BOTOX poddać rekonstytucji, stosując jałowy roztwór soli fizjologicznej niezawierający środków konserwujących (0,9% chlorek sodu do wstrzykiwań). **Sposób podawania**: Szczegółowe zalecenia do poszczególnych wskazań zostały opisane poniżej. BOTOX może być podawany jedynie przez lekarzy posiadających odpowiednie kwalifikacje i udokumentowane doświadczenie w prowadzeniu terapii i stosowaniu wymaganego sprzętu. Ogólnie obowiązujący poziom optymalnej dawki oraz liczba miejsc wstrzyknięć do jednego mięśnia nie zostały ustalone do wszystkich wskazań. W takich przypadkach lekarz powinien opracować indywidualne schematy podawania produktu. Optymalny poziom dawki należy ustalić w wyniku prób z użyciem różnych stężeń produktu. ZABURZENIA NEUROLOGICZNE: *Ogniskowa spastyczność kończyny dolnej u dzieci.* **Zalecana igła:** Jałowa igła w odpowiednim rozmiarze. Długość igły należy określić na podstawie położenia i głębokości mięśni. **Wskazówki dotyczące podania:** Zaleca się zlokalizowanie chorych mięśni za pomocą technik, takich jak elektromiograficzne prowadzenie igły, stymulacja nerwów lub ultrasonografia. Przed wstrzyknięciem można zastosować znieczulenie miejscowe lub znieczulenie miejscowe w połączeniu z minimalną lub umiarkowaną sedacją, zgodnie z lokalną praktyką. Nie oceniano bezpieczeństwa i skuteczności produktu leczniczego BOTOX w leczeniu spastyczności u dzieci, w znieczuleniu ogólnym lub głębokiej sedacji / analgezji. **Zalecana dawka:** Zalecana dawka w leczeniu spastyczności kończyny dolnej u dzieci wynosi 4 jednostki/kg do 8 jednostek/kg masy ciała i jest dzielona na mięśnie zajęte procesem chorobowym. **Dawkowanie produktu BOTOX w zależności od mięśnia w leczeniu spastyczności kończyny dolnej u dzieci: BOTOX 4 j./kg* (maksymalna ilość jednostek na mięsień):** *Obowiązkowe mięśnie stawu skokowego - Głowa przyśrodkowa m. brzuchatego łydki* - 1 j./kg (37.5 j.) - *Głowa boczna m. brzuchatego łydki* - 1 j./kg (37.5 j.). *Płaszczkowaty* - 1 j./kg (37.5 j.). *Piszczelowy tylny* - 1 j./kg (37.5 j.). | Liczba ostrzykiwanych miejsc - 2. **BOTOX 8 j./kg** (maksymalna ilość jednostek na mięsień):** *Obowiązkowe mięśnie stawu skokowego - Głowa przyśrodkowa m. brzuchatego łydki* - 2 j./kg (75 j.). *Głowa boczna m. brzuchatego łydki* - 2 j./kg (75 j.). *Płaszczkowaty* - 2 j./kg (75 j.). *Piszczelowy tylny* - 2 j./kg (75 j.)..| Liczba ostrzykiwanych miejsc - 2. * nie przekraczać całkowitej dawki 150 jednostek. ** nie przekraczać całkowitej dawki 300 jednostek. **Dawka całkowita:** Całkowita dawka produktu leczniczego BOTOX, podawana podczas jednej sesji terapeutycznej dla kończyny dolnej nie powinna przekraczać 8 jednostek/kg masy ciała lub 300 jednostek – w zależności, która dawka jest niższa. Jeżeli lekarz prowadzący uważa to za właściwe, u pacjenta należy rozważyć ponowne wstrzyknięcie, gdy efekt kliniczny poprzedniego wstrzyknięcia zmniejszył się, ale nie wcześniej niż 12 tygodni po poprzedniej iniekcji. W przypadku leczenia obu kończyn dolnych, dawka całkowita nie powinna przekraczać niższej z następujących wartości: 10 jednostek/kg masy ciała lub 340 jednostek, w odstępie 12 tygodni. **Informacje dodatkowe:** Leczenie produktem leczniczym BOTOX nie ma na celu zastąpienia standardowych schematów leczenia rehabilitacyjnego. Kliniczna poprawa następuje zazwyczaj w ciągu pierwszych dwóch tygodni po wstrzyknięciu produktu. Kolejne dawki powinny być podane po ustąpieniu poprawy klinicznej od ostatniej dawki, jednak nie wcześniej niż po trzech miesiącach. *Ogniskowa spastyczność kończyn górnych u pacjentów dorosłych po udarze*: **Zalecana igła**: jałowa igła o rozmiarze 25, 27 lub 30 Ga. Długość igły należy dobrać w oparciu o głębokość i umiejscowienie mięśni. **Wskazówki dotyczące podania**: W lokalizacji zajętych mięśni może być przydatna kontrola EMG lub techniki stymulacji nerwów. Dzięki licznym miejscom wstrzyknięcia, uzyskuje się równomierny kontakt produktu BOTOX z unerwionymi obszarami mięśnia, co jest szczególnie ważne w przypadku większych mięśni. **Zalecana dawka**: Dokładna dawka i liczba miejsc wstrzyknięć powinna być ustalona indywidualnie w zależności od wielkości, liczby i lokalizacji zaatakowanych mięśni, nasilenia spastyczności, miejscowego osłabienia siły mięśniowej oraz odpowiedzi pacjenta na wcześniejsze leczenie. W kontrolowanych badaniach klinicznych podawane były następujące dawki (Całkowita dawka; liczba miejsc): *Flexor digitorum profundus:* 15 - 50 jednostek; 1-2 miejsca. *Flexor digitorum sublimis:* 15 - 50 jednostek; 1-2 miejsca. *Flexor carpi radialis:* 15 - 60 jednostek; 1-2 miejsca. *Flexor carpi ulnaris:* 10 - 50 jednostek; 1-2 miejsca *Adductor pollicis:* 20 jednostek; 1-2 miejsca. *Flexor pollicis longus:* 20 jednostek; 1-2 miejsca.**Maksymalna Dawka całkowita**: W kontrolowanych i otwartych niekontrolowanych badaniach klinicznych podawano dawki pomiędzy 200 i 240 jednostek, które były dzielone pomiędzy wybrane mięśnie i podawane podczas jednego zabiegu. **Informacje dodatkowe**: W kontrolowanych badaniach klinicznych pacjenci byli obserwowani przez 12 tygodni po pojedynczym zabiegu. Poprawa kliniczna w zakresie napięcia mięśniowego występuje w okresie 2 tygodni, a maksymalny skutek uzyskuje się po 4 - 6 tygodniach. W otwartym niekontrolowanym badaniu, będącym kontynuacją poprzedniego badania, większości pacjentom ponownie wstrzyknięto produkt po przerwie 12 do 16 tygodni, gdy napięcie mięśniowe uległo zmniejszeniu. Pacjenci ci otrzymali do 4 wstrzyknięć o maksymalnej skumulowanej dawce 960 jednostek w ciągu 54 tygodni. Leczenie może być powtórzone po zaniknięciu skutku działania toksyny, jeżeli w opinii lekarza prowadzącego jest to zasadne. Nie należy podawać kolejnych wstrzyknięć przed upływem 12 tygodni. Stopień i rodzaj spastyczności mięśni może wymagać dopasowania dawek produktu BOTOX w czasie ponownych wstrzykiwań. Należy stosować najmniejsze skuteczne dawki. *Ogniskowa spastyczność kończyn dolnych u pacjentów dorosłych po udarze*: **Zalecana igła**: jałowa igła o rozmiarze 25, 27 lub 30 Ga. Długość igły należy dobrać w oparciu o głębokość i umiejscowienie mięśni. **Wskazówki dotyczące podania**: W lokalizacji zajętych mięśni może być przydatna kontrola EMG lub techniki stymulacji nerwów. Dzięki licznym miejscom wstrzyknięcia, uzyskuje się równomierny kontakt produktu BOTOX z unerwionymi obszarami mięśnia, co jest szczególnie ważne w przypadku większych mięśni. **Zalecana dawka**: Dawkowanie produktu leczniczego BOTOX w leczeniu kończyny dolnej u dorosłych z wyszczególnieniem mięśni (Całkowita dawka; liczba miejsc): Brzuchaty łydki: głowa przyśrodkowa: 75 jednostek; 3 miejsca; głowa boczna: 75 jednostek; 3 miejsca. Płaszczkowaty: 75 jednostek; 3 miejsca. Piszczelowy tylny: 75 jednostek; 3 miejsca. Zginacz długi palucha: 50 jednostek; 2 miejsca. Zginacz długi palców: 50 jednostek; 2 miejsca. Zginacz krótki palców: 25 jednostek;1 miejsce. Zalecana dawka w leczeniu spastyczności kończyny dolnej u dorosłych, obejmującej staw skokowy i stopę, wynosi od 300 jednostek do 400 jednostek podzielonych na maksymalnie do 6 mięśni, zgodnie z powyższą tabelą. Maksymalna zalecana dawka podczas jednego zabiegu wynosi 400 jednostek. **Informacje dodatkowe**: Leczenie może być powtórzone po zaniknięciu skutku działania toksyny, jeżeli w opinii lekarza prowadzącego jest to zasadne. Nie należy wstrzykiwać kolejnych dawek przed upływem 12 tygodni. *Kurcz powiek blefarospazm)/połowiczy kurcz twarzy*: **Zalecana igła**: jałowa igła o rozmiarze 27 - 30 Ga (0,40 – 0,30 mm) **Wskazówki dotyczące podania**: Nie jest konieczne podawanie toksyny pod kontrolą elktromiograficzną. **Zalecana dawka**: Zalecaną wstępną dawką jest 1,25 - 2,5 jednostek podawanych do przyśrodkowej i bocznej części mięśnia okrężnego oczu powieki górnej i bocznej części mięśnia okrężnego oczu powieki dolnej. Niekiedy dodatkowo podaje się toksynę w okolice brwi i mięśni górnej części twarzy, jeśli ich skurcze utrudniają patrzenie. **Dawka całkowita**: Początkowa dawka nie powinna przekraczać 25 jednostek na jedno oko. W leczeniu kurczu powiek (blefarospazm) całkowita dawka podana w ciągu 12 tygodni nie powinna przekraczać 100 jednostek. **Informacje dodatkowe**: W celu zmniejszenia ryzyka opadania powieki należy unikać wstrzyknięć w pobliżu mięśnia dźwigacza powieki górnej. Aby zredukować występowanie komplikacji podwójnego widzenia należy unikać wstrzyknięć w przyśrodkową część dolnej powieki, w skutek czego zmniejsza się zewnętrzne skośne rozprowadzenie toksyny. Zazwyczaj pierwszy wynik działania toksyny jest zauważalny w ciągu trzech dni, zaś maksymalny skutek działania uzyskuje się w ciągu tygodnia lub dwóch po wstrzyknięciu. Uzyskany skutek utrzymuje się przez około 3 miesiące, po których można powtarzać leczenie. Przy kolejnych wstrzyknięciach dawkę można zwiększyć nawet dwukrotnie, jeżeli skuteczność pierwszego wstrzyknięcia została uznana za niewystarczającą. Wydaje się jednak, że nie uzyskuje się większego skutku po podaniu dawek większych niż 5 jednostek w jedno miejsce. Zazwyczaj nie uzyskuje się większej skuteczności przez podawanie produktu leczniczego częściej, niż co trzy miesiące. Pacjenci z połowiczym kurczem twarzy lub zaburzeniami nerwu VII powinni być leczeni tak jak z jednostronnym kurczem powiek (blefarospazm), z dodatkowymi wstrzyknięciami w inne zaatakowane mięśnie twarzy zgodnie z wymaganiami. *Dystonia szyjna* **Zalecana igła**: jałowa igła o rozmiarze 25 - 30 Ga (0,5 – 0,3 mm) **Wskazówki dotyczące podania**: W badaniach klinicznych leczenie dystonii szyjnej zazwyczaj obejmowało wstrzykiwanie produktu leczniczego BOTOX w mięśnie: sternocleidomastoideus, levator scapulae, scalenus, splenius capitis, semispinalis, longissimus i (lub) trapezius. W razie konieczności leczeniu mogą być poddane również inne mięśnie odpowiedzialne za kontrolę pozycji głowy. Masa mięśnia i stopień hipertrofii lub atrofii są czynnikami, jakie należy wziąć pod uwagę przy wyborze odpowiedniej dawki. W dystonii szyjnej rodzaj aktywności mięśnia może ulec spontanicznej zmianie bez zmian w obrazie klinicznym dystonii. W przypadku trudności identyfikacji poszczególnych mięśni, należy dokonywać wstrzyknięć pod kontrolą EMG. **Zalecana dawka**: Nie można podawać więcej niż 200 jednostek na początku leczenia. Ewentualne zmiany dawki są możliwe w kolejnych wstrzyknięciach w zależności od reakcji na leczenie. We wstępnych kontrolowanych badaniach klinicznych dotyczących ustalenia bezpieczeństwa i skuteczności w przypadku dystonii szyjnej, dawki po rekonstytucji produktu BOTOX wahały się od 140 do 280 jednostek. W najnowszych badaniach dawki wahały się od 95 do 360 jednostek (ze średnią 240 jednostek). Tak jak w wypadku każdego podawania produktu leczniczego, dawki początkowe u pacjenta pierwszy raz przyjmującego dany produkt powinny stanowić najmniejsze skuteczne dawki. Nie należy podawać więcej niż 50 jednostek w jedno miejsce. Nie można podawać więcej niż 100 jednostek do mięśnia sternocleidomastoideus. W celu ograniczenia przypadków zaburzeń połykania nie należy podawać toksyny do obydwu mięśni mostkowo-obojczykowo-sutkowych jednocześnie. **Dawka całkowita**: Nie należy przekraczać całkowitej dawki 300 jednostek podanej podczas jednego zabiegu. Optymalna liczba miejsc wstrzyknięć zależy od wielkości mięśnia. Nie zaleca się krótszych odstępów pomiędzy wstrzyknięciami niż 10 tygodni. **Informacje dodatkowe**: Kliniczna poprawa zauważalna jest zazwyczaj w ciągu pierwszych dwóch tygodni po wstrzyknięciu produktu. Maksymalny skutek kliniczny uzyskuje się zwykle po około 6 tygodniach od wstrzyknięć. Nie zaleca się krótszych odstępów pomiędzy wstrzyknięciami niż 10 tygodni. Skuteczność terapeutyczna, jak wykazały badania kliniczne, może utrzymywać się przez różny okres (od 2 do 33 tygodni), zazwyczaj jednak około 12 tygodni. *Przewlekła migrena*: **Zalecana igła**: jałowa igła o rozmiarze 30 G, 0,5 cala **Wskazówki dotyczące podania:** Rozpoznanie chronicznej migreny, a także podanie produktu leczniczego BOTOX powinno odbywać się wyłącznie pod nadzorem lekarza neurologa, specjalisty z zakresu leczenia migreny. Wstrzyknięć dokonuje się w mięśnie 7 okolic głowy/szyi, zgodnie z rycinami i tabelą zamieszczoną poniżej. U pacjentów o bardzo grubych mięśniach szyi może zachodzić potrzeba użycia igły 1-calowej. Z wyjątkiem mięśnia podłużnego, do którego produkt leczniczy należy wstrzyknąć w jedno miejsce (w linii środkowej mięśnia), wszystkie mięśnie należy ostrzyknąć obustronnie. Połowę zastrzyków należy podać w mięśnie po lewej, a drugą połowę w mięśnie po prawej stronie głowy i szyi. Jeśli ból dominuje w określonej okolicy/ach, można wykonać dodatkowe wstrzyknięcia po jednej lub obu stronach do 3 określonych grup mięśni (potylicznego, skroniowego i czworobocznego); do każdego mięśnia można wstrzyknąć dawkę maksymalną. **Zalecana dawka**: W leczeniu przewlekłej migreny zaleca się od 155 do 195 jednostek (j.) po rekonstytucji produktu leczniczego BOTOX wstrzykiwanego domięśniowo (im.) po 0,1 ml (5 j.) do 31 maksymalnie 39 miejsc. Dawkowanie produktu leczniczego BOTOX u pacjentów z przewlekłą migreną z wyszczególnieniem mięśni (Dawka całkowita (liczba miejsc[a]): **Mięśnie głowy/ szyi |** *Mięsień marszczący brwi*[b]: 10 j. (2 miejsca). *Podłużny:* 5 j. (1 miejsce). *Czołowy*[b]: 20 j. (4 miejsca). *Skroniowy*[b]: 40 j. (8 miejsc) do 50 j. (do 10 miejsc). *Potyliczny*[b]: 30 j. (6 miejsc) do 40 j. (do 8 miejsc). *Grupa mięśni przykręgosłupowych*[b]: 20 j. (4 miejsca). *Czworoboczny*[b]: 30 j. (6 miejsc) do 50 j. (do 10 miejsc). **Całkowity zakres dawkowania: 155 j. do 195 j. 31 do 39 miejsc.** a 1 wstrzyknięcie im. = 0,1 ml = 5 j. produktu leczniczego BOTOX. b Dawka wstrzykiwana obustronnie. **Informacje dodatkowe**: Leczenie może być powtórzone po zaniknięciu skutku działania toksyny, jeżeli w opinii lekarza prowadzącego jest to zasadne. Nie należy wstrzykiwać kolejnych dawek przed upływem 12 tygodni. *Kurcz powiek blefarospazm)/połowiczy kurcz twarzy*: **Zalecana igła**: jałowa igła o rozmiarze 27 - 30 Ga (0,40 – 0,30 mm) **Wskazówki dotyczące podania**: Nie jest konieczne podawanie toksyny pod kontrolą elktromiograficzną. **Zalecana dawka**: Zalecaną wstępną dawką jest 1,25 - 2,5 jednostek podawanych do przyśrodkowej i bocznej części mięśnia okrężnego oczu powieki górnej i bocznej części mięśnia okrężnego oczu powieki dolnej. Niekiedy dodatkowo podaje się toksynę w okolice brwi i mięśni górnej części twarzy, jeśli ich skurcze utrudniają patrzenie. **Dawka całkowita**: Początkowa dawka nie powinna przekraczać 25 jednostek na jedno oko. W leczeniu kurczu powiek (blefarospazm) całkowita dawka podana w ciągu 12 tygodni nie powinna przekraczać 100 jednostek. **Informacje dodatkowe**: W celu zmniejszenia ryzyka opadania powieki należy unikać wstrzyknięć w pobliżu mięśnia dźwigacza powieki górnej. Aby zredukować występowanie komplikacji podwójnego widzenia należy unikać wstrzyknięć w przyśrodkową część dolnej powieki, w skutek czego zmniejsza się zewnętrzne skośne rozprowadzenie toksyny. Zazwyczaj pierwszy wynik działania toksyny jest zauważalny w ciągu trzech dni, zaś maksymalny skutek działania uzyskuje się w ciągu tygodnia lub dwóch po wstrzyknięciu. Uzyskany skutek utrzymuje się przez około 3 miesiące, po których można powtarzać leczenie. Przy kolejnych wstrzyknięciach dawkę można zwiększyć nawet dwukrotnie, jeżeli skuteczność pierwszego wstrzyknięcia została uznana za niewystarczającą. Wydaje się jednak, że nie uzyskuje się większego skutku po podaniu dawek większych niż 5 jednostek w jedno miejsce. Zazwyczaj nie uzyskuje się większej skuteczności przez podawanie produktu leczniczego częściej, niż co trzy miesiące. Pacjenci z połowiczym kurczem twarzy lub zaburzeniami nerwu VII powinni być leczeni tak jak z jednostronnym kurczem powiek (blefarospazm), z dodatkowymi wstrzyknięciami w inne zaatakowane mięśnie twarzy zgodnie z wymaganiami. *Dystonia szyjna* **Zalecana igła**: jałowa igła o rozmiarze 25 - 30 Ga (0,5 – 0,3 mm) **Wskazówki dotyczące podania**: W badaniach klinicznych leczenie dystonii szyjnej zazwyczaj obejmowało wstrzykiwanie produktu leczniczego BOTOX w mięśnie: sternocleidomastoideus, levator scapulae, scalenus, splenius capitis, semispinalis, longissimus i (lub) trapezius. W razie konieczności leczeniu mogą być poddane również inne mięśnie odpowiedzialne za kontrolę pozycji głowy. Masa mięśnia i stopień hipertrofii lub atrofii są czynnikami, jakie należy wziąć pod uwagę przy wyborze odpowiedniej dawki. W dystonii szyjnej rodzaj aktywności mięśnia może ulec spontanicznej zmianie bez zmian w obrazie klinicznym dystonii. W przypadku trudności identyfikacji poszczególnych mięśni, należy dokonywać wstrzyknięć pod kontrolą EMG. **Zalecana dawka**: Nie można podawać więcej niż 200 jednostek na początku leczenia. Ewentualne zmiany dawki są możliwe w kolejnych wstrzyknięciach w zależności od reakcji na leczenie. We wstępnych kontrolowanych badaniach klinicznych dotyczących ustalenia bezpieczeństwa i skuteczności w przypadku dystonii szyjnej, dawki po rekonstytucji produktu BOTOX wahały się od 140 do 280 jednostek. W najnowszych badaniach dawki wahały się od 95 do 360 jednostek (ze średnią 240 jednostek). Tak jak w wypadku każdego podawania produktu leczniczego, dawki początkowe u pacjenta pierwszy raz przyjmującego dany produkt powinny stanowić najmniejsze skuteczne dawki. Nie należy podawać więcej niż 50 jednostek w jedno miejsce. Nie można podawać więcej niż 100 jednostek do mięśnia sternocleidomastoideus. W celu ograniczenia przypadków zaburzeń połykania nie należy podawać toksyny do obydwu mięśni mostkowo-obojczykowo-sutkowych jednocześnie. **Dawka całkowita**: Nie należy przekraczać całkowitej dawki 300 jednostek podanej podczas jednego zabiegu. Optymalna liczba miejsc wstrzyknięć zależy od wielkości mięśnia. Nie zaleca się krótszych odstępów pomiędzy wstrzyknięciami niż 10 tygodni. **Informacje dodatkowe**: Kliniczna poprawa zauważalna jest zazwyczaj w ciągu pierwszych dwóch tygodni po wstrzyknięciu produktu. Maksymalny skutek kliniczny uzyskuje się zwykle po około 6 tygodniach od wstrzyknięć. Nie zaleca się krótszych odstępów pomiędzy wstrzyknięciami niż 10 tygodni. Skuteczność terapeutyczna, jak wykazały badania kliniczne, może utrzymywać się przez różny okres (od 2 do 33 tygodni), zazwyczaj jednak około 12 tygodni. **UWAGI DOTYCZĄCE WSZYSTKICH WSKAZAŃ**: W przypadku niepowodzenia terapeutycznego po pierwszym zabiegu, definiowanego jako brak znamiennej poprawy po miesiącu od podania produktu w porównaniu ze stanem wyjściowym, należy rozważyć następujące strategie postępowania: Kliniczną weryfikację, która może obejmować badanie elektromiograficzne w celu oceny działania toksyny w mięśniu/mięśniach, po wstrzyknięciu. Analizę przyczyn niepowodzenia, do których można zaliczyć między innymi: - niewłaściwy wybór mięśni do wstrzyknięcia, - za małą dawkę produktu, - nieprawidłową technikę wstrzyknięć, - występowanie stałego przykurczu, - za słabe mięśnie antagonistyczne, - powstanie przeciwciał neutralizujących toksynę.Ponowne rozważenie wskazania do leczenia z zastosowaniem toksyny botulinowej typu A. Jeśli nie wystąpiły jakiekolwiek działania niepożądane po pierwszym zabiegu, należy rozważyć powtórzenie leczenia ze zwróceniem uwagi na następujące problemy: a) właściwy dobór dawki produktu w oparciu o analizę wcześniejszego niepowodzenia terapeutycznego, b) zastosowanie EMG, c) zachowanie trzymiesięcznego odstępu pomiędzy kolejnymi zabiegami. W przypadku braku lub niezadowalającego skutku leczniczego po drugim cyklu leczenia należy rozważyć zastosowanie alternatywnych metod postępowania. W leczeniu dorosłych pacjentów, w tym leczenia z powodu wielu wskazań, maksymalna łączna dawka nie powinna przekraczać 400 jednostek, w odstępach 12-tygodniowych. **PRZECIWWSKAZANIA**: BOTOX jest przeciwwskazany: - u osób o znanej nadwrażliwości na kompleks neurotoksyny Clostridium botulinum typu A lub na którąkolwiek substancję pomocniczą ; - jeśli w miejscu, w którym ma być podany, występuje zakażenie.W przypadku leczenia zaburzeń czynności pęcherza moczowego produkt leczniczy BOTOX jest przeciwwskazany także: - u pacjentów z zakażeniem dróg moczowych w momencie leczenia; - u pacjentów z ostrym zatrzymaniem moczu w momencie terapii, którzy nie są rutynowo poddani cewnikowaniu; - u pacjentów, którzy nie chcą i (lub) nie mogą rozpocząć cewnikowania po terapii, jeśli byłoby to konieczne. **SPECJALNE OSTRZEŻENIA I ŚRODKI OSTROŻNOŚCI DOTYCZĄCE STOSOWANIA**: Ogólne ostrzeżenia dotyczące wszystkich wskazań: Nie należy przekraczać zalecanych dawek ani częstości podawania produktu leczniczego BOTOX z uwagi na ryzyko przedawkowania, nadmiernego osłabienia mięśni, rozprzestrzeniania się toksyny w miejsca odległe od miejsca podania oraz powstania przeciwciał neutralizujących. Dawkowanie początkowe u pacjentów dotychczas nieleczonych należy rozpocząć od najmniejszej dawki zalecanej w poszczególnych wskazaniach.Zarówno lekarze przepisujący produkt, jak i pacjenci powinni być świadomi, że działania niepożądane mogą wystąpić mimo dobrej tolerancji wcześniejszych wstrzyknięć. Należy zatem zachować ostrożność za każdym razem kiedy produkt jest podawany. Donoszono o występowaniu działań niepożądanych związanych z rozprzestrzenianiem się toksyny w miejsca odległe od miejsca podania (patrz: punkt 4.8). Niekiedy powodowały one śmierć pacjenta, w niektórych przypadkach związaną z utrudnieniem połykania (dysfagią), zapaleniem płuc i (lub) znacznym osłabieniem. Objawy te są zgodne z mechanizmem działania toksyny botulinowej, a ich występowanie stwierdzano w kilka godzin do kilku tygodni po podaniu. Ryzyko wystąpienia w/w objawów jest prawdopodobnie większe w przypadku pacjentów z chorobami współistniejącymi oraz zaburzeniami, które mogą predysponować do ich wystąpienia, w tym również u dzieci i dorosłych leczonych z powodu spastyczności oraz w przypadku pacjentów otrzymujących duże dawki produktu leczniczego. U pacjentów leczonych terapeutycznymi dawkami także może wystąpić nadmierne osłabienie mięśni. Należy zachować ostrożność stosując produkt u pacjentów w podeszłym wieku oraz u pacjentów znacznie osłabionych. Zasadniczo, badania kliniczne z udziałem produktu leczniczego BOTOX nie wykazały różnic w odpowiedzi pomiędzy pacjentami w podeszłym wieku w porównaniu z pacjentami młodszymi. Należy ostrożnie ustalać dawkowanie u pacjentów w podeszłym wieku, zaczynając od dolnej granicy zakresu dawkowania. Lekarz powinien decydować o podjęciu leczenia, w oparciu o stosunek korzyści do ryzyka, indywidualnie dla każdego pacjenta. Donoszono o występowaniu zaburzeń połykania również wówczas, gdy produkt podawany był w inne miejsca, niż mięśnie szyi. U pacjentów z subklinicznymi lub klinicznymi objawami nieprawidłowości przewodzenia nerwowo-mięśniowego, jak myasthenia gravis czy zespół Lamberta-Eatona u pacjentów z obwodowymi neuropatiami ruchowymi (np. stwardnienie zanikowe boczne albo neuropatia ruchowa) produkt BOTOX powinien być stosowany z dużą ostrożnością i pod ścisłą kontrolą. Może u nich występować nadmierna wrażliwość na takie czynniki, jak toksyna botulinowa, co może prowadzić do nadmiernego osłabienia mięśni, zaś ryzyko wystąpienia klinicznie istotnych układowych działań niepożądanych (w tym ciężkiej dysfagii i zaburzeń układu oddechowego) może być zwiększone nawet w wyniku zastosowania typowych dawek tego produktu. U takich pacjentów produkt powinien być stosowany pod ścisłą kontrolą lekarza specjalisty i tylko wówczas, gdy uważa się, że korzyści z leczenia przeważają nad ryzykiem. Pacjenci z dysfagią i zachłyśnięciem w wywiadzie powinni być leczeni z zachowaniem największej ostrożności. Pacjenci lub udzielający pomocy powinni wezwać natychmiast pomoc medyczną, jeżeli nastąpią trudności w połykaniu, mowie lub oddychaniu. Tak jak w przypadku każdego leczenia, które umożliwia pacjentowi o siedzącym trybie życia powrót do aktywności, należy zwrócić uwagę aby aktywność zwiększać stopniowo. Należy zapoznać się z anatomią i ewentualnymi zmianami wynikającymi z przebytych zabiegów chirurgicznych miejsca planowanego wstrzyknięcia przed podaniem produktu BOTOX. Obserwowano przypadki odmy związane ze wstrzyknięciem produktu BOTOX w pobliżu klatki piersiowej. Należy zachować ostrożność podczas wstrzykiwania w bezpośredniej bliskości płuc, zwłaszcza w okolice wierzchołków płuc lub innych wrażliwych struktur anatomicznych. Ciężkie przypadki działań niepożądanych, w tym przypadki zgonów obserwowano u pacjentów, którym BOTOX wstrzyknięto poza zarejestrowanymi wskazaniami, bezpośrednio w gruczoły ślinowe, okolice ustno-językowo-gardłową, w przełyk lub żołądek. Niektórzy z opisywanych pacjentów mieli wcześniej zaburzenia połykania lub znacznego stopnia osłabienie. W rzadkich przypadkach donoszono o występowaniu ciężkich i (lub) natychmiastowych reakcji nadwrażliwości, w tym anafilaksji, choroby posurowiczej, pokrzywki, obrzęku tkanek miękkich i duszności. Niektóre z nich występowały po zastosowaniu produktu BOTOX w monoterapii bądź w leczeniu skojarzonym z innymi lekami, których stosowanie związane jest z występowaniem podobnych reakcji. W przypadku wystąpienia takiej reakcji należy przerwać stosowanie produktu BOTOX i bezzwłocznie rozpocząć odpowiednie leczenie farmakologiczne, np. podawanie epinefryny. Odnotowano jeden przypadek reakcji anafilaktycznej u pacjenta, który zmarł w skutek podania nieprawidłowo rozcieńczonego produktu razem z 5 ml 1% roztworu lidokainy. Podobnie jak w przypadku innych wstrzyknięć, może dojść do wystąpienia zaburzeń w miejscu wstrzyknięcia związanego z podaniem. Wstrzyknięcie może spowodować miejscowe zakażenie, ból, stan zapalny, parestezje, niedoczulicę, tkliwość uciskową, obrzęk, rumień i (lub) krwawienie/siniak. Ból i (lub) lęk związany z podaniem może spowodować wystąpienie reakcji wazowagalnych, np. omdleń, niedociśnienia itp. **Należy zachować ostrożność podczas podawania produktu BOTOX, gdy w miejscu proponowanego wstrzyknięcia występuje stan zapalny, a także w tych przypadkach, w których występuje znaczne osłabienie lub zanik mięśni wybranych do iniekcji. Ponadto, należy zachować ostrożność stosując BOTOX u pacjentów z obwodowymi neuropatiami ruchowymi (np. stwardnieniem zanikowym bocznym lub neuropatią ruchową).** Odnotowano przypadki działań niepożądanych dotyczących układu sercowo-naczyniowego, łącznie z arytmią i zawałem mięśnia sercowego, niektóre ze skutkiem śmiertelnym. U niektórych pacjentów stwierdzono istniejące wcześniej czynniki ryzyka, w tym istniejącą chorobę układu sercowo-naczyniowego. Donoszono o wystąpieniu nowych lub nawrocie drgawek, zazwyczaj u pacjentów, u których występuje predyspozycja do ich występowania. Nie ustalono dokładnego związku między nimi a podawaniem produktu BOTOX. Wśród dzieci dominowały zgłoszenia u pacjentów ze spastycznością (przykurczami) w mózgowym porażeniu dziecięcym. Wytworzone przeciwciała przeciwko toksynie botulinowej typu A mogą zmniejszać skuteczność leczenia poprzez inaktywację tej toksyny. Wyniki niektórych badań sugerują, że do powstawania przeciwciał dochodzi częściej wówczas, gdy czas pomiędzy kolejnymi dawkami produktu BOTOX jest krótki oraz gdy stosowane są duże dawki. W stosownych przypadkach, możliwość powstawania przeciwciał może być zminimalizowana poprzez podawanie najmniejszej skutecznej dawki, zachowując w oparciu o ocenę kliniczną możliwie najdłuższe odstępy między kolejnymi wstrzyknięciami. Kliniczne nieprawidłowości powstałe podczas powtórnego stosowania produktu BOTOX (dotyczy to wszystkich toksyn botulinowych) mogą być wynikiem różnych procedur rozpuszczania zawartości fiolki, przerw między wstrzyknięciami, różnych mięśni do których produkt jest wstrzykiwany i nieznacznej różnicy mocy podanej dawki, która została określana metodą biologiczną. **Dzieci i młodzież**: Nie określono bezpieczeństwa stosowania ani skuteczności produktu BOTOX we wskazaniach innych, niż te, które, dotyczą dzieci i młodzieży. W okresie po wprowadzeniu produktu leczniczego do obrotu rzadko zgłaszano przypadki rozprzestrzeniania się toksyny w miejsca odległe od miejsca podania u dzieci i młodzieży, u których występowały choroby współistniejące, zazwyczaj dziecięce porażenie mózgowe. W zgłaszanych przypadkach zastosowana dawka zazwyczaj przekraczała dawkę zalecaną. Odnotowano rzadkie przypadki zgonów związane z zachłystowym zapaleniem płuc u dzieci z ciężkim dziecięcym porażeniem mózgowym, po zastosowaniu toksyny botulinowej, poza zarejestrowanymi wskazaniami (off - label) (np. podanie w obszarze szyi). Należy zachować szczególną ostrożność podczas leczenia dzieci i młodzieży ze znacznym osłabieniem neurologicznym, utrudnieniem połykania (dysfagia) lub niedawno przebytym zachłystowym zapaleniem płuc lub inną chorobą płuc. Leczenie pacjentów w złym stanie ogólnym możliwe jest tylko wówczas, jeżeli oceniono, że w przypadku danego pacjenta, potencjalne korzyści przeważają nad ryzykiem. ZABURZENIA NEUROLOGICZNE: Ogniskowa spastyczność stawu skokowego i stopy związana z dynamiczną deformacją stopy końsko-szpotawej u dzieci z mózgowym porażeniem dziecięcym oraz ogniskowa spastyczność stawu skokowego i stopy, nadgarstka i dłoni u pacjentów dorosłych po udarze. Podawanie produktu BOTOX w leczeniu ogniskowej spastyczności zostało zbadane jedynie w połączeniu ze standardowymi schematami leczenia i nie jest przeznaczone do zastąpienia tych procedur. BOTOX prawdopodobnie nie jest skuteczny w poprawie zakresu ruchu stawów zmienionych w wyniku stałego przykurczu. Produkt leczniczy BOTOX nie powinien być stosowany w leczeniu ogniskowej spastyczności stawu skokowego i stopy u dorosłych pacjentów po udarze, jeżeli nie oczekuje się aby zmniejszenie napięcia mięśni mogło spowodować poprawę czynności (np. poprawę chodu), lub poprawę objawów podmiotowych (np. zmniejszenie bólu) lub ułatwienie opieki nad pacjentem. Ponadto, poprawa w zakresie zaburzeń czynności stawu skokowego może być ograniczona jeżeli leczenie produktem leczniczym BOTOX rozpoczęto po okresie dłuższym niż 2 latach od udaru, lub u pacjentów ze spastycznością stawu skokowego o mniejszej ciężkości (Zmodyfikowana Skala Ashwortha (MAS) <3). Należy zachować ostrożność podczas leczenia dorosłych pacjentów ze spastycznością poudarową, z uwagi na większe ryzyko przewrócenia się pacjenta. Produkt leczniczy BOTOX należy stosować ostrożnie w leczeniu ogniskowej spastyczności stawu skokowego i stopy po udarze u pacjentów w podeszłym wieku, z istotnymi chorobami współistniejącymi, a leczenie należy rozpoczynać wyłącznie wtedy, gdy uważa się, że korzyści z niego wynikające przewyższają potencjalne ryzyko. Produkt leczniczy BOTOX należy stosować wyłącznie w leczeniu poudarowej spastyczności kończyn dolnych po ocenie przeprowadzonej przez lekarza specjalistę, mającego doświadczenie w rehabilitacji pacjentów po udarze. Po wprowadzeniu produktu do obrotu donoszono o przypadkach śmierci po podaniu toksyny botulinowej (w niektórych przypadkach związanych z zachłystowym zapaleniem płuc) związanych z rozprzestrzenianiem się toksyny w miejsca odległe od miejsca podania u dzieci z chorobami współistniejącymi, głównie porażeniem mózgowym. Kurcz powiek (Blefarospazm): Zmniejszenie częstości mrugania występujące po wstrzyknięciu toksyny botulinowej do mięśnia okrężnego oka, może prowadzić do patologicznych zmian rogówki. Należy dokładnie sprawdzać wrażliwość rogówki oka po podaniu produktu oraz unikać wstrzyknięć w dolną powiekę, aby nie doprowadzić do wywinięcia powieki, a w przypadku pojawienia się uszkodzeń nabłonka rogówki, należy je intensywnie leczyć. Leczenie może wymagać podania kropli ochronnych, maści, miękkich soczewek terapeutycznych, przymknięcia oka opaską lub innych zabiegów. W miękkich tkankach powieki łatwo występują wybroczyny. Można temu zapobiegać przez łagodny ucisk w miejscu wstrzyknięcia. Ze względu na antycholinergiczne działanie toksyny botulinowej, należy zachować szczególną ostrożność u pacjentów z ryzykiem jaskry z zamkniętym kątem przesączania. Dystonia szyjna: Pacjentów z dystonią szyjną należy poinformować o możliwości wystąpienia zaburzenia połykania (dysfagii), które może być łagodne lub bardzo silne. Trudności w połykaniu mogą utrzymywać się przez dwa do trzech tygodni po wstrzyknięciu toksyny, ale były zgłaszane przypadki dysfagii utrzymujące się do pięciu miesięcy po wstrzyknięciu. W konsekwencji zaburzenia połykania może wystąpić duszność, aspiracja i czasami potrzeba karmienia przez zgłębnik. W rzadkich przypadkach donoszono o występowaniu zapalenia płuc a nawet przypadków śmiertelnych po aspiracji w przebiegu dysfagii. Ograniczenie dawki toksyny botulinowej wstrzykiwanej do mięśnia sternocleidomastoideus do wartości poniżej 100 jednostek może zmniejszyć występowanie dysfagii. Wyższe ryzyko wystąpienia dysfagii obserwowano u pacjentów o mniejszej masie mięśni szyjnych lub u pacjentów, którym obustronnie wstrzyknięto toksynę w mięsień sternocleidomastoideus. Wystąpienie dysfagii jest przypisywane rozprzestrzenianiu toksyny w mięśniach przełyku. Podanie produktu do mięśnia dźwigacza łopatki może być związane ze zwiększonym ryzykiem wystąpienia zakażenia górnych dróg oddechowych i zaburzeń połykania. Zaburzenia połykania mogą przyczyniać się do zmniejszenia ilości przyjmowanych płynów i pokarmów, co może prowadzić do odwodnienia i zmniejszenia masy ciała. U pacjentów z subkliniczną dysfagią ryzyko wystąpienia cięższych zaburzeń połykania po zastosowaniu produktu BOTOX może być zwiększone. Przewlekła migrena: Nie ustalono skuteczności w profilaktyce bólu głowy u pacjentów z migreną epizodyczną (bóle głowy < 15 dni w miesiącu). ZABURZENIA CZYNNOŚCI PĘCHERZA MOCZOWEGO: Podczas wykonywania cystoskopii należy stosować odpowiednie medyczne środki ostrożności.U pacjentów niecewnikowanych należy oceniać objętość moczu zalegającego po mikcji w ciągu 2 tygodni po leczeniu oraz okresowo zgodnie z oceną lekarza przez okres do 12 tygodni. Należy poinstruować pacjentów, by skontaktowali się z lekarzem, jeśli odczują trudności w oddawaniu moczu, ponieważ może być konieczne cewnikowanie. Idiopatyczna nadreaktywność pęcherza moczowego: Mężczyźni z idiopatyczną nadreaktywnością pęcherza moczowego i przedmiotowymi lub podmiotowymi objawami niedrożności dróg moczowych nie powinni być leczeni produktem leczniczym BOTOX. Nietrzymanie moczu wskutek neurogennej nadczynności mięśnia wypieracza. Może wystąpić autonomiczna dysrefleksja związana z procedurą. Konieczne może być bezzwłoczne zapewnienie opieki medycznej. ZABURZENIA SKÓRY I JEJ PRZYDATKÓW: Pierwotna nadpotliwość pach Zaleca się przeprowadzenie wywiadu i badania pacjenta, jak również dodatkowych testów swoistych, w celu wykluczenia potencjalnych przyczyn wtórnej nadpotliwości (np. nadczynność tarczycy, guz chromochłonny). Pomoże to uniknąć leczenia objawowego nadpotliwości bez rozpoznania i (lub) leczenia choroby zasadniczej. Zmarszczki gładziny czoła widoczne przy maksymalnym zmarszczeniu brwi oraz zmarszczki typu „kurze łapki" widoczne przy pełnym uśmiechu i (lub) zmarszczki poziome czoła widoczne przy maksymalnym uniesieniu brwi. Nie zaleca się stosowania produktu leczniczego BOTOX u osób w wieku poniżej 18 lat. Dane z badań klinicznych 3 fazy dotyczących stosowania BOTOX u pacjentów powyżej 65. roku życia są ograniczone. Należy zachować ostrożność i upewnić się, że BOTOX nie zostanie podany do naczynia krwionośnego podczas iniekcji w obrębie zmarszczek gładziny czoła widocznych podczas maksymalnego zmarszczenia brwi, zmarszczek w okolicy bocznego kąta oka widocznych przy pełnym uśmiechu oraz zmarszczek poziomych czoła widocznych przy maksymalnym uniesieniu brwi .W następstwie leczenia istnieje ryzyko wystąpienia opadania powieki. Informacje o sposobie ograniczenia ryzyka opadania powieki. **DZIAŁANIA NIEPOŻĄDANE**: a) Ogólne W kontrolowanych badaniach klinicznych działania niepożądane klasyfikowane jako mające związek z podaniem produktu leczniczego BOTOX obserwowano u 35% pacjentów z kurczem powiek (blefarospazm), u 28% pacjentów z dystonią szyjną, u 8% pacjentów ze spastycznością dziecięcą, u 11% pacjentów z nadpotliwością pach, u 16% pacjentów z ogniskową spastycznością górnej kończyny powiązanej z udarem oraz u 15% pacjentów z ogniskową spastycznością kończyny dolnej powiązanej z udarem. W badaniach klinicznych dotyczących przewlekłej migreny częstość występowania działań niepożądanych wyniosła 26% podczas pierwszej terapii ze spadkiem do 11% podczas drugiej terapii. W badaniach klinicznych nad idiopatyczną nadreaktywnością pęcherza moczowego częstość występowania wyniosła 26% podczas pierwszej terapii ze spadkiem do 22% podczas drugiej terapii. W badaniach klinicznych dotyczących zastosowania tego produktu w przypadkach nietrzymania moczu wskutek neurogennej nadczynności mięśnia wypieracza działania niepożądane obserwowano u 32% pacjentów podczas pierwszej terapii ze spadkiem do 18% podczas drugiej terapii. W pierwszym cyklu leczenia, w badaniach klinicznych dotyczących leczenia zmarszczek poziomych czoła widocznych przy maksymalnym uniesieniu brwi, zdarzenia niepożądane uznane przez badaczy za związane z podaniem produktu leczniczego BOTOX zgłosiło 20,6% pacjentów, którzy otrzymali 40 jednostek (20 jednostek do mięśnia czołowego i 20 jednostek podanych w okolicę gładziny czoła) i 14,3% pacjentów leczonych dawką 64 jednostek (20 jednostek do mięśnia czołowego, 20 jednostek podanych w okolicę gładziny czoła i 24 jednostki w okolice kurzych łapek), w porównaniu z 8,9% pacjentów, którzy otrzymali placebo. W większości przypadków, działania niepożądane występują w ciągu pierwszych kilku dni po wstrzyknięciu i mają charakter przejściowy. W rzadkich przypadkach działania niepożądane mogą utrzymywać się przez kilka miesięcy lub dłużej. Miejscowe osłabienie mięśni stanowi spodziewane farmakologiczne działanie toksyny botulinowej. Zgłaszano również występowanie osłabienia sąsiadujących mięśni i (lub) mięśni oddalonych od miejsca wstrzyknięcia. Tak jak w przypadku każdego wstrzyknięcia, w miejscu wstrzyknięcia mogą wystąpić: miejscowy ból, zapalenie, parestezje, niedoczulica, tkliwość, obrzęk, rumień, miejscowe zakażenie, krwawienie i (lub) zasinienie, działania niepożądane związane z samą procedurą wstrzyknięcia. Ból i (lub) lęk związany z igłą mogą doprowadzić do wystąpienia reakcji wazowagalnej, obejmującej przemijające objawowe niedociśnienie i omdlenia. Po podaniu toksyny botulinowej zgłaszano także przypadki gorączki i objawów grypopodobnych. b) Działania niepożądane – częstość w zależności od wskazań. Działania niepożądane przedstawiono według następujących kategorii, w zależności od częstości ich występowania: Bardzo Często - (≥1/10); Często - (≥1/100 do <1/10); Niezbyt często - (≥1/1 000 do <1/100); Rzadko - (≥1/10 000 do <1/1000); Bardzo rzadko - (<1/10 000). Poniżej przedstawiono działania niepożądane w zależności od miejsca podania produktu leczniczego BOTOX. **ZABURZENIA NEUROLOGICZNE**: ***Ogniskowa spastyczność kończyny dolnej u dzieci*** | *Zaburzenia skóry i tkanki podskórnej:* wysypka - często. *Zaburzenia mięśniowo-szkieletowe i tkanki łącznej:* osłabienie mięśni - niezbyt często. *Urazy, zatrucia i powikłania po zabiegach:* skręcenie więzadła, otarcie skóry - często. *Zaburzenia ogólne i stany w miejscu podania:* zaburzenia chodu, ból w miejscu wstrzyknięcia - często. ***Ogniskowa spastyczność kończyn górnych u pacjentów dorosłych po udarze*** | *Zaburzenia psychiczne:* depresja, bezsenność - niezbyt często. *Zaburzenia układu nerwowego:* wzmożone napięcie - często; przeczulica, ból głowy, parestezja, brak koordynacji i utrata pamięci - niezbyt często. *Zaburzenia ucha i błędnika:* zawroty głowy - niezbyt często. *Zaburzenia naczyniowe:* niedociśnienie ortostatyczne - niezbyt często. *Zaburzenia żołądka i jelit:* nudności, parestezje okołoustne - niezbyt często. *Zaburzenia skóry i tkanki podskórnej:* wybroczyny, plamica - często; zapalenie skóry, świąd i wysypka - niezbyt często. *Zaburzenia mięśniowo-szkieletowe i tkanki łącznej:* ból kończyny i osłabienie mięśni - często; ból stawów i zapalenie kaletki - niezbyt często. *Zaburzenia ogólne i stany w miejscu podania:* krwawienie i podrażnienie w miejscu podania, ból w miejscu wstrzyknięcia, gorączka, objawy grypopodobne - często; astenia, ból, nadwrażliwość w miejscu podania, złe samopoczucie i obrzęki obwodowe - niezbyt często. Niektóre z niezbyt częstych działań mogą być związane z samą chorobą. ***Ogniskowa spastyczność kończyn dolnych u pacjentów dorosłych po udarze*** | *Zaburzenia skóry i tkanki podskórnej:* wysypka - często. *Zaburzenia mięśniowo-szkieletowe i tkanki łącznej:* ból stawów, sztywność mięśniowo-szkieletowa, osłabienie mięśni - często. *Zaburzenia ogólne i stany w miejscu podania:* obrzęki obwodowe - często. *Urazy, zatrucia i powikłania po zabiegach:* przewracanie się - często. Nie obserwowano zmian ogólnego profilu bezpieczeństwa w przypadku kolejnych podań. ***Kurcz powiek (blefarospazm), połowiczy kurcz twarzy i związane z nim ogniskowe dystonie*** | *Zaburzenia układu nerwowego:* zawroty głowy, niedowład nerwu twarzowego, porażenie nerwu twarzowego - niezbyt często. *Zaburzenia oka:* opadanie powieki - bardzo często; punkcikowate zapalenie rogówki, niedomykalność powieki, suchość oka, światłowstręt, nasilenie łzawienia, podrażnienie oka - często; zapalenie rogówki, wywinięcie powieki, podwójne widzenie, podwinięcie powieki, zaburzenia widzenia i niewyraźne widzenie - niezbyt często; obrzęk powiek - rzadko; wrzodziejące zapalenie rogówki, ubytek nabłonka i perforacja rogówki - bardzo rzadko. *Zaburzenia skóry i tkanki podskórnej:* wybroczyny - często; wysypka/zapalenie skóry - niezbyt często. *Zaburzenia ogólne i stany w miejscu podania:* podrażnienie i obrzęk twarzy - często; zmęczenie - niezbyt często. ***Dystonia szyjna*** | *Zakażenia i zarażenia pasożytnicze:* zapalenie śluzówki nosa, zakażenie górnych dróg oddechowych - często. *Zaburzenia układu nerwowego:* zawroty głowy, wzmożone napięcie mięśniowe, niedoczulica, senność i ból głowy - często. *Zaburzenia oka:* podwójne widzenie, opadanie powieki - niezbyt często. *Zaburzenia układu oddechowego, klatki piersiowej i śródpiersia:* duszność i dysfonia - niezbyt często. *Zaburzenia żołądka i jelit:* dysfagia (patrz podpunkt „Informacje dodatkowe") - bardzo często; suchość w jamie ustnej i nudności - często. *Zaburzenia mięśniowo-szkieletowe i tkanki łącznej:* osłabienie mięśni - bardzo często; sztywność i bolesność układu mięśniowo-szkieletowego - często. *Zaburzenia ogólne i stany w miejscu podania:* ból - bardzo często; astenia, choroba grypopodobna, złe samopoczucie - często; gorączka - niezbyt często. **Informacje dodatkowe** Poniższa lista obejmuje działania niepożądane lub inne medycznie istotne zdarzenia niepożądane, które zostały zgłoszone, po wprowadzeniu produktu do obrotu, niezależnie od wskazania terapeutycznego a nie zostały wymienione w punkcie „Specjalne ostrzeżenia i środki ostrożności dotyczące stosowania" oraz w punkcie „Działania niepożądane". *Zaburzenia układu immunologicznego:* wstrząs anafilaktyczny, obrzęk naczynioruchowy, choroba posurowicza i pokrzywka. *Zaburzenia metabolizmu i odżywiania:* anoreksja. *Zaburzenia układu nerwowego:* neuropatia splotu ramiennego, dysfonia, zaburzenia mowy, niedowład twarzy, zaburzenia czucia, osłabienie mięśni, miastenia, neuropatia obwodowa, parestezje, neuropatia korzeni rdzeniowych, drgawki, omdlenieoraz porażenie nerwu twarzowego. *Zaburzenia oka:* jaskra z zamkniętym kątem (w przypadku leczenia kurczu powiek), opadanie powiek, niedomykalność powieki, zez, niewyraźne widzenie i zaburzenia widzenia, suchość oka, obrzęk powiek. *Zaburzenia ucha i błędnika:* niedosłuch, szum w uszach i zawroty głowy. *Zaburzenia serca:* zaburzenia rytmu serca, zawał mięśnia sercowego. *Zaburzenia układu oddechowego, klatki piersiowej i śródpiersia:* zachłystowe zapalenie płuc (niektóre śmiertelne), duszność, depresja oddechowa i niewydolność oddechowa. *Zaburzenia żołądka i jelit:* ból brzucha, biegunka, zaparcia, suchość w ustach, zaburzenia połykania, nudności i wymioty. *Zaburzenia skóry i tkanki podskórnej:* łysienie, opadanie brwi, łuszczycowe zapalenie skóry, rumień wielopostaciowy, nadmierne pocenie się, wypadanie rzęs, świąd i wysypka. *Zaburzenia mięśniowo-szkieletowe i tkanki łącznej:* zanik mięśni i bóle mięśni, miejscowe drżenia mięśni/ mimowolne skurcze mięśni. *Zaburzenia ogólne i stany w miejscu podania:* atrofia wskutek odnerwienia, złe samopoczucie i gorączka. **Zgłaszanie podejrzewanych działań niepożądanych**: Po dopuszczeniu produktu leczniczego do obrotu istotne jest zgłaszanie podejrzewanych działań niepożądanych. Umożliwia to nieprzerwane monitorowanie stosunku korzyści do ryzyka stosowania produktu leczniczego. Osoby należące do fachowego personelu medycznego powinny zgłaszać wszelkie podejrzewane działania niepożądane za pośrednictwem Departamentu Monitorowania Niepożądanych Działań Produktów Leczniczych Urzędu Rejestracji Produktów Leczniczych, Wyrobów Medycznych i Produktów Biobójczych: Al. Jerozolimskie 181C, 02-222 Warszawa, Tel.: + 48 22 49 21 301, Faks: + 48 22 49 21 309, Strona internetowa: https://smz.ezdrowie.gov.pl **Działania niepożądane można zgłaszać również podmiotowi odpowiedzialnemu.** PODMIOT ODPOWIEDZIALNY POSIADAJĄCY POZWOLENIE NA DOPUSZCZENIE DO OBROTU: Allergan Pharmaceuticals Ireland, Castlebar Road, Westport, Co. Mayo, Irlandia. NUMER POZWOLENIA NA DOPUSZCZENIE DO OBROTU WYDANEGO PRZEZ MINISTRA ZDROWIA: R/6748. Produkt leczniczy wydawany na receptę. Przed zastosowaniem należy zapoznać się z pełną informacją o leku. Opracowano na podstawie ChPL z dnia 08.04.2021. Dodatkowe informacje dostępne są u Przedstawiciela podmiotu odpowiedzialnego: Allergan Sp. z o.o., ul. Marynarska 15, 02-674 Warszawa, tel.: (+48) 22 256 37 00, faks: (+48) 22 256 37 01, E-mail: poland@allergan.com

EDITORIAL NOTE

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Editors of the *Polish Journal of Neurology and Neurosurgery* announce the first issue featuring a *Leading Topic*

Zbigniew K. Wszolek[1], Łukasz Stolarczyk[2], Jarosław Sławek[3]

[1]Co-Editor-in-Chief, Department of Neurology, Mayo Clinic, Jacksonville, Florida, United States
[2]Journal Administrator, Via Medica™, Gdansk, Poland
[3]Co-Editor-in-Chief, Department of Neurology and Psychiatry, Medical University of Gdansk, Gdansk, Poland

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As announced last year, and enthusiastically supported by the Editorial Board members [1], in this issue of the *Polish Journal of Neurology and Neurosurgery* (*Neurologia i Neurochirurgia Polska*), we present the first *Leading Topic* (a compilation of several articles dealing with a common theme) with an accompanying *Invited Editorial*. We hope that this new feature will be welcomed by our readers. We encourage you to let us know your thoughts regarding any improvements you would like to see, and to contact us if you would like to contribute to a future *Leading Topic*. We plan at least one issue (preferably two) per year that features a *Leading Topic*.

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Address for correspondence: Zbigniew K. Wszolek, M.D., Department of Neurology, Mayo Clinic Florida, 4500 San Pablo Rd, Jacksonville, FL 32224, USA, e-mail: wszolek.zbigniew@mayo.edu

INVITED EDITORIAL

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LEADING TOPIC

Botulinum neurotoxin in neurological practice — a leading topic in neurology

Jarosław Sławek[1,2], Wolfgang H. Jost[3]

[1]Division of Neurological and Psychiatric Nursing, Faculty of Health Sciences, Medical University of Gdansk, Poland
[2]Department of Neurology and Stroke, St. Adalbert Hospital, Gdansk, Poland
[3]Parkinson-Klinik Ortenau, Wolfach, Germany

Key words: botulinum neurotoxin, dystonia, spasticity, migraine, neuropathic pain

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In this issue of the Polish *Journal of Neurology and Neurosurgery*, we introduce a new form of publication of collected papers regarding one topic. This we call a 'leading topic'. As guest editors of this special series of papers, we would like to present selected papers regarding botulinum neurotoxin (BoNT) treatment in neurology.

Botulinum neurotoxin is a leading treatment option in many indications in neurology such as focal/segmental dystonias (blepharospasm, Meige syndrome, cervical dystonia, writer's cramp or spasmodic dysphonia), spasticity in children (cerebral palsy) and adults (post-stroke), overactive bladder, chronic migraine or hyperhidrosis and siallorhea (Tab. 1). The list of as-yet unlicensed or off-label indications is long and some examples will be discussed (Tab. 2). A PubMed database search using the key word 'Botulinum toxin' found 10,568 records at the end of March 2021, making this treatment option a leading topic in neurology.

There are three major botulinum neurotoxin type-A preparations according to the FDA (the US Food & Drug Administration) requirements: onabotulinumtoxinA (ONA--BoNT/A), abobotulinumtoxinA (ABO-BoNT/A), and incobotulinumtoxinA (INCO-BoNT/A). These have the trade names Botox®, Dysport® and Xeomin® respectively. Botulinum neuroxin type B (rhimabotulinumtoxinB) with the trade name Myobloc/Neurobloc® was intended to be used in secondary unresponsiveness to type-A with the formation of neutralising antibodies. The efficacy and safety of BoNT/A and B have been positively assessed and rated at level A or B (for different indications and preparations) by the American Academy of Neurology in its Task Force guidelines [1]. Their effectiveness has been confirmed in many open-label studies including ones also published in this journal, and indeed in this issue [2–5].

However, although this treatment has been offered to patients for the last 30 years, many unresolved problems and unmet needs remain.. One of them is the inability to make a direct comparison in terms of efficacy and the lack of a universal dose-ratio between different products. In two papers published in this issue, we have reviewed both the basic [6] and the clinical [7, 8] research in terms of bioequivalence of currently available preparations in major indications. Many of them are indirect, showing the overall results achieved with pre-established doses of different preparations. Direct comparisons were made difficult because of pre-fixed ratios, different methodologies, and the relatively low quality of studies.

We have concluded that universal ratios between products cannot be therefore established. Methods of assessment of clinical efficacy differ between companies. Also the methodologies of studies published so far has been rather poor, based on laboratory or electrophysiological methods in healthy volunteers or small groups of patients. This is especially important, because new BoNT/A fomulations (e.g. daxibotulinumtoxinA, prabotulinumtoxinA) are now in clinical trials, and therefore a switch between products in future might be even more difficult. Switching from one preparation to another is common in clinical practice, as shown in many open label studies with long follow ups. Lengthy treatment is a risk factor for the formation of neutralising antibodies, and therefore treatment regimens should respect optimal (not maximal) doses and intervals between injections [9].

Address for correspondence: Jarosław Sławek, MD, PhD, Department of Neurology and Stroke, St. Adalbert Hospital, Al. Jana Pawła II 50 Str., 80-462 Gdansk, Poland, e-mail: jaroslaw.slawek@gumed.edu.pl

Table 1. Licensed indications for BoNT/A in neurology and beyond (according to SPCs for all three types of BoNT/A) [36–38]

Indication	ONA-BoNT/A	ABO-BoNT/A	INCO-BoNT/A
Cervical dystonia	+	+	+
Blepharospasm	+	+	+
Strabismus (> 5yrs old)	+	-	-
Hemifacial spasm	+*	+	+
Upper limb spasticity (post-stroke)	+	+	+
Lower limb spasticity (post-stroke)	+	+	-
Spasticity in cerebral palsy (upper limbs)	+	+	-
Spasticity in cerebral palsy (lower limbs)	+	+	-
Overactive bladder	+	-	-
Detrusor hyperactivity in neurological conditions (MS, SCI) and paediatric patients > 5 yrs old	+	-	-
Sialorrhea	-	-	+
Hyperhidrosis (axillary)	+	+	-
Chronic migraine	+	-	-

MS — multiple sclerosis; SCI — spino-cerebral injury; *not present in US SPC.
For ONA-BoNT/A the term 'Blepharospasm, hemifacial spasm and other associated dystonias' is used in SPC. Therefore, there is no specific indication for laryngeal dystonia or oromandibular dystonia

Table 2. Off-label indications for BoNT/A in neurology and beyond [26, 29, 32, 34, 35, 39–41]

Axial dystonia
Essential tremor (and other tremors)
Focal tics
Focal myoclonus
Tardive dyskinesia
Bruxism
Thoracic outlet syndrome
Stiff-person syndrome
Restless legs syndrome
Parkinson's Disease (jaw tremors, axial dystonia, rectal dystonia, freezing of gait, camptocormia, striatal toe)
Neuropathic pain (diabetic neuropathy, trigeminalgia)
Myofascial pain
Piriformis muscle syndrome
Lower back pain
Arthritis
Tennis elbow
Depression
Gastroenterology (anal fissure, constipation, achalasia, oesophageal spasm, pyloric dysfunction- gastroparesis)
Frey syndrome
Rhinitis
Scar healing

In conclusion, we should respect the specific doses recommended in the summary product characteristics of specific BoNT/A medications and take into consideration the dose modifiers as being body and muscle mass, dysphagia, and dyspnoea. In spasticity, treatment has to be adjusted to functional impairment: if function is preserved, the dose should be decreased.

Cervical dystonia (CD) remains the most challenging indication due to its complexity and the need for life-long treatment. The wide spectrum of motor and non-motor problems (recognised in recent years) was discussed also in our journal in 2020 [10, 11] and now we continue this topic in this issue [5, 12, 13]. We emphasise the unmet needs for this kind of treatment: the as yet not widely used or accepted Col-Cap concept and the most frequent patterns,the lack of specific scales for this new classification, the need for standardised ultrasound/ /electromyographical guided injections (and scientific proof that they really are superior to anatomical landmarks), and the lack of standardised treatments of non-motor symptoms. The doses of BoNT/A in CD and spasticity were arbitrarally established in clinical trials. In this issue, an international group of authors present the results of a multicentre study showing real-life treatment where doses were lower than in published guidelines, presumably due to more precise injections under US guidance [13]. As there have been no studies published so far looking for the optimal dose per muscle, this is perhaps not the best, but still a valuable, way of showing the effectiveness of doses used in clinical practice in experienced centres. The choice of muscle should be adjusted to the specific pattern of CD. The number of involved muscles varies, usually between four and six.

We should respect the maximal dose in the summary product characteristics of all three BoNT/A preparations [14, 15].

Muscle hypertonia in cerebral palsy has been a licensed indication for BoNT/A for the last 25 years. The authors of the evidence-based review on efficacy and safety published in this issue have shown that all major BoNT/A preparations have been established to reduce hypertonia in both upper and lower extremities, with some conflicting evidence regarding function. There are no differences in treatment safety, with a low incidence of adverse events which are mostly temporary and mild. Similarly to dystonia and spasticity in adults, there is no universal ratio enabling the calculation of dose when switching between preparations [9].

This long-term treatment is complementary to rehabilitation with the use of physiotherapy, orthotics and casting. Although BoNT/A treatment alone was positively assessed by the American Academy of Neurology and Child Neurology Society [16], almost a decade later there is still scant evidence regarding its comparative treatment with different rehabilitation methods and moderate with placebo [17]. In severe generalised hypertonia, a multilevel approach is recommended by different centres. The unresolved issues are the length of time between injections, the overall time of treatment, and how to define functional improvement. All these unresolved problems are valid also for spasticity in adults. This is usually severe in more pronounced paresis, and therefore functional improvement in the form of the recovery of complex and precise limb movements is usually not possible [18]. Therefore, so-called 'goal-attainment treatment' is now preferred to establish realistic goals with the patients and their care-giver before injection [19]. New studies have focused on early (< 3 months) spasticity after stroke and combined treatment with physiotherapy, casting, and orthoses. So far the quality of evidence on combined treatment is low. This early treatment with BoNT is a promising approach, and may decrease the severity of spasticity in the following months or years. In the first three months, the neural component dominates over the biomechanical one with the ability to influence plasticity and central motor learning [20–23]. Nevertheless, it requires further long-term studies to prove the concept.

In chronic migraine (CM), BoNT/A therapy is now an established and licensed indication (exclusively for ONA-BoNT/A after the successful PREEMPT studies). Nevertheless, new licensed and emerging biological therapies with anti-CGRP anibodies (mAbs such as erenumab, fremanezumab, galcanezumab etc) have given rise to the problem of how to position them in clinical practice and reimbursement systems. There are no head-to-head studies between mAbs and BoNT/A. Those pivotal studies performed to license mAbs also differed in methodology with BoNT/A studies. Therefore, positioning should be based on indirect comparisons, expert consensus, and pharmacoeconomic considerations. Further comparative studies are needed.

The spectrum of potential clinical indications for BoNT is still growing, with treatment of sialorrhea being a newly licensed indication (exclusively for INCO-BoNT/A) [24]. There is also a growing number of so-called 'off-label indications' such as: essential tremor (the systematic review published recently in our journal suggests that improvement is usually biased by muscle weakness) [25], focal tics, myoclonus, bruxism [26], neuropathic pain (due to diabetic or postherpetic neuropathy and of central origin) [27, 28] or even depression [29].

Not strictly neurological, but helpful in our patients' indications (published earlier, but discussed also in this issue) is megacolon following a stroke and successfully treated with BoNT/A [30, 31]. Botulinum toxin is used also in other gastroenterological indications for the treatment of anal fissure, constipation (puborectal muscle) in Parkinson's Disease or achalasia and many other conditions, along with cosmetic purposes (e.g. to remove frown lines, wrinkles) that are not discussed here (Tab. 2) [32–35].

Botulinum toxin over the last 30 years has changed the treatment modalities in many neurological disorders or symptoms. We hope and believe that the story is not over.

Conflicts of interest: *Both authors have lectured and consulted for Merz, Ipsen and Allergan.*

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LEADING TOPIC

Botulinum neurotoxin in cervical dystonia revisited — recent advances and unanswered questions

Jarosław Sławek[1,2*], Wolfgang H. Jost[3*]

[1]Division of Neurological and Psychiatric Nursing, Faculty of Health Sciences, Medical University of Gdansk, Poland
[2]Department of Neurology and Stroke, St. Adalbert Hospital, Gdansk, Poland
[3]Parkinson-Klinik Ortenau, Wolfach, Germany

ABSTRACT

Cervical dystonia (CD) usually presents a complex pattern of head/neck movements accompanied by tremor, myoclonic jerks and a wide spectrum of non-motor disturbances such as pain, depression, anxiety, and sleep problems. This is the most challenging indication for botulinum neurotoxin (BoNT) treatment. It can offer significant improvement, but it can be difficult after the first injection. Thorough examination and identification of the proper CD pattern, the identification of the muscles responsible, and adjusting doses given precisely under ultrasound and/or electromyographic guidance seem to be the key success modifiers. Nevertheless, this is a lifelong treatment and should be planned and conducted carefully to avoid failures and drop outs. The aim of this paper was to examine the current concepts in terms of anatomy, physiology and CD patterns (Col-Cap concept) as well as the proper dosages and any possible obstacles impeding successful treatment.

Key words: botulinum neurotoxin, cervical dystonia, electromyography, ultrasonography, deep brain stimulation

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Introduction and aim

Cervical dystonia (CD) remains the most challenging indication for botulinum neurotoxin (BoNT) treatment. However effective, the improvement is usually suboptimal and unsatisfactory for many patients. In recent years, the approach to this treatment has evolved, with new concepts emerging regarding muscle involvement in the clinical patterns of CD (the Col-Cap concept) [1]. Unfortunately, for this new classification we do not have any proper scales to rate the improvement. Non-motor symptoms accompanying motor presentation may not respond to BoNT and can result in worse self-assessment of patients despite the head/neck correction. Guided injections (electromyography EMG, and ultrasound US), currently considered to be the standard approach, lack proof of their superiority over treatment based on anatomical landmarks and clinical judgment only. We still do not know the optimal dose per muscle. The growing number of toxins with different pharmacological properties and different dosing regimens (BoNT/A as onabotulinumtoxinA: ONA-BoNT/A, abobotulinumtoxinA: ABO-BoNT/A and incobotulinumtoxinA: INCO-BoNT/A and BoNT/B as rimabotulinumtoxinB: RIMA-BoNT/B) renders this problem even more complicated. Refractory cases should be assessed carefully for pseudoresistance, and deep brain stimulation (DBS) may be an alternative treatment [2].

However, the American Academy of Neurology Task Force has placed ABO-BoNT/A and RIMA-BoNT/B at level A, and ONA- and INCO-BoNT/A at level B [3]. The recently published report of the Cochrane Library stated: "We are moderately certain in the evidence that a single BONT/A treatment session resulted in a clinically relevant reduction of CD specific impairment, and pain, and highly certain that it is well tolerated, compared with placebo. There are no data from RCTs evaluating the effectiveness and safety of repeated BtA injection cycles. There is no evidence from RCTs to allow us to draw definitive conclusions on the optimal treatment intervals and doses, the usefulness of guidance techniques

Address for correspondence: Jarosław Sławek, MD, PhD, Department of Neurology and Stroke, St. Adalbert Hospital, Al. Jana Pawła II 50 Str., 80-462 Gdansk, Poland; e-mail: jaroslaw.slawek@gumed.edu.pl

*Both authors equally participated in the preparation of this manuscript.

for injection, the impact on quality of life, or the duration of treatment effect." [4]

The aim of this paper was to revisit the treatment concepts of CD in terms of recently published papers, and look for unresolved questions to be addressed in future studies.

History and clinical examination

Over the last 30 years, BoNT has become established as the therapy of choice for CD. Early therapeutic work on CD considered it to be synonymous with spasmodic torticollis, and therapeutic recommendations corresponded mainly to the rotatory form. As a consequence, the sternocleidomastoid muscle and the contralateral splenius capitis muscle were injected. The good results of this early work led to approval studies being conducted, and then to approval being granted for the relevant muscles in rotatory spasmodic torticollis. Injection at that time was done according to clinical considerations, landmarks, and occasionally under EMG guidance [5].

In the last decade however, new considerations have become relevant: on the one hand more muscles are now being injected, and on the other hand a good many novel sub-forms have been identified. Another step forward concerns major progress in the use of US technology. One problematical aspect here is how to prove that with differentiating sub-forms and with the help of extensive diagnostic tools, results would be much better. Nonetheless, it is overall advantageous when recent developments are kept in mind for the purposes of medical training and, even more so, for improving on therapeutic attempts [1, 6, 7].

Since the introduction of a new classification system and of new techniques, a number of very useful modifications and extensions have been established in recent years for taking the medical history as well as for the clinical examination [1, 6, 7]. The patient is interviewed as to their initial symptoms, the course of their development, ensuing symptoms (such as pain) and sensory tricks. Keeping the Col-Cap classification in mind, the primary relevant information on CD is obtained as soon as the patient enters the examination room and sits opposite the physician during anamnesis. Importantly, the patient should be seated parallel to the physician (not, as is too often the case, at an oblique angle) and should remove necklaces, scarves or turtle neck pullovers so that the position of the head and neck can be fully assessed. This usually suffices to evaluate the relevant head mispositioning and any possible sensory tricks.

At examination, a seat without a backrest is best used so that the patient does not have the opportunity to lean back, and also so that the physician can walk completely around him or her, or alternatively the patient can turn around while seated [8]. The patient should be asked to close his or her eyes so as to avoid possible positional correction through visual control and should be prevented from returning the head to the neutral position. In case of rotation of the trunk or raising one shoulder, a third person can best fixate that shoulder. The patient is then requested to demonstrate a sensory trick (geste antagoniste). The function and its possible reduction can be examined by having the patient rotate their head in the different planes of movement: flexing it ventrally and laterally, and extending it dorsally. Subsequently, the patient is examined while standing and while walking so as to judge movement and the influence of walking behaviour on the position of the head and possible compensatory mechanisms. This is followed by a clinical examination of the head position and the planes of movement, the muscle tonus and strength [8].

In cases of tremor-predominating types (e.g. 'no-no,') careful observation of tremor disappearance when turning the head to one side may help to establish the dominant direction of the dystonia. On the other hand, enhancement of tremor may suggest the activity of compensatory muscles.

After this initial examination, one must classify properly the subtype(s) of CD [1, 6, 7]. It is very rare that movements are found at one level alone; a combination of several forms is more common. It is frequently quite difficult to judge which movements are the paramount ones, which are the resultant compensatory ones, and which muscles play an agonistic or antagonistic role in the different subtypes [7]. Therefore, our personal practice is to limit ourselves to the lead pattern and the relevant muscles. In subsequent treatments, doses and muscle selection will be adjusted. The muscles to be injected are selected depending on the type of CD under examination. In complex cases, electromyography (EMG) is also useful for better differentiation between active and non-active muscles. This is especially true for muscles without a phasic component, but EMG may be useful in identifying muscles involved in tremor, where compensatory contraction is less likely to be a confounder. The EMG examination is likewise best done under ultrasound guidance.

Anatomy and classification

While in previous decades we selected muscles for injection based on the form of CD, today we pay more attention to anatomical considerations. While earlier we made use of a deductive (top-down) methodology, today we apply rather an inductive (bottom-up) or individual approach [6, 7]. Muscle origins, their insertions, and their functions, are the basics required for understanding CD patterns. According to the so called 'Col-Cap concept', three dimensions of movement in two levels can be distinguished [1, 6]. From a functional point of view, there are two levels in which we differentiate the upper level between the skull and C2 and the lower one between C2 and C7, with the C2 vertebra regarded as a kind of fixed point. Dystonic activity of muscles with C2 (and above) and skull insertions form the so-called 'caput' and those with insertions below C2 and vertebral (or other) insertions are responsible for the so-called 'collis' subtypes (Fig. 1) In addition to the classical definitions of laterocollis, retrocollis,

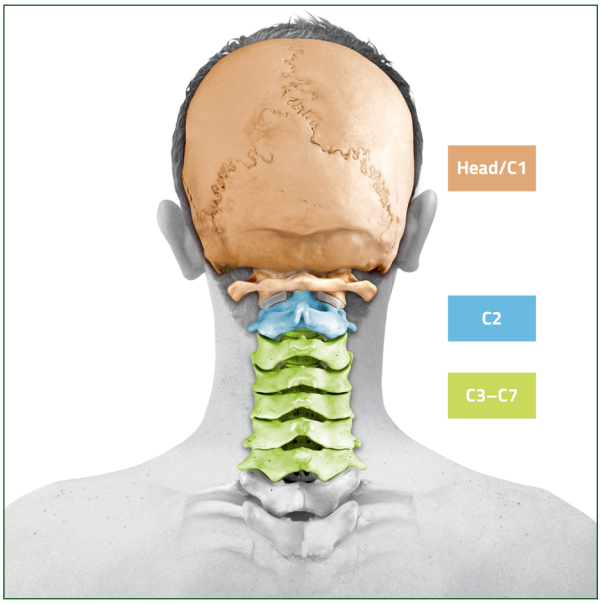

Figure 1. Anatomical basis of Col-Cap concept: Two levels of movement with C2 as a fixed point (modified as per Jost W. Atlas of Botulinum Toxin Injection, 3rd edition, KVM Verlag, Berlin, 2019)

anterocollis, and rotatory torticollis, we must add laterocaput, retrocaput, antecaput, and rotatory torticaput. Furthermore, three different forms of shift, as a combination of simple patterns, should be added. Lateral shift is a combination of laterocollis to one side and laterocaput to the opposite side; anterior shift is a combination of anterocollis and retrocaput; and retroshift is a combination of retrocollis and antecaput [6, 7]. Data regarding this extended list of patterns can be found in our previous papers [5, 6].

It is not yet clear whether certain muscles constitute a single functional unit, or rather whether there are complete muscle chains. We do now know that some muscles are preferentially involved and that certain combinations present together more frequently [9, 10]. In a recent study of 306 patients, splenius capitis was the most commonly involved muscle (83%), followed by sternocleidomastoid (79.1%) and trapezius (58.5%). This was followed by levator scapulae, semispinalis capitis, and obliquus capitis inferior in 38.2%, 48.7% and 35.3% respectively. In torticaput, three muscles were injected in over half of the patients, splenius capitis (88%), sternocleidomatoid (84%), and trapezius (60.7%) [9].

The most common primary form was torticaput (49%), followed by laterocaput (16.7%). Within this group, 16.3% of the patients had only one subtype of CD, 40.2% had two subtypes, 24.5% had three subtypes, and 19% had four or more subtypes [10]. In the whole group, only 9.8% presented with laterocollis, and 8.8% with torticollis. All other subforms made up less than 5%. The frequency of head tremor was 57.6%, and torticaput was the most common dystonic subtype associated with tremor [11]. Many simple subtypes formed a complex pattern.

Torticaput (n = 150) was combined in 46% with laterocaput, and in 20.7% with retrocaput. Furthermore it was combined in 18.7% with torticollis, and 12.7% with laterocollis. Laterocaput, the second most common primary pattern (n = 51), was combined mainly with torticaput (45.1%), laterocollis (33.3%), retrocaput (23.5%), and antecollis (15.7%). Laterocollis (n = 30) was accompanied by laterocaput in 67.7%, torticaput in 46.7%, and in 16.7% by antecollis or retrocaput. The highest positive correlations were found for retrocaput with retrocollis [10].

The mean number of injected muscles in all patients was 4.2 (SD 1.6). In patients with torticaput, it was 4.4 (SD 1.6), in laterocaput 4.4 (SD 1.4), in laterocollis 4.0 (SD 1.4), and in torticollis (n = 27) 4.2 (SD 1.8) [9].

BoNT/A dose per muscle and per session

In the majority of studies, the doses per muscle or the total dose per session have been established arbitrarily. The recommendations published to date are not based on relevant studies finding the proper dose, but on the clinical experience of experts and pre-established doses used in the pivotal clinical studies and then adopted in summary product characteristics (SPC). According to the SPCs, it is recommended that for ONA-BoNT/A, a maximal dose of 200U should be administered at first and should not exceed 300 U in the following treatment sessions [12]. There is a similar recommendation for INCO-BoNT/A [13]; for ABO- BoNT/A, the recommended starting dose is 500 U with a subsequent possibility to increase up to 1,000 U if appropriate and if no dysphagia has been observed at the lower dose [14]. The US Food and Drug Administration recommends doses up to 400 U for both ONA- and INCO-BoNT/A, 1,000 U for ABO-BoNT/A, and 10,000 U for RIMA-BoNT/B [15].

In a group of 305 patients representing real life treatment with stable and effective doses in the previous sessions, 154 patients received ONA-BoNT/A, 53 patients INCO-BoNT/A, and 98 patients ABO-BoNT/A. The mean total doses for a treatment session with ONA-, INCO- and ABO-BoNT/A were 159.5 U (SD = 62.4), 173.4 U (SD = 99.2), and 652.5 U (SD = 285.5) respectively. The doses injected into each muscle in the ONA- or INCO-BoNT/A groups were between 19.7 U and 49.2 U. The highest dose was injected into the splenius capitis, 49.2 ± 26.0 U, with the highest total dose per session being 130 U. The doses in the ABO-BoNT/A group were between 75.4 and 139.6 U per muscle, with the highest dose injected into the splenius capitis: 139.6 ± 80.7 U [16]. These real-life doses were lower than those recommended by experts [17, 18]. We assume that the use of US guidance in our group [16] may be an advantage, and that more precise injections may result in lower doses being used subsequently, although this is only an indirect supposition. Keeping doses at effective, but also not too high, levels is recommended because doses that are too high may

result in the formation of neutralising antibodies in long-term treatment [19].

Injection and the use of EMG and US

Since the very beginning of BoNT therapy, injections have been conducted taking into consideration anatomical landmarks. The use of EMG has become a well established tool. It improves the precision of the injection, especially the accuracy of needle placement within active muscles [5, 20]. Thus, it may also improve safety and efficacy. It allows identification of the target and the most active muscles, but is unable to differentiate between 'dystonic' and 'non-dystonic' (compensatory) muscles.

At present US still competes with EMG [5]. Strictly speaking, there is no actual competition for the better position, but rather a debate on which gives better training for medical personnel. US outlines the anatomical structures more exactly [21], while EMG portrays function better. The two methods are thus not substitutes for one another, but rather complement each other (visibility and function) [5, 22].

In addition, US, in improving the precision of injection, thereby improves safety and possibly efficacy. Furthermore, it allows for standardisation, because we can record in detail just which muscles we are injecting with which doses. During training, we can adequately portray the muscles involved, as well as their relationships to other muscles and structures such as nerves, vessels and bones. We have learned that muscles can often differ between individuals, and that individual muscles can be very thin (e.g. trapezius), meaning that a precise injection can only be guaranteed with the help of US. This is the only way to offer assurance that BoNT is applied precisely where we intend it [21–23].

We are more successful now in pinpointing injections, and in reaching muscles which we could not target earlier [22–25]. As a case in point, we should mention OCI (obliquus capitis inferior) which plays an essential role in the most frequent form of CD and which used to be only rarely targeted for injection [22, 26].

In summary, we have found that US is indispensable and that EMG is useful in complicated cases and in combination with US [22].

Nevertheless, an unresolved problem remains regarding the clinical superiority of guided injections versus blinded ones, as we do not have comparative studies showing better results achieved by guided injections. However, in cadaver studies, the accuracy of needle placement was 100% with US *vs.* 79.2% without US for superficial muscles and 95.8% *vs.* 54.2% for deep muscles (with statistical significance) [25]. This should translate into a better clinical effect, but we need further studies performed on living patients.

One study assessed the impact of monitoring techniques such as US and/or CT in a small group of eight patients requiring injections in deep cervical muscles (obliquus capitis inferior, longus colli, obliquus capitis superior, scalenus anterior and scalenus posterior). The Tsui Scale confirmed a significant improvement occurring within four weeks (11.75 *vs.* 1.50) and on the TWSTRS (Toronto Western Spasmodic Torticollis Rating Scale) in each of the subscales (20.0 *vs.* 5.25, 20.0 *vs.* 7.0, and 13.1 *vs.* 6.5) [27].

Non-motor symptoms and rating scales

In addition to abnormal head postures, many patients present with so-called non-motor symptoms (NMS) [28–30]. It is a matter of debate whether these are direct or indirect symptoms of the disease. Non-motor symptoms have been reported in several studies: lack of self-confidence due to stigmatisation (61.8%), sleep problems (59.8%), and fatigue (51%) [28]. In the study by Sławek et al., the authors reported depression in 47.5% of patients, and this was the major determinant of poor quality of life. Furthermore, after BoNT/A injection, the size effect for motor improvement in TWSTRS was favourable (1.1 SD 0.6) and much lower (0.5 SD 0.7) for depression (Montgomery-Asberg Depression Rating Scale) [31]. This might suggest that abnormal head posture and stigmatisation have no indirect impact and that depression is part of the spectrum of symptoms of CD itself. This was further proved by Berardelli et al. in 2015 when the authors demonstrated that after five years the successful treatment of motor problems (a statistically significant reduction in TWSTRS from 33.4 ± 11.1 to 26.9 ± 10.9) did not correlate with an improvement of neuropsychiatric symptoms (65% *vs.* 64%) [32]. In a recent publication by Klingelhöfer et al., pain, insomnia and stigma were most prevalent, and emotional well-being and pain had a major impact on quality of life. Most NMS, with the exception of pain, stigma and daily activity, did not correlate with motor severity [29].

Self-awareness of motor dysfunction is higher in CD than in other patients with dyskinesias (e.g Parkinson's and Huntington's Diseases) and groups have been matched for depression, which may explain the poor impact of CD on emotional well-being [33].

Stamelou et al. concluded that NMS are not mere epiphenomena of dystonia and demand the same level of attention as motor ones. They should be considered in future pathophysiological models of dystonia [34].

Therefore, in conclusion we have to assess improvement based both on motor and NMS. Unfortunately, evaluation using the old version of TWSTRS and Tsui score did not consider NMS [35]. They are however taken into consideration in the new version of the TWSTRS, but this does not include the Col-Cap classification. Basically, the decision has to be made as to whether all symptoms should be considered, or only those symptoms which are improved by specific therapeutic measures. Any future rating scale must satisfy these requirements.

Lack of improvement of NMS despite good head position after BoNT injection may be responsible for treatment failures and drop outs in long-term treatment.

Treatment failures

Supnet et al. noted long-term treatment discontinuation in 36.2% of a relatively large group of patients. Fifty seven percent of them described suboptimal effect, high costs and long distance to the treatment centre. Eight per cent reported the lack of any improvement, only 47% had regular treatment sessions every 12 weeks, and the results were statistically worse in males [36]. Treatment failures include a long list of possible causes from the misidentification of proper CD pattern, muscle profiles, doses per muscle, side effects, and technical issues (too deep injections, too short needles used, no treatment guidance like EMG or US) to the formation of neutralising antibodies. Also, secondary or symptomatic dystonias as well as pseudodystonias have to be considered if the treatment is not effective. Pseudodystonias were revisited by Berlot et al. in 2019 and new disorders e.g. *fibrodysplasia ossificans progressiva* have been recognised as possible misdiagnoses [5, 37, 38].

Fresh insights into possible treatment failures were noted by Hefter et al. who analysed how disease progression during treatment may influence the outcome. They included 74 patients with a mean time of treatment of 9.9 years. Mean improvement of CD reported by the patients and scored by the physician was about 50%. The frequency of all symptoms (abnormal head position, reduced mobility, head tremor, muscle tension, pain) increased with duration of therapy. The longer the gap between the onset of symptoms and the onset of BoNT therapy, the poorer the long-term outcome, independent of the duration of BoNT treatment [39]. Another group noted in a cohort of 149 patients followed for 14 years the spread of dystonia from isolated to more complex forms in 23.5% cases [36]. In a series of studies, Marciniec et al. reported that compared to moderate/good treatment satisfaction, CD patients with none/low BoNT efficacy had increased incidence of cervical pain, enhanced mean VAS score for pain, and higher coexistence of oromandibular dystonia (spread of dystonia). In addition, worse treatment satisfaction correlated with enhanced scores of Tsui, TWSTRS, as well as TWSTRS subscales: severity, disability and pain [40, 41]. Neutralising antibodies may still be a real problem: Hefter et al. noted them in 16.2% of patients in long-term treatment. This was correlated with higher doses of BoNT used, longer treatment, and higher scores in CD severity scales [39].

We must systematically assess our patients at subsequent sessions, looking for new patterns evolving or new muscles involved, and adjust our injection regimens accordingly.

In a case of treatment failure at the onset of treatment, or if there is a loss of initial good effect, other treatment options such as DBS should be considered. If the patient did not respond from the very beginning, we recommend an algorithm and consultation at a secondary or tertiary movement disorder centre experienced in BoNT therapy (Fig. 2).

Duration of symptom relief between injections

It is a well-established rule to treat patients no more frequently than every 12 weeks. So-called booster injections (it was a common practice in the early years to inject patients with an additional dose after several weeks) have been identified as the chief culprit of antibody formation and secondary non-responsiveness. Many patients have a shorter beneficial period (mean 10.5 weeks in 88% of patients) [42], and therefore physicians are tempted to inject earlier. They may be encouraged by no reports on antibody formulation after new BoNT/A preparation without complexing proteins (INCO-BoNT/A) [43]. Nevertheless, despite the potential risk of antibody formation, it may also result in dose accumulation and adverse effects such as dysphagia or muscle weakness. Walter et al., in a long-term treatment [9.8 ± 6.2 years (range, 0.5–30 years; adherence, 70.6% with 31.2 ± 22.5 (3–112) treatment cycles], showed that independent risk factors for neutralising antibodies were high BoNT dose per treatment, switching between onabotulinumtoxinA and other BoNT formulations (except for switching to incobotulinumtoxinA), and treatment of neck muscles. They did not find antibodies in a group of 49 patients treated with incobotulinumtoxinA for up to 14 years. The authors recommended the use of the lowest possible dose for CD patients and avoiding unnecessary switching between formulations. The mean cumulative dose over time was a risk factor for antibodies formulation after ABO-, but not ONA- or INCO-BoNT/A [19]. This means also that we should avoid shortening the time between injections. On the other hand, ABO-BoNT/A injections for CD or spastic paresis (500-1,000 U) had prolonged efficacy, and 72.6%, 77% and 81.5% of patients did not require injections at week 12 in three consecutive cycles. Moreover, 22.6%, 26.5% and 22.8% respectively did not require injections even after 24 weeks [44]. In real life, however, Supnet et al. reported that only 47% received injections every 12 weeks [36].

Alternative treatments in refractory cases

Pallidal DBS seems to be the most effective alternative treatment option for refractory patients [45, 46]. The authors of a systematic review of 18 studies concluded that both surgical peripheral denervation and DBS are associated with a significant reduction in absolute TWSTRS total score, with no significant difference in the magnitude of reduction observed between the two treatments [47]. A small series of patients confirmed the long-term treatment effects (10–12.8 years): CD scores improved by 53% (total TWSTRS); by 54.1% (severity score); and by 70.1% (disability score). Pain did not improve significantly. Improvement was stable over time. Patients with a tonic pattern of CD responded less to DBS than patients with a phasic pattern, and the effects were unrelated to aetiology [48]. According to analysis by the Cochrane group, severity of symptoms of CD after DBS GPi has been reduced across studies, but quality of life and safety concerns are still uncertain [2].

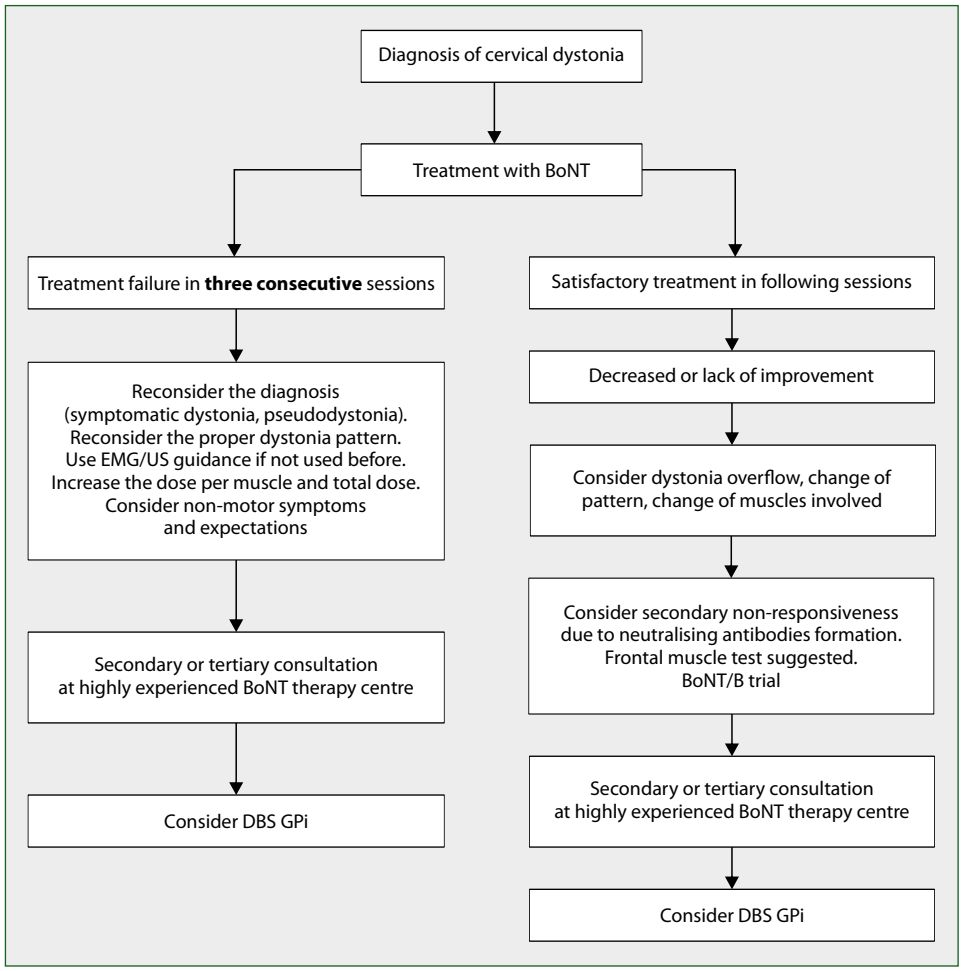

Figure 2. Algorithm for identification of possible treatment failures when starting and continuing treatment of patients with cervical dystonia

The unmet need seems to be a lack of clear protocols (as in Parkinson's Disease) regarding patient selection.

The next interventional procedure is selective muscle denervation. Wang et al. recently published a large series of 648 patients operated on successfully between 1995 and 2013, with a significant improvement observed between preoperative and postoperative TWSTRS evaluation (73.5 ± 11.9 %) [49]. These results are in concordance with the earlier (between 1988 and 1996) study by the Mayo Clinic Group with a long-term follow up of a mean 3.4 years in 130 patients. The original level of moderate-to-excellent improvement in head position and pain was retained in at least 71 patients (70%) [50]. Both these studies were retrospective. In the era of DBS, further prospective studies are required to confirm these results in randomised and blinded studies.

Conclusions

Botulinum neurotoxins offer effective treatment of CD, but challenges remain. The Col-Cap concept seems convincing. However, it is not widely used, nor are US/EMG guided injections. One possible obstacle seems to be the lack of well-documented studies showing Col-Cap superiority over the traditional approach. The lack of specific rating scales is probably one of the reasons.

Treatment protocols should also take into consideration non-motor symptoms (especially neuropsychiatric and sensory ones like pain) and the real expectations of patients. Also, unresolved issues include the proper dose per muscle/session and the correct treatment interval so as to avoid pseudo- or secondary failures (too small or too high doses, potentially resulting in lack of efficacy in the former or antibody formation in the latter). Alternative treatment options such as DBS GPi should be offered after careful selection of refractory patients, but there is as yet no consensus on selection and outcome protocols. Further studies are needed to answer all these unresolved questions.

Conflict of interest: *Both authors are consultants for Allergan, Ipsen and Merz.*

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REVIEW ARTICLE

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LEADING TOPIC

Botulinum toxin type-A preparations are not the same medications — basic science (Part 1)

Halina Car[1], Andrzej Bogucki[2], Marcin Bonikowski[3], Małgorzata Dec-Ćwiek[4], Artur Drużdż[5], Dariusz Koziorowski[6], Monika Rudzińska-Bar[7], Iwona Sarzyńska-Długosz[8], Jarosław Sławek[9]

[1]Department of Experimental Pharmacology, Medical University of Bialystok, Bialystok, Poland
[2]Department of Extrapyramidal Disorders, Medical University of Lodz, Poland
[3]Neuro Rehabilitation Department, Movement Analysis Lab., Mazovian Neuropsychiatry Centre, Limited Liability Company, Zagorze, Poland
[4]Department of Neurology, Collegium Medicum, Jagiellonian University, Krakow, Poland
[5]Department of Neurology, Municipal Hospital in Poznan, Poland
[6]Department of Neurology, Medical University of Warsaw, Warsaw, Poland
[7]Department of Neurology, Faculty of Medicine and Health Sciences. Andrzej Frycz Modrzewski Krakow University, Krakow, Poland
[8]Second Department of Neurology, Neurorehabilitation Ward, Institute of Psychiatry and Neurology, Warsaw, Poland
[9]Division of Neurological and Psychiatric Nursing, Faculty of Health Sciences, Medical University of Gdansk, Poland; Department of Neurology and Stroke, St. Adalbert Hospital, Gdansk, Poland

ABSTRACT

Botulinum neurotoxin type-A (BoNT/A) formulations are widely used in clinical practice. Although they share a common mechanism of action resulting in presynaptic block in acetylocholine release, their structure and pharmacological properties demonstrate some similarities and many differences. Bioequivalence has been discussed since the onset of the clinical use of BoNT/A. In this review, we provide an update on the studies and compare the molecular structure, mechanisms of action, diffusion and spread, as well as immunogenicity and dose equivalence of onabotulinumtoxinA, abobotulinumtoxinA and incobotulinumtoxinA.

Key words: botulinum toxin A formulation, pharmacological similarities and differencies, abobotulinumtoxinA, onabotulinumtoxinA, incobotulinumtoxinA

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Introduction

Botulinum toxins are 'natural products' of living bacteria of the genus Clostridium. Particular therapeutics of botulinum toxin, although based on the same serotype A formulations (BoNT/A), have distinct properties. The main three BoNT/A products commercially available worldwide today are derived from Clostridium botulinum Hall strain: onabotulinumtoxinA (ONA-BoNT/A) marketed as Botox/Vistabel by Allergan Inc. (Irvine, CA, USA); abobotulinumtoxinA (ABO-BoNT/A) marketed as Dysport/Azzalure by Ipsen/Galderma (Paris, France); and incobotulinumtoxinA (INCO-BoNT/A) marketed as Xeomin/Bocouture by MerzPharmaceuticalGmbh (Frankfurt, Germany).

New BoNT/A formulations have recently been introduced to the market: prabotulinumtoxinA-xvfs (PRA-BoNT/A) marketed as Jeuveau/Nabota/Nuceiva by Evolus/Daewoong and daxibotulinum toxin A (DAXI-BoNT/A) (formerly RT002) by Revance. Additionally, letibotulinum toxinA (Croma/Hugel with Botulax) is in Phase III trials although results have not been published yet.

Botulinum neurotoxin type-A preparations use in clinical practice is based on presynaptic chemical denervation of cholinergic synapses due to the cleavage of specific synaptic

Address for correspondence: Jarosław Sławek, MD, PhD, Department of Neurology and Stroke, St. Adalbert Hospital, Al. Jana Pawła II 50 Str., 80-462 Gdansk, Poland, e-mail: jaroslaw.slawek@gumed.edu.pl

Table 1. Comparison of selected characteristics of botulinum toxin type-A preparations based on Frevert 2015 [3], Kutschenko et al. 2016 [42]*, Pirazzini et al. 2017 [11], Ferrari et al. 2018 [80], and Field et al. 2018 [81]**

	Botox/Vistabel	Dysport/Azzalure	Xeomin/Bocouture
Generic name/short name	OnabotulinumtoxinA/ /(ONA-BoNT/A)	AbobotulinumtoxinA/ /(ABO-BoNT/A)	IncobotulinumtoxinA/ /(INCO-BoNT/A)
C. botulinum strain	Hall A-hyper	Hall A	Hall A (ATCC 3502)
Toxin type	A1	A1	A1
Molecular Weight (MW)	900 kDa complex	Not reported	150 kDa
Purification method	Crystallisation	Chromatography	Chromatography
Pharmaceutical form for reconstitution	Vacuum-dried powder	Freeze-dried powder	Freeze-dried powder
Shelf life	2–8°C/36 months	2–8°C/24 months	Room temperature/36 months
Storage after reconstitution	Up to 24 h at 2–8°C	Up to 8 h at 2–8°C	Up to 24 h at 2–8°C
pH (reconstituted)	7.4	7.4	7.4
Excipients in vial	100 U: human serum albumin 0.5 mg, NaCl 0.9 mg	500 U: human serum albumin 0.125 mg, lactose 2.5 mg	100 U: human serum albumin 1 mg, sucrose 4.7 mg
Unit/vial	100 U or 200 U Botox/50 U Vistabel	300 U or 500 U Dysport/ 125 U Azzalure	100 U or 200 U Xeomin/ /50 U Bocouture
Protein load/vial	5 ng/100 U	4.35 ng/500 U	0.44 ng/100 U
Quantity of neurotoxin (ng protein/100 U)	~0.73ng/100 U ~0.90 ng/100 U**	~0.65 ng/100 U ~0.54 ng/100 U**	~0.44 ng/100 U ~0.40 ng/100 U**
Specific potency of 150 kD BoNTA neurotoxin	137 units/ng	154 units/ng	227 units/ng
Wheel-running performance of mice study activity in relation to ONA- BoNTA*	1	2.0	1.3–2.0
Unit testing	Cell-based potency assay specific to Allergan BoNT/A product	LD_{50} assay specific to Ipsen BoNT/A product	LD_{50} assay specific to Merz BoNT/A product

proteins. This results in a decrease of acetylocholine release. Despite the common mechanism, these preparations are distinct medications, with many differences in terms of their structure, potency and immunogenicity. These differences may result in differing clinical efficacy and safety as well as pharmacoeconomic profiles, and have been discussed in medical literature over many years.

The aim of this paper was to show pharmacological similarities among, and differences between, the three most widely used BoNT/A preparations: ONA-, ABO-, and INCO-BoNT/A.

Structure

ONA-BoNT/A and ABO-BoNT/A are purified neurotoxin complexes including the BoNT/A1 and BoNT/A2 toxin molecules, respectively, and neurotoxin accessory proteins: NAPs - three haemagglutinin (HA) proteins and one non-toxic non-HA protein. It has been suggested that non-toxic HA not only stabilises the biological activity of the product *in vivo*, but also enables HA-botulinum toxin complex to adhere to muscle tissue [1]. INCO-BoNT/A contains only purified BoNT/A1 [2–4]. Results from a few studies have shown that ~150 kDa BoNT/A protein is mostly linked with NAPs [5, 6] at physiological pH levels, but other studies have suggested that prior to or shortly after injection the NAPs dissociate from botulinum toxin [7, 8]. Another study concluded that ONA-BoNT/A and ABO-BoNT do not contain neurotoxins in complexed form [8]. All commercial products contain an excipient, known as human serum albumin (HSA), which improves toxin stability and diminishes toxin loss during lyophilisation, prevents protein aggregation and surface adsorption, as well as extends shelf life [4].

ONA-BoNT/A is vacuum dried, while ABO-BoNT/A and INCO-BoNT/A are freeze dried. All formulations before clinical use are reconstituted with sterile normal saline buffer, yielding a solution that is slightly acidic [9, 10]. The reconstitution processes of ONA-BoNT/A results in a complete dissociation of 900 kDa complexes and the release of more than 85% of neurotoxins in free form [8].

A comparison of selected characteristics of BoNT/A preparations is set out in Table 1.

Mechanism of action

The activity of the botulinum toxin known as 'chemical denervation' refers to the decrease of the pre-synaptic release of acetylcholine, and temporary muscle paresis or inhibition

of glandular secretion. Additionally, BoNT/A inhibits the release of other neurotransmitters and influences inflammatory cells. This is probably the basis of its antinociceptive activity [11].

The mechanism of action of botulinum toxin A includes: 1. binding to nerve terminals; 2. internalisation within an endocytic compartment; 3. translocation into the cytosol; 4. the cleavage of SNARE complex by L chain; and 5. reduction of acetylcholine release from the pre-synaptic terminal.

1. In detail, according to 1., the C-terminal heavy chain (H) contains a translocation domain (HN) and a receptor binding domain (HC). The HC includes an N-terminal subdomain (HCN) of unspecified function and a C-terminal subdomain (HCC) that selectively bonds to dual neuron-specific receptors - ganglioside GT1b, and the protein receptor SV2C on the presynaptic plasma membrane in particular neurons [12, 13]. BoNT serotype A1 and A2 binds to the glycosylated SV2C receptor synaptic vesicle glycoprotein 2C (SV2C) [13], which allows for rapid penetration of toxins, at similar rates, via the same synaptic vesicles. HCA2 has higher affinity for receptor and neurons than HCA1 [14]. Glycosylation Asn559 in SV2C is critical for binding of BoNT/A to presynaptic plasma membrane. Glycosylation patterns in this site vary among adult individuals [15]. Pirazzini et al. have suggested that this feature may be responsible for a different onset and duration of induced neuroparalysis in humans following administration of the same dose of BoNT/A1; probably, different amounts of bound toxin are likely to match different numbers of L chains entering the cytosol in nerve terminal [11].
2. The toxin enters the synaptic vesicles of motor axon terminals by endocytosis. Internalisation of BoNT/A is mediated by receptor of a polysialoganglioside (PSG), the glycosylated luminal domain of a synaptic vesicle protein and unique N-glycans attached to synaptic vesicle (SV) glycoproteins [16], as well as to E-cadherin [17–19], fibroblast growth factor and vanilloid receptors [20, 21]. The increased endocytosis rate of BoNT/A and a frequent exposure of the SV lumen was observed during stimulation of nerves. It has been demonstrated [18] that nontoxic HA protein (present in ONA- and ABO-BoNT/A) sequesters E-cadherin in the monomeric state, disrupts the intercellular epithelial barrier, and facilitates paracellular absorption of BoNT/A [20, 22].
3. The L chain (L) of toxin is translocated across the vesicle membrane into the cytosol. Acidification of the synaptic vesicle lumen triggers HN to form a channel to L translocation. Next, the L chain is released from H chain by reduction of the interchain disulfide bond.
4. Next, L chain cleaving the soluble N-ethylmaleimide-sensitive factor attachment protein receptors (SNAREs), particularly synaptosomal associated protein of 25 kDa, SNAP-25.
5. Finally, SNAP-25 prevents the docking and exocytosis of acetylcholine from pre-synaptic vesicles at neurosecretory and neuromuscular junctions. Detailed mechanism of nerve paresis by BoNT/A is described in a review by Pirazzini et al. [11].

The study by Grando and Zachary [23] presented the non-neuronal and non-muscular mechanisms and effects of BoNT/A in many normal and cancer cell lines. Differentially altered genes expression by BoNT/A involved in signal transduction, immunity and defence, protein metabolism and modification, neuronal activities, intracellular protein trafficking and muscle contraction [24] show the huge range of mechanisms and possible effects of botulinum toxin. For example, ONA-BoNT/A injection markedly reduced, by 53%, urothelial ATP release in patients with spinal cord injury [25], increased nitric oxide (NO) release from the urothelium in the bladder detrusor [26], decreased expression of purinergic receptors (P2X3) in the bladder mucosa [27], inhibited the evoked release of CGRP from afferent nerve terminals in the bladder reducing pain [28], reduced bladder inflammation by decreasing urothelial apoptosis and the expression of vascular endothelial growth factor in the bladders of patients with interstitial cystitis (IC)/bladder pain syndrome (BPS) [29]. Recent studies have revealed that BoNT/A has antinociceptive peripheral effects by blocking synaptic transmission of glutamate, dopamine, ATP and gamma-aminobutyric acid regulation and serotonin [30].

The results of analysis of over 40,000 BoNT/A treatment reports indicate that patients who received BoNT/A in a broad range of injection sites had a significantly lower number of depression reports compared to patients undergoing different treatments for the same conditions [31]. Such results have allowed for the introduction of ONA-BoNT/A in Phase III studies designed so as to obtain FDA indication for major depression [32, 33].

The main mechanism of the ability of BoNT/A to weaken hyperactive secretory cells and relax tense muscles is the same for currently registered preparations, while the detailed additional effects mentioned above are described for ONA--BoNT/A only.

Diffusion and spread out

Distant effects of BoNT/A formulations may be the result of haematogenous spread defined as migration in local and regional muscles [34, 35], or as distant migration in areas non-contiguous with the injection [36–39]. Diffusion is characterised as microscopic movement of a soluble molecule's dispersion by passive transport to local and distant tissues [40] away from the intended area to nearby anatomical structures. The local spread of all BoNT/A formulations after injection depends on dilution, needle size, dose and volume, as well as injection technique [41]. Kutschenko et al. [42] suggested that the volume of injection is one of the major factors influencing the degree of muscle paralysis. The volume-dependent

reduction of paresis in a wheel-running test was observed in mice injected with INCO-BoNT/A. Kutschenko et al. suggested that larger volumes induce more intense paresis [42]. Pirazzini et al. suggested that the amount of toxin needed for a certain application should be diluted according to the size of the muscle/area [11]. Based on this data, it may be considered that the diffusion of BoNT/A from the injection site is increased by its gradual dilution in increasing volumes of extracellular fluids thus diminished binding to the presynaptic membrane. Additionally, different degrees of paresis after ONA-BoNT/A, ABO-BoNT/A and INCO-BoNT/A were presented after injecting identical volumes (10 μL) containing the same number of mouse units of BoNT/A into both hind leg muscles. Based on this experiment, the conversion ratio of INCO-BoNT/A and ONA-BoNT/A was estimated as being between 1:0.75 and 1:0.5. ONA-BoNT/A has shown a two-fold greater potency than ABO- BoNT/A [42].

Aoki et al. [36] proposed that protein complex size and pharmacological properties influence the diffusion of BoNT/A. That study showed that high-molecular-weight toxin complex of ONA-BoNT/A limits tissue distribution compared to ABO-BoNT/A [36]. More recent studies in which the size of anhidrotic halos was measured have shown different results. A comparison of ONA-BoNT/A and ABO-BoNT/A (using dose ratios of 1:2.5, 1:3, and 1:4, and identical injection volumes) presented a larger area of anhidrosis after ABO--BoNT/A [43]. Kerscher et al. obtained different mean maximal areas of the forehead anhidrosis of patients at 6 weeks after injection of BoNT/A formulations: comparable spread to ONA-BoNT/A and INCO-BoNT/A, and significantly greater to ABO-BoNT/A [44]. In another study, no significant differences between the mean size of halos produced by ONA-BoNT/A and ABO-BoNT/A were observed [45]. Similarly, no differences in diffusion of ONA-BoNT/A and INCO-BoNT/A injected to forehead at the same dose and using the same technique were demonstrated after 6 weeks and 6 months [46]. In other study, similar, limited to a distance of 30–45 mm [41], diffusion from the site of injection has been well documented by N-CAM staining and characterised ONA-BoNT/A, INCO-BoNT/A and ABO-BoNT/A when they were used in a ratio of 1: 1: 4 and in the same toxin injection volume (25 μL) [47].

Results from the study by Brodsky et al. showed that the presence of complexing proteins in ONA-BoNT/A and ABO--BoNT/A does not reduce migration of the neurotoxin [48]. The diffusion for all formulations of BoNT/A is similar in the majority of studies, but the dose and volume of injection may be the most important factors in differentiating diffusion efficiency.

The retrograde axonal transport of BoNT/A to spinal motor neurons, followed by anterograde transport to the other motor units, has also been suggested [49]. Caleo et al. [50] showed that BoNT/A physically leaves the motoneurons to enter second-order neurons. After injection of ONA- BoNT/A into the nasolabial musculature of rats and mice, catalytically active ONA-BoNT/A was transported to the facial nucleus. The authors suggested that these findings highlight cell-specific, direct central actions of BoNT/A, which are important to fully understand its mechanisms of action and therapeutic effectiveness in movement disorders and pain treatment.

A few studies have shown that BoNT/A, injected intramuscularly, is transported both anterogradely along sensory axons and retrogradely by central neurons and motoneurons axons to the motoneuron soma in the spinal cord [51–54]. Autophagosomes undergo dynein-dependent retrograde axonal transport to the neuronal soma [55]. Moreover, Antonucci et al. observed SNAP-25 cleavage in the contralateral hemisphere after unilateral BoNT/A delivery to the hippocampus [51]. Harper et al. and Restani et al. showed that BoNT/A-HC is internalised in synaptic vesicles and undergoes retrograde trafficking [56, 57]. The retrograde axonal transport and transcytosis to second-order nociceptive neurons explains mechanisms of action of ONA-BoNT/A in migraine [58]. ONA-BoNT/A is the only one approved for the treatment of chronic migraine. Selected papers have presented retrograde transport for ONA-BoNT/A only.

According to the Simpson et al. study, botulinum toxin accesses the perineuronal fluid compartment and does not cross the blood-brain barrier [59]. These authors suggested that BoNT/A is a large molecule and it is not able to cross the blood–brain barrier.

Immunogenicity

Antibody formation against the accessory proteins was observed in patients after injection of BoNT/A formulation with associated proteins, but they did not interfere with the biological activity of the toxin ('non-neutralising') [60]. Results from a preclinical study suggest that the NAPs may physically secure neurotoxin against the immune system and finally against the formation of toxin-neutralising antibodies interfering with clinical response [61]. However, antibodies formed against the heavy chain may or may not prevent its biological activity. The immunological response of humans to BoNT/A is very low, ranging from 0% to 3%: 0% was reported for ONA-BoNT/A [62, 63] and for ABO-BoNT/A used in glabellar lines [63], 1.2% for ONA-BoNT/A [62, 63], less than 3% for ABO-BoNT/A in cervical dystonia [63], and 1.1% for INCO-BoNT/A in upper limb spasticity. Each patient injected with INCO-BoNT/A was previously treated with a botulinum toxin A product which contained complexing proteins [7, 64]. A comprehensive meta-analysis of 61 studies by Fabbri et al. [65] analysed the frequency of antibodies among 8,525 patients receiving all registered types of BoNT/A across several clinical indications. Generally, the prevalence of antibodies among clinically responding patients was lower (3.5%) than in secondary nonresponse patients (53.5%). The frequencies of antibody formation independent of clinical responsiveness

to BoNT/A formulations across all analysed clinical indications were 1.5% for ONA- BoNT/A, 1.7% for ABO-BoNT/A, and 0.5% for INCO-BoNT/A. The results of this analysis indicate the lowest frequency of antibody formation after INCO-BoNT/A. The prospective, single-arm, dose-titration TOWER study showed that no patient with spasticity with a cerebral cause developed secondary nonresponse due to neutralising antibodies after administration of INCO-BoNT/A in a range of doses between 400 j and 800 j [66].

Based on the results of the aforementioned studies, the presence of complexing proteins in BoNT/A formulations may increase the risk of the formation of neutralising antibodies.

The immunogenicity of the BoNT/A formulations depends on some factors that differ in the manufacturing process, mainly the source of toxin and the antigenic protein load and the presence of inactive or denatured toxin acting as a toxoid. Treatment-related factors such as the toxin dose, frequency of injections, as well as prior exposure via other routes (intradermal or distant to the target muscle), different formulations (e.g. first application of ONA-BoNT/A or ABO--BoNT/A and second of INCO-BoNT/A) and site of anatomical region (especially near lymph nodes) seem to play a role in the immunogenic response. Based on this knowledge, clinical practice suggests the use of the lowest effective doses and to maintain 12 weeks of minimal interval treatment [67]. On the other hand, shorter, less than half as long, intervals of injection of INCO-BoNT/A have been described as well tolerated and free of antibodies [68].

Doses

A dose equivalence of BoNT/A formulations is still being discussed. The potency of BoNT/A preparations is expressed as Units (U) and 1U corresponds to one LD50 in mouse bioassay [69, 70]. Different diluents for LD50 testing have used by manufacturers: Allergan uses saline [71]; Ipsen uses gelatin phosphate buffer [72]; human serum albumin as a stabiliser was added by Merz to undisclosed diluent [73]. However, it has been suggested that stabilisers can enhance the activity of BoNT/A products at low concentrations in preclinical tests [74]. It is suggested that the diluent buffer significantly influences biological activity of BoNT/A products. Nonparallel dose-response curves of ONA-BoNT/A and ABO-BoNT/A with different relative potencies can explain a dose conversion ratio between Botox and Dysport of 1:2.5–3 [74, 76] or 1:2 [43].

There are no internationally accepted standardised tests for BoNT/A product comparisons. For this reason, different assay methods with different proprietary product-specific reference standards for testing potency units are used. The clinical effect of one unit is not interchangeable between formulations due to differences in the bioassay methodologies used by producers [77]. The clinical literature has reported an equivalent potency between ONA-BoNT/A and INCO-BoNT/A [3], but this was not the case in an animal (mouse) study [42]. The potency of INCO-BoNT/A and ONA-BoNT/A in inducing hind limb paresis in the wheel-running performance test in mice showed a conversion rate of between 1: 0.75 and 1: 0.5 [42]. The Allergan LD50 assay used ONA-BoNT/A and INCO-BoNT/A diluted in normal saline [72] to compare their activity. The obtained results showed that one INCO-BoNT/A vial contained less than 100 Allergan units (i.e. 69-78 units for three different lots) and clearly suggested the non-interchangeability of units in the studied products. Additionally, these results were confirmed in an enzymatic cleavage assay, the Digit Abduction Score assay, as well as replication of the LD50 results [78, 79]. Dressler et al. [73] indicated that assay conditions markedly influence potency measurements. Moreover, dose-response data of BoNT/A formulations is used to determine the therapeutic dose range as the 'benefit–risk' rate from acceptable efficacy and safety profiles. Significantly different muscle weakening efficacies identified as 50% maximal (median effective dose -ED50) have been reported for the three main BoNT/A products, and furthermore not equipotent units of the botulinum toxin formulations that are under experimental conditions were presented [36, 79].

Additionally, different quantities of 150 kDa (ng protein/100 U) of BoNT/A in formulation (the lowest in INCO-BoNT/A and the highest in ONA-BoNT/A) were shown by Ferrari et al. [80] and Field et al. [81] (see also Table 1). Calculated analysis shows differences between BoNT/A formulations. The highest amount of neurotoxin per product unit (in pg) and the total amount of active BoNT-A (in ng) injected at the recommended dose for an adult lower limb and an adult upper limb were obtained for ABO-BoNT/A. However, the relative quantity of rBoNT/A assessed as a ratio quantity obtained by the EndoPep method to protein quantity tested by ELISA method demonstrated not significant differences in LC activity-tested BoNT/A formulations. This indicates that the 150 kDa neurotoxin molecules in each product are equally active [81].

Some studies have shown the non-interchangeability of units of ONA-BoNT/A and INCO-BoNT/A. The highest total amount of active BoNT/A being found after injection of ABO-BoNT/A to lower and upper limbs may suggest a focus on the conversion rate between ONA-BoNT/A and ABO-BoNT/A or INCO-BoNT/A and ABO-BoNT/A.

Summary

The major difference in structure between BoNT/A formulations concerns the presence or absence of complexing proteins. The effectiveness of BoNT/A preparations is not dependent on complexing proteins, but they may increase the risk of the formation of neutralising antibodies. The mechanism of action of all BoNT/A is similar, but the central effects of ONA-BoNT/A may expand indications for its use in major depression. Diffusion and spread out for all formulations of BoNT/A is similar in most studies. The retrograde axonal transport and transcytosis to second-order nociceptive neurons described for

ONA-BoNT/A only justifies its usefulness in the treatment of chronic migraine. The non-interchangeability of units of ONA-BoNT/A and INCO-BoNT/A was shown in an animal study, and the highest total amount of active BoNT/A after ABO-BoNT/A injection to lower and upper limbs may suggest the need for additional studies in other indications to confirm the correct conversion rate doses between BoNT/A preparations.

Based on the differences in biological assays and the variations of biological activity [82, 83], regulatory agencies in most countries worldwide require a statement of unit non-interchangeability among BoNT/A products.

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LEADING TOPIC

Botulinum toxin type-A preparations are not the same medications – clinical studies (Part 2)

Jarosław Sławek[1], Andrzej Bogucki[2], Marcin Bonikowski[3], Halina Car[4], Małgorzata Dec-Ćwiek[5], Artur Drużdż[6], Dariusz Koziorowski[7], Iwona Sarzyńska-Długosz[8], Monika Rudzińska[9]

[1]Division of Neurological and Psychiatric Nursing, Faculty of Health Sciences, Medical University of Gdansk, Poland; Department of Neurology and Stroke, St. Adalbert Hospital, Gdansk, Poland
[2]Department of Extrapyramidal Disorders, Medical University of Łodz, Poland
[3]Mazovian Neuropsychiatry Centre, Limited Liability Company, Neuro Rehabilitation Department, Movement Analysis Laboratory, Zagorze, Poland
[4]Department of Experimental Pharmacology, Medical University of Bialystok, Poland
[5]Department of Neurology, Jagiellonian University Medical College, Krakow, Poland
[6]Department of Neurology, Municipal Hospital in Poznan, Poland
[7]Department of Neurology, Faculty of Heath Science, Medical University of Warsaw, Poland
[8]Second Department of Neurology, Neurorehabilitation Ward, Institute of Psychiatry and Neurology, Warsaw, Poland
[9]Department of Neurology, Faculty of Medicine and Health Sciences. Andrzej Frycz Modrzewski Krakow University, Krakow, Poland

ABSTRACT

The growing number of botulinum neurotoxin type-A (BoNT/A) preparations on the market has resulted in a search for pharmacological, clinical and pharmacoeconomic differences. Patients are occasionally switched from one botulinum toxin formulation to another.

The aim of this paper was to review studies that have made direct comparisons of the three major BoNT/A preparations presently on the market: ona-, abo- and incobotulinumtoxinA. We also review the single medication Class I pivotal and occasionally Class II-IV studies, as well as recommendations and guidelines to show how effective doses have been adopted in well-established indications such as blepharospasm, hemifacial spasm, cervical dystonia and adult spasticity.

Neither direct head-to-head studies nor single medication studies between all preparations allow the formation of universal conversion ratios. All preparations should be treated as distinct medications with respect to their summary of product characteristics when used in everyday practice.

Key words: botulinum toxin type-A, cervical dystonia, blepharospasm, spasticity, hemifacial spasm

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Introduction

Currently, there are three commercially available botulinum neurotoxin type-A (BoNT/A) preparations available, widely used and licensed in a majority of countries: onabotulinumtoxinA (ONA-BoNT/A, Botox); abobotulinumtoxinA (ABO-BoNT/A, Dysport); and incobotulinumtoxinA (INCO-BoNT/A, Xeomin).

They have similar mechanisms of action. However, their chemical formulations, clinical potency, dosing and safety profiles are different. This can result in bio- and pharmacoeconomical equivalence problems. The discussion on bioequivalence and switching from one to another preparation is still ongoing [1, 2]. This discussion will certainly be continued in future as new preparations (e.g. daxibotulinumtoxinA, prabotulinumtoxinA) are now in clinical trials.

Address for correspondence: Jarosław Sławek, MD, PhD, Department of Neurology and Stroke, St. Adalbert Hospital, Al. Jana Pawła II 50 Str., 80-462 Gdansk, Poland, e-mail: jaroslaw.slawek@gumed.edu.pl

Table 1. Selected studies on BoNT/A in treatment of blepharospasm and hemifacial spasm (dose ratio comparison between different products)

Reference	Study design	Patient characteristics and outcome	BoNT/A and dose (U)	Muscle injected/ /injection guide	Efficacy outcome/ /adverse events
Nussgens et al. 1997 [9]	Class II study DB, prospective, crossover design; comparison of ONA- and ABO-BoNT/A	n = 212 BS Duration of effect	ONA-BoNT/A Mean dose 44 U ABO-BoNT/A Mean dose 182 U Mean ratio: 1:4	Orbicularis oculi muscle	AEs: ONA-BoNT/A: 17%; ABO-BoNT/A: 24%; Ptosis (less with ONA--BoNT/A)
Sampaio et al. 1997 [8]	Prospective randomised study: a single-blind, randomised, parallel comparison	n = 91 with BS or HFS	ONA-BoNT/A or ABO-BoNT/A pre-estimated ratio: 1:4	Orbicularis oculi muscle	Similar duration of effect: 13.3 +/- 5.9 weeks for ABO-BoNT/A, and 11.2 +/- 5.8 for ONA-BoNT/A. Adverse events noted in 50% of both
Roggenkamper et al. 2006 [14]	Class I study DB, randomised, prospective, parallel design; comparison of ONA-BoNT/A and INCO-BoNT/A	n = 300 BS adjusted mean change in JRS, BDI at weeks 3, 16 Duration of effect	ONA -BoNT/A Mean dose 40.8 U INCO-BoNT/A Mean dose 39.6 U Mean ratio: 1:1	Orbicularis oculi muscle	Efficacy, AEs, duration: similar for both
Wabbels et al. 2011 [16]	Class I, DB, randomised, prospective, parallel design; comparison of ONA-BoNT/A and INCO-BoNT/A	n = 65 BS Change in BDI at weeks 4 and 8; Change in JRS; Change in patient global assessment at week 4	ONA-BoNT/A: Mean dose 29 U/eye; INCO-BoNT/A: Mean dose 27 U/eye Mean ratio: 1:1	Orbicularis oculi muscle	Similar efficacy and duration for both
Saad and Gourdeau 2014 [15]	Class II DB, randomised, split-face design; comparison of ONA-BoNT/A and INCO-BoNT/A	n = 48 BS 4 consecutive treatments JRS, BDI score at each visit. Likert scale for Orbicularis oculi strength at each visit. Likert scale for spasm severity at each visit. Patient preference	ONA-BoNT/A or INCO-BoNT/A mean dose 19.9 U/eye. Mean ratio: 1:1	Orbicularis oculi muscle	Similar effects. AEs: not available
Grosset et al. 2015 [19]	Open study comparison of ABO-BoNT/A and INCO-BoNT/A	n = 19 BS n = 91 HFS 4 consecutive treatments Patient assessment of treatment efficacy (7-point scale comprising excellent, very good, good, fairly good, fair, poor, or negligible) and duration of treatment effect (a 4-point scale comprising excellent, good, a few weeks, or short-lived)	ABO -BoNT/A: Mean dose BS 80 U HFS 46 U. INCO-BoNT/A: Mean dose BS 20 U HFS 11 U. Mean ratio: 4:1	Orbicularis oculi muscle	Similar duration of effect
Kollewe et al. 2015 [20]	Open study	n = 288 BS 8 consecutive treatments GCI	Mean doses: ONA-BoNT/A 47.1 U; INCO-BoNT/A 62.11 U; ABO-BoNT/A 120.35 U. Mean ratios: ONA-BoNT/A to ABO-BoNT/A 1:2.3 ONA- BoNT/A to INCO-BoNT/A 1:1.2 INCO-BoNT/A to ABO-BoNT/A 1:2.0	Orbicularis oculi muscle 3-4 site injections	Similar effects and AEs in all three

ABO-A — abobotulinumtoxinA; AE — adverse event; BDI — Blepharospasm Disability Index; BDS — Blepharospasm Disability Scale; BoNT — botulinum neurotoxin; CI — confidence interval; DB — double-blind; INCO-A — incobotulinumtoxinA; JRS — Jankovic Rating Scale; ONA-A — onabotulinumtoxinA; PBO — placebo; PC — placebo-controlled; U — unit(s)

In Part 1 of this discussion, we presented the basic pharmacological differences between all three preparations [3]. Here in Part 2, the same group of authors provide a summary of product characteristics (SPC) and review the available clinical studies on major neurological indications (i.e. blepharospasm, BS; hemifacial spasm, HFS; cervical dystonia, CD; and upper and lower limb spasticity, ULS, LLS in adults), comparing all three BoNT/A preparations in terms of their bioequivalence, which is understood as clinical effectiveness, dosing and safety. Guidelines and recommendations are also included. We have prioritised randomised, double-blind studies, those directly comparing different preparations of BoNT/A, but where these are lacking we have also looked at Class II–IV studies. We review also single medication studies to make indirect comparisons for the same indication.

Blepharospasm and hemifacial spasm

BoNT/A is considered to be the first line treatment of BS and HFS, but only a few studies have been published comparing the different preparations. According to SPC, ONA-BoNT/A and INCO-BoNT/A are injected into the medial and lateral orbicularis oculi of the upper lid and the lateral orbicularis oculi of the lower lid. The initial recommended dose is 1.25–2.5 U at each site, and it should not exceed 25 U per eye. At subsequent treatment sessions, the dose may be increased up to two-fold if the response to the initial treatments is considered insufficient. In the management of BS, the dose should not exceed 100 U in total every 12 weeks. ABO-BoNT/A is injected in an initial dose of 40 U per eye. The injection site should be localised into the junction between the preseptal and orbital parts of both the upper and lower orbicularis oculi muscles of each eye 10 U medially and 10 U into four sites. If the response to initial treatment is inadequate, it may be necessary to increase the dose at subsequent visits up to 60 U, 80 U or even 120 U. In the management of BS and HFS, the total dose should not exceed 120 U per eye every 12 weeks [4–6].

We set out the short characteristics of comparative studies in Table 1. Single medication studies are shown in Table 2.

ONA-BoNT/A *vs.* ABO-BoNT/A

The first study comparing different types of BoNT/A was published more than 25 years ago. In the 1995 study by Marion et al., 111 patients with BS and HFS with a good response to ABO-BoNT/A over at least 12 months of treatment were switched to ONA-BoNT/A with dose ratio 3:1, obtaining similar effects [7]. Two other double-blind studies included 300 patients with both BS and HFS and compared ONA-BoNT/A to ABO-BoNT/A. The authors did not observe any difference in clinical efficacy of effect duration at a dose ratio of 1:4 [8, 9]. Bihari (2005) in a cross-over prospective, open label study in a group of 27 patients with BS and nine patients with HFS, confirmed the same efficacy of both products at a dose ratio of 1:4–1:5 [10]. A retrospective study by Marchetti et al. (2005) published the results of 114 patients with BS who received for at least 12 months ONA-BoNT/A (mean dose 33 ± 12 U) before switching to ABO-BoNT/A (mean dose 147 ± 58 U), or conversely started with ABO-BoNT/A (mean dose 125 ± 49 U) before switching to ONA-BoNT/A (mean dose 31 ± 10 U) with treatment continuing for one year. The ratio of mean dose of ONA-BoNT/A and ABO-BoNT/A ranged from a low of 1:2 up to a high of 1:11 (mean 1:3 to 1:4) [11]. Bentivoglio et al. (2012) compared the pairs of treatments with a switch from one brand to another (ONA-BoNT/A and ABO-BoNT/A) in the same patient (n = 46 with BS and n = 31 with HFS) in consecutive sessions with overlapping clinical outcomes, and found ratios to be highly variable (range: 1:1.2–13.3). In most cases (65%), it was between 1:3 and 1:5 [12].

ONA-BoNT/A *vs.* INCO-BoNT/A

Dressler et al. (2009) published the results of a prospective study comparing ONA-BoNT/A to INCO-BoNT/A in a group of patients with different disorders. Two hundred and sixty-three patients (including 12 with BS and 17 with HFS) who had been previously treated with ONA-BoNT/A for at least 12 months under stable conditions were converted, in a blinded fashion, to INCO-BoNT/A using a 1:1 conversion ratio and with other treatment parameters identical. Patients with BS received a mean total dose of 85.1 ± 32.6 U ONA- and INCO-BoNT/A and patients with HFS received 44.7 ± 19.5 U. There were no subjective or objective differences between both products with respect to onset latency, maximum duration of therapeutic effect, or adverse effects [13]. The same 1:1 ratio was confirmed by two other studies [14, 15].

Wabbels et al. found that ONA-BoNT/A *vs.* INCO-BoNT/A (mean dose 29 U/eye and 27 U/eye respectively) had comparable magnitude and duration of benefit (13 weeks). However, a post hoc analysis showed a significantly greater number of ONA-BoNT/A treated patients reaching a responder threshold of 4 points on the total score of disability [14]. Other studies have shown that patients with BS and HFS who were treated with INCO-BoNT/A had a significantly shorter treatment interval (10.2 weeks *vs.* 13.0 weeks) or required a higher average dose compared to ONA-BoNT/A [2, 15, 16].

Similar results were confirmed in the TRUEDOSE Pilot Study. The objective was a retrospective evaluation of the dose utilisation of ONA-BoNT/A and INCO-BoNT/A in 14 BS patients treated over four years. Patients were switched from ONA- (mean dose 14.41 U per eye) to INCO-BoNT/A (mean dose 17.09 U). For BS, the average annual dose per patient year for ONA-BoNT/A was 50.4 ± 50.6 U, and significantly lower *vs.* INCO-BoNT/A with an average dose of 64.01 ± 53.2 U ($p = 0.002$). Average total dose ratio (mean dose/year) was 1:1.27. The inter-injection intervals were significantly longer (16.25 *vs.* 14.24 weeks) for ONA- than for INCO-BoNT/A ($p = 0.04$) [2].

Table 2. Selected studies on BoNT/A in treatment of blepharospasm and hemifacial spasm (single toxin, indirect comparisons possible only)

References	Study design	Patients characteristics and outcome measures	BoNT/A and dose (U)	Muscles injected	Efficacy outcome/adverse events
Jankovic and Orman 1987 [21]	Class II study blinded, prospective, crossover design	n = 12 BS Fahn scale and patient subjective scale	ONA-BoNT/A 25 U/eye, if ineffective then 50 U/eye	Orbicularis oculi muscle	Improvement, AEs, reported but no percentage numbers reported
Yoshimura et al. 1992 [22]	Randomised, double blind crossover design	n = 11 HFS Subjective improvement; analogue 10-point scale. Objective improvement (blinded review of videotapes made one month after each injection) assessed with categorical 10-point scale	ONA-BoNT/A three different doses compared to placebo Total dose 5-90 U	Selection of muscles to inject were based on clinical examination	Subjective improvement after 79% of injections. Objective improvement after 84% of injections. AEs: facial weakness (97%), facial bruising (20%), diplopia (13%), ptosis (7%)
Girlanda et al. 1996 [23]	Class II study comparing two eyes of same patient with normal saline control	n = 6 BS Subjective scale in blinded video rating	ONA-BoNT/A 20 U/eye or normal saline	Orbicularis oculi muscle	Reduction in blepharospasm AEs: not available
Truong et al. 2008 [24]	Class II study, DB, randomised, parallel group, PC	n = 123 BS Primary measure: difference in BDS	ABO-BoNT/A 40 U, 80 U, or 120 U per eye	Orbicularis oculi muscle	Disability improved in dose-related manner. AEs: ptosis (13-39-58%), blurred vision (23-19-42%), diplopia (10-16-16%) for doses 40-80-120 U respectively Comments: 80 U/eye preferred as efficacious and safe. High number of withdrawals. 35% of PBO group completed study
Jankovic et al. 2011 [25]	Class I, DB, randomised, prospective, parallel design; randomised 2:1 to INCO-BoNT/A *vs.* PBO	n = 109 BS JRS, BDI score at weeks 3, 6 and end of study. Time for need for new injection on basis of JRS score > 2, up to 20 weeks investigator global assessment	INCO-BoNT/A up to 50 U/eye	Orbicularis oculi muscle	Statistically significant improvement. AEs: ptosis (18.9%), dry eye (18.9%)

ABO-A — abobotulinumtoxinA; AEs — adverse events; BDI — Blepharospasm Disability Index; BDS — Blepharospasm Disability Scale; BoNT — botulinum neurotoxin; CI — confidence interval; DB — double-blind; INCO-A — incobotulinumtoxinA; JRS — Jankovic Rating Scale; ONA-A — onabotulinumtoxinA; PBO — placebo; PC — placebo-controlled; U — unit(s)

ABO-BoNT/A vs. INCO-BoNT/A

Grosset et al. in a retrospective 12-month study assessed dose equivalence ratio between ABO-BoNT/A and INCO-BoNT/A in a group of 257 cases including 19 patients with BS and 91 with HFS. Patients were switched from ABO- (mean dose for BS 89 U and for HFS 46 U) to INCO-BoNT/A and observed for at least one year. Switching from ABO-BoNT/A to INCO-BoNT/A at a 4:1 unit ratio resulted in good therapeutic effectiveness in terms of treatment efficacy, duration of treatment effect, and adverse events profile [17].

ONA-BoNT/A vs. INCO-BoNT/A vs. ABO-BoNT-A

Kollewe et al. published the first study comparing the efficacy and adverse effects of all three major BoNT/A preparations over a treatment time of 11.2 ± 4.1 years. Two hundred and eighty-eight patients with BS were included and 85% were treated with a stable dose: 128 patients with ONA-BoNT/A (mean dose 47 ± 10 U), 84 patients with ABO-BoNT/A (mean dose 120 ± 35 U), and 76 patients with INCO-BoNT/A (mean dose 62 ± 11 U). No patient was switched between preparations throughout the observation period. The Clinical Global Improvement Scale score (2.5 ± 0.6) and adverse effects frequency (3%) were similar in all compared preparations. ONA-BoNT/A doses were 16.7 % lower than INCO-BoNT/A ($p < 0.001$), and the dose ratio between them was calculated as 1:1.2. Dose ratios between ONA- and ABO-BoNT/A was 1:2.3; between INCO- and ABO-BoNT/A it was 1:2.0. Therapeutic effects started after 6.1 days and lasted for 10 weeks and were not significantly different between all three products [18]. Papers including direct comparisons between preparations are set out in Table 1.

Conclusions

- The range of conversion ratios between all three products extracted from all studies was wide: ONA- *vs.* INCO-BoNT/A from 1:1 to 1:1.27, and between ONA- and ABO-BoNT/A from 1:3 to 1:5
- The number of adverse effects is similar in most studies, but duration was slightly longer in ABO- *vs.* ONA- and ONA- *vs.* INCO-BoNT/A
- Based on a SPC, and having reviewed studies on the efficacy and safety of BS and HFS treatment, making comparisons between the available preparations remains difficult. This is due to the small number of Class I and II trials, differing study designs (sometimes with adopted conversion rate) and assessment scales used in these studies (VAS, Jankovic scale, blepharospasm disability scale), and differing sites of injections (pretarsal or preseptal region). We believe this results in an inability to establish a fixed conversion factor
- Dosing should be based on individual patient need according to the recommendation of the SPC for each BoNT/A preparation.

Cervical dystonia (CD)

Due to the insufficient effects of oral pharmacological treatment of CD, BoNT/A is currently considered to be the first line therapy. According to the SPC, it is recommended that for ONA-BoNT/A a maximal dose of 200 U should be administered initially, and the dose should not exceed 300 U in subsequent treatment sessions [4]. There is a similar recommendation for INCO-BoNT/A [6]. For ABO-BoNT/A, the recommended starting dose is 500 U. As treatment is continued, the doses may be appropriately adjusted according to the treatment effects and observed side effects (e.g. dysphagia). However, the maximum dose administered must not exceed 1,000 U [5].

We set out selected comparative (direct comparison) studies in Table 3 and single medication studies (indirect comparison) in Table 4.

Comparative studies

There is still little data on direct comparisons of individual toxin preparations in CD patients. Studies have compared mainly ONA- *vs.* ABO- and INCO-BoNT/A preparations and were aimed at comparing the effectiveness or side effects, searching for a conversion ratio.

ONA-BoNT/A *vs.* ABO-BoNT/A

Odergren et al. included 73 patients in a randomised trial comparing ONA- and ABO-BoNT/A, who had previously been treated with BoNT/A with good results. They adopted a fixed 1:3 ratio between products and obtained a similar duration, number of side effects, and overall Tsui scale improvement [26].

A similar approach was applied by Ranoux et al. in a crossover study comparing ONA- and ABO-BoNT/A with pre-fixed conversion factors of 1:3 and 1:4. The study included patients treated successfully at least twice with ONA-BoNT/A. Each patient was subjected to three cycles of therapy. ABO--BoNT/A efficacy was significantly higher for both conversion ratios (Tsui scale, pain scale), and the effect lasted longer. However, in patients receiving ABO-BoNT/A, adverse events (mostly dysphagia) were twice as frequent regardless of the dose ratio [27].

The aim of the study conducted by Marchetti et al. was to evaluate the real-world dose utilisation of ONA- and ABO--BoNT/A for CD and BS. They abstracted utilisation data for patients who received ABO- before switching to ONA-BoNT/A, or conversely. Patients were identified during scheduled clinic visits and selected if they met the study criteria, which included treatment for at least two consecutive years (at least one year with ABO- or ONA-BoNT/A, then switched and maintained on one of them for at least another year, adjusting the dose to achieve a similar effect). A total of 114 patients were included in the assessment. Ratios of mean dose for ABO- to ONA-BoNT/A ranged from a low of 2:1 to a high of 11:1. Thirty-one percent of patients fell into the ABO- to ONA-BoNT/A ratio group of 5:1 to less than 6:1; 30% with a ratio of 4:1 to less than 5:1; and only 21% was in a range of 3:1 to less than 4:1 [11].

A double-blind, randomised crossover trial by Rystedt et al. compared ONA-BoNT/A and ABO-BoNT/A in two different dose conversion ratios (1:3 and 1:1.7) when diluted to the same concentration (100 U/mL). Forty-six patients received three different treatments: ONA- in two different doses and ABO-BoNT/A as a control treatment. Efficacy was evaluated four and 12 weeks after treatment using, among others, Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS); no differences were observed. At week 12, a statistically significant difference in effect between ONA-BoNT/A (1:3) and ABO-BoNT/A was noticed, suggesting a shorter duration of effect for ONA-BoNT/A. This study showed that the ratio of 1:3 resulted in suboptimal efficacy of Botox, and indicates that the dose conversion ratio between ONA-BoNT/A 100 U/mL and ABO-BoNT/A 100 U/mL may be lower than 1:3, but this needs to be validated in a larger study [28].

In a randomised, double-blind, multicentre, non-inferiority, two-period crossover study performed by Yun et al., patients were randomly assigned to initial treatment with ABO- or ONA-BoNT/A, and they were followed up for 16 weeks after the injection. After a 4-week washout period, they were switched to the other formulation and followed up for another 16 weeks. The primary outcome was the change in the Tsui scale between the baseline and week 4 after each injection. Mean changes in the Tsui scale between baseline and 4 weeks after each injection tended to favour ONA-BoNT/A; however, this was not statistically significant (4.0 ± 3.9 points for the ABO- treatment *vs.* 4.8 ± 4.1 points for ONA-BoNT/A; $p = 0.091$). The mean changes in the Tsui scale, TWSTRS, the

Table. 3. Selected studies on BoNT/A in treatment of cervical dystonia (dose ratio comparison between different products)

References	Study design	Patients characteristics and outcome	BoNT/A and dose (U)	Muscles injected/ /injection guide	Efficacy outcome/ /adverse events
Odergren et al. 1998 [26]	RCT, DB, parallel group, prospective multicentre study, comparison of ONA- and ABO-BoNT/A	n = 73 Patients with a minimum of four previous ONA--BoNT/A treatments, randomised to receive either clinically indicated dose of ONA-BoNT/A or ABO-BoNT/A with fixed ratio 1:3 Tsui scores, duration, adverse events	ABO-BoNT/A mean dose of 477U (range 240-720) ONA-BoNT/A mean dose of 152U (range 70-240)	Anatomical landmarks, multiple injections within muscles allowed	Tsui score, similar effect at week 4 (ABO-BoNT/A, 49%, ONA-BoNT/A, 44%) Similar duration: ABO-BoNT/A mean 83.9 days ONA-BoNT/A mean 80.7 days Similar number of AEs
Ranoux et al. 2002 [27]	RCT, DB, three cycles crossover study	n = 54 Tsui scores, TWSTRS pain scores, duration, adverse events	Effective dose of ONA-BoNT/A was changed to ABO--BoNT/A at fixed ratio 1:3 or 1:4	Anatomical landmarks. All injections performed by same neurologist blinded to treatment and using same technique: one single injection point per muscle, close to motor point	Better effect of ABO-BoNT/A at 1:3 and 1:4 ratios AEs: higher with both ABO-BoNT/A treatments Dysphagia: ONA-BoNT/A 3%, ABO--BoNT/A 15.6%, and 17.3% for conversion ratios 1:3 and 1:4, respectively
Marchetti et al. 2005 [11]	Multicentre evaluation real-world dose utilisation of ABO-BoNT/A and ONA- BoNT/A for CD and BS	n = 114 (both for BS and CD) Patients received ABO--BoNT/A or ONA- BoNT/A for at least one year before and after drug crossover	Ratios of mean dose for ABO- and ONA--BoNT/A ranged from 2:1 to 11:1	Anatomical landmarks, doses and muscles injected were determined by physician based on individual clinical presentation and outcome	ABO- *vs.* ONA-BoNT/A 5:1 to less than 6:1, (31%) 4:1 to less than 5:1, (30%) 3:1 to less than 4:1, (21%)
Benecke et al. 2005 [30]	DB non-inferiority study comparing INCO-and ONA-BoNT/A	n = 463 TWSTRS, pain scores, duration, adverse events	Fixed dose conversion ratio 1:1	Anatomical landmarks; doses and muscles injected were determined by physician based on individual clinical presentation	Effect, duration and AEs similar for both
Rystedt et al. 2015 [28]	DB, randomised crossover, ONA- BoNT/A and ABO-BoNT/A in two different dose conversion ratios (1:3 and 1:1.7)	n = 46 pts TWSTRS	Two different dose conversion ratios (1:3 and 1:1.7), diluted to same concentration (100 U/mL)	Anatomical landmarks; doses and muscles injected were determined by physician based on individual clinical presentation	Similar effect at week 4 (TWSTRS) Shorter duration of effect for ONA- BoNT/A AEs: similar
Yun et al. 2015 [29]	DB, randomised,multicentre, non-inferiority, two-period crossover study	n = 103 Tsui scores, TWSTRS pain scores, adverse events	Fixed dose conversion ratio 1:2.5 between ONA-BoNT/A and ABO-BoNT/A, concentration (100 U/mL)	Anatomical landmarks; doses and muscles injected were determined by physician based on individual clinical presentation	Similar effects and AEs -

RCT — Randomised Controlled Trial; DB — double-blind; TWSTRS — Toronto Western Spasmodic Torticollis Rating Scale

proportion of improvement in clinical global impression and patient global impression, and the incidences of adverse events, were not significantly different between the two treatments. In conclusion, the study showed no differences between the ABO- and ONA-BoNT/A at a conversion rate of 2.5:1 [29].

ONA-BoNT/A *vs.* INCO-BoNT/A

In a study comparing the effectiveness of treatment with ONA- *vs.* INCO- BoNT/A, Benecke et al. included a large group of 463 patients [23]. The efficacy and safety of both preparations were compared in a 1:1 dose ratio (209 patients treated with INCO- and 205 with ONA-BoNT/A) and observed for 16 weeks. Groups did not differ significantly regarding TWSTRS scores, pain intensity, duration of improvement, or side effects [30].

Single medication studies

We identified 11 randomised, double-blind studies on the treatment of CD with the use of various BoNT/A

Table 4. Selected studies on BoNT/A in treatment of cervical dystonia (single toxin with indirect comparisons only possible)

References	Study design	Patients characteristics and outcome measure	BoNT/A and dose (U)	Muscles injected/ injection guide	Efficacy outcome/ adverse events
Poewe et al. 1998 [34]	RCT, double-blind, dose-ranging, placebo-controlled	n = 75 Tsui scale, pain scale and global assessment at weeks 2, 4 and 8, AEs	ABO- BoNT/A, 250, 500, 1,000 U, placebo	Anatomical landmarks, fixed muscles: splenius capitis and contralateral sternocleidomastoid	Significant improvement at week 4 for both doses
Truong et al. 2005 [35]	RCT, double-blind, multicentre, placebo-controlled	n = 80 TWSTRS, pain scale and self-report visual analogue scale (VAS)	ABO- BoNT/A 500 U, placebo	Study medication administered by intramuscular injection into two, three, or four clinically indicated neck muscles in a single dosing session, with or without EMG guidance. Investigator determined number of injection sites per muscle and dose at each site	Significant improvement at weeks 4, 8, and 12 Median duration: 18.5 weeks AEs: similar, except blurred vision (14 *vs.* 0%) and muscle weakness (11 vs 0%) in ABO-BoNT/A *vs.* placebo group, Dysphagia (16 *vs.* 9%), but not significant
Comella et al. 2011 [36]	RCT, double-blind, multicentre dose-ranging, placebo controlled	n = 223 TWSTRS total score (baseline *vs.* week 4 AEs	INCO- BoNT/A 120 U, 240 U, or placebo	Anatomical landmarks, number of injection sites per muscle, volume injected into each muscle, and use of EMG guidance were determined at discretion of investigator	Improvement at week 4 AEs: dysphagia (2.7% *vs.* 11.5% *vs.* 24% in placebo, 120 and 240U respectively)
Charles et al. 2012 [37]	RCT, double-blind, multicentre, placebo-controlled	n = 170 CDSS and physician GAS at week 6	ONA-BoNT/A 95-360 U (mean 236 U), or placebo	Anatomical landmarks, doses and muscles injected were determined by physician based on individual clinical presentation and previously established treatment regimen	Improvement at week 6 AEs: rhinitis (6.8% and 3.7% in double -blind and open period *vs.* 0% placebo. Statistically significant dysphagia (6.8% *vs.* 8.4% *vs.* 3.7% placebo in double-blind open period, not statistically significant)

RCT — Randomised Controlled Trial; TWSTRS — Toronto Western Spasmodic Torticollis Rating Scale; VAS — Visual Analogue Scale; GAS — Global Assessment Scale; CDSS — Cervical Dystonia Severity Scale; EMG — electromyography

preparations. All these studies showed that BoNT/A is effective in CD therapy over a placebo. However, the used doses to achieve the effect of improvement were 500–1,000 U of ABO-BoNT/A, 95–360 U of ONA-BoNT/A, and 120–240 U of INCO-BoNT/A [31–38].

The use of EMG or US guidance *vs.* no guidance may have influenced the amount of BoNT/A needed, but it was not controlled for in any of these studies.

Conclusions

- The treatment of CD is very challenging. Many factors can influence outcomes, such as: a proper pattern of CD recognition, utilising different approaches in terms of muscle selection (e.g. adopting Col-Cap concept), and injection guidance with EMG or ultrasound [39–42]
- Reviewing all cited studies, we note various approaches from real life practice up to pre-fixed ratios, different solutions, various scales used, and timelines
- The range of conversion ratios between all three products extracted from all studies is wide (ONA- *vs.* INCO-BoNT/A 1:1, and between ONA- and ABO-BoNT/A from 1:1.7 to 1:5)
- Regarding the studies performed, in comparing different BoNT/A preparations it is impossible to establish a fixed ratio between doses. When switching patients from one to another, one must respect the SPC specific recommendations.

Upper limb spasticity

Botulinum neurotoxin-A is widely used in clinical practice for the treatment of this major complication following a stroke, affecting 30–40% of patients [43, 44]. Nevertheless, to date there have been no guidelines offering a unified dosage standard for consecutive muscles and different BoNT/A formulations. All three major formulations recommend different muscles and doses in their SPCs. The total dose per treatment session varies from 400 U for ONA-, 500 U for INCO-, and 1,500 U for ABO-BoNT/A [4–6]. Table 5 sets out the muscle patterns and doses extracted from SPCs of three products. With the aim of finding the possible conversion ratio between different BoNT/A products, we analysed the most important studies on the treatment of ULS with all three preparations. Adhering to the methodology that we have adopted for this

Table 5. Product registration recommendations in upper limb spasticity treatment for three major BoNT/A preparations

Recommended muscle	ONA-BoNT/A (Botox) (recommended dose range)	ABO-BoNT/A (Dysport) (recommended dose range)	INCO-BoNT/A (Xeomin) (recommended dose range)
Flexor carpi radialis	15–50 U	100–200 U	25–100 U
Flexor carpi ulnaris	10–50 U	100–200 U	20–100 U
Flexor digitorum profundus	15–50 U	100–200 U	25–100 U
Flexor digitorum superficialis	15–50 U	100–200 U	25–100 U
Adductor pollicis	20 U	25–50 U	5–30 U
Flexor pollicis longus	20 U	100–200 U	10–50 U
Flexor pollicis brevis / opponens pollicis	-	-	5–30 U
Brachialis	-	200–400 U	25–100 U
Biceps brachii	-	200–400 U	50–200 U
Brachio-radialis	-	100–200 U	25–100 U
Pronator teres	-	100–200 U	25–75 U
Pronator quadratus	-	-	10–50 U
Triceps brachii (long head)	-	150–300 U	-
Pectoralis major	-	150–300 U	20–200 U
Subscapularis	-	150–300 U	15–100 U
Latissimus dorsi	-	150–300 U	25–150 U
Deltoideus	-	-	20–150 U
Teres major	-	-	20–100 U
Maximal recommended dose per treatment session (according to SPCs)	400 U	1,500 U	500 U

paper, we included in our analysis double-blind, randomised, placebo-controlled trials evaluating the efficacy and safety of various preparations of BoNT/A in the treatment of upper limb spasticity (Tab. 6) [45–58]. Almost all studies evaluated BoNT/A effectiveness in post-stroke (PS) spasticity, except for Gracies et al. [54] which included post-stroke patients as well as subjects with post-traumatic brain injury.

We did not identify studies directly comparing the clinical efficacy and safety of all three BoNT/A products. All of them compared the BoNT/A preparations versus a placebo. Based on studies included in our analysis, direct comparisons of the efficacy and tolerability of these three products are impossible. Indirect comparisons of the results are also limited and inconclusive due to different patient characteristics and various treatment and evaluation methods, e.g. injected muscle groups, guidance, used scales, or follow-up duration. These different approaches can be seen in Table 6 where we set out major data from trials.

Conclusions

- All studies confirm the effectiveness (in terms of reduction of muscle tone and in some also in simple functions) and safety of the used doses of BoNT/A market products in the treatment of ULS for a wide range of maximal doses: ONA-BoNT/A: 120–400 U; ABO-BoNT/A: 100–1,000 U; and INCO-BoNT/A: 150–400 U
- The choice of medical preparation and dose of BoNT/A should be adapted to individual patient need, but it is recommended not to exceed the maximum doses per treatment session according to the SPC
- However, in a few studies higher doses were used safely: 1,500 U of ABO-, 600 U of ONA- and 800 U of INCO-BoNT/A [59, 60]. Looking at these dosages, it is impossible to translate one result into another using a simple conversion ratio. We cannot present the recommended conversion ratio. Switching patients from one preparation to another should therefore respect the product characteristics recommendations.

Lower limb spasticity

Product characteristics of ONA-BoNT/A recommend the administration of 300-400 U in a single treatment session of focal lower limb spasticity (LLS). The total injected dose of BoNT/A should be divided among up to six muscles (*m. gastrocnemius, m. soleus, m. tibialis posterior, m. flexor hallucis longus, m. flexor digitorum longus, and m. flexor digitorum brevis*), whereas SPC of ABO-BoNT/A recommend doses of up to 1,500 U with a spread in the distal muscles (*m. soleus, m. gastrocnemius, m. tibialis posterior, m. flexor digitorum longus, m. flexor digitorum brevis, m. flexor hallucis longus, m. flexor hallucis brevis*) as well as in the proximal muscles of the lower limb

Table 6. Selected studies on BoNT/A in treatment of upper limb spasticity

References	Study design	Patient characteristics and outcome measures	BoNT-A and dose (U)	Muscles injected/ /njection guide	Efficacy outcome/ /adverse events
Bakheit et al. 2001 [45]	RCT, multi-centre, double-blind, placebo-controlled	n = 59 PS – over 3 months MAS, PROM, BI, pain sore, GAS, physician and patient global assessment of benefit	1,000 U ABO-BoNT/A and placebo	BB, FCR, FCU, FDS, FDP / according to anatomical landmarks	Improvement at week 16 AEs: in 16 in ABO-BoNT/A group and in 20 in placebo group (mainly accidental injury, respiratory and urinary tract infections)
Brashear et al. 2002 [46]	RCT, multi-centre, double-blind, placebo-controlled	n = 126 PS – over 6 months with AS scores of at least 3 in the wrist and at least 2 in the fingers; AS for wrist, fingers, thumb; DAS in principal target domain (limb position, dressing, hygiene, pain), GAS, measurement of neutralising antibodies, AEs	200-240 U ONA-BoNT/A or placebo	FCR, FCU, FDS, FDP, FPL, ADDP / NA	Improvement up to 12 weeks; No major AEs
Childers et al. 2004 [47]	RCT, multi-centre, double-blind, placebo-controlled, dose-ranging	n = 90 PS – mean 25.8 months from stroke onset (0.9–226.9 months) with wrist, elbow, and finger flexor spasticity MAS, physician and patient global assessments, pain, FIM and SF-36, AEs	E1: 90 U ONA-BoNT/A E2: 180 U ONA-BoNT/A E3: 360 U ONA-BoNT/A or placebo	BB, FCR, FCU, FDS, FDP / EMG guidance	Dose dependent MAS reduction in: wrist and elbow flexors up to 9 weeks, and in finger flexors up to 3 weeks. No significant changes in pain, FIM or SF-36 AEs in 83.1% (54/65) of ONA--BoNT/A group and 65.4% (17/26) of placebo group
McCorry et al. 2009 [48]	RTC, multi-centre, double-blind, placebo-controlled	n = 96 PS – over 6 months with ≥ 2 on MAS for at least two of elbow, wrist and finger flexors; AQoL, GAS, VAS for pain evaluation, HADs, MAS, MMAS, Carer Burden Scale, Patient Disability Scale, Global Assessment of Benefit by investigator and patient, AEs	750-1,000 U ABO-BoNT/A in first cycle, 500-1,000 U in second cycle or placebo	BB, BR, B-R, TRIC, FCR, FCU, FDS, FDP, FPL/ ADDP/FPB / EMG and/or ES guidance	Significant reduction in spasticity (MAS), higher GAS scores and greater global benefit up to 20 weeks in ONA-BoNT/A *vs.* placebo No changes in AQoL; AEs: treatment-related in 5.5% of ONA-BoNT-A and 9.5% placebo
Kanovsky et al. 2009 [49]	RTC, multi-centre, double-blind, placebo-controlled	n = 148 PS – over 6 months with ≥ 2 AS for wrist and finger flexors; AS, DAS, Carer Burden Scale, Global Assessment of Treatment Benefit by investigator, patient and caregiver, development of neutralising antibodies, AEs	Up to 400 U (mean 320 U) INCO-BoNT/A or placebo	Principal therapeutic target was flexed wrist and clenched fist (FCR, FCU, FDS, FDP), and additionally as needed: BB, BR, B-R, ADDP, OPPP, FPL, FPB, PT, PQ / EMG and/or ES guidance	Improvement of ≥ 1 point in AS score at 4 weeks, improvement until week 12 in principal therapeutic target, and in some tasks of Carer Burden Scale AE in 21 pts (28.8%) in INCO-BoNT/A and 20 (26.7%) in placebo group; incidence of AEs were similar
Kaji et al. 2010 [50]	RTC, multi-centre, double-blind, placebo-controlled, dose-ranging	n = 109 PS over 6 months with focal pattern of both wrist and fingers, 3 or 4 MAS for wrist flexors, and 2+ for finger flexors on MAS for wrist, finger flexors and thumb, DAS, CGI, ADL, AEs	E1: 120–150 U ONA-BoNT/A E2: 200–240 U ONA-BoNT/A or placebo	FCR, FCU, FDP, FDS, FPL, ADDP / EMG or ES guidance	Reduction of spasticity and improvement in ADL in limb position and dressing in E2; E2 more effective than E1 in reduction of wrist spasticity; investigator's and patient's CGI significantly higher in E2 compared to placebo group; patient's CGI significantly higher at weeks 1 and 4 in E1 compared to placebo group; AEs: 47% in E2, 38% in E1 and 57% in placebo group

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Table 6 cont. Selected studies on BoNT/A in treatment of upper limb spasticity

References	Study design	Patient characteristics and outcome measures	BoNT-A and dose (U)	Muscles injected/ /njection guide	Efficacy outcome/ /adverse events
Wolf et al. 2012 [51]	RCT, prospective, single-centre, double-blind, placebo-controlled	n = 25 PS after 3-24 months with unilateral ULS focal spasticity in wrist or fingers, ability to initiate wrist extension of at least 10° from a fully flexed position; WMFT, MAS, AROM, SIS (quality of life), AEs	ONA-BoNT/A 300 U or placebo	Wrist and fingers flexors / according to anatomical landmarks	Improvement in MAS No significant changes in WMFT, AROM, SIS; AEs: one related to study (swelling and localised haematoma after injections)
Marciniak et al. 2012 [52]	RCT, prospective, two-centre, double-blind, placebo-controlled	n = 21 PS – over 6 months with 3 or 4 MAS for shoulder adductors/ internal rotator and shoulder pain; MAS, PROM, daily pain ratings using VAS, DAS for dressing, hygiene, pain and cosmesis, FIM - upper body dressing, hygiene, McGill Pain Questionnaire Short Form; Fugl-Meyer Scale, AEs	ONA-BoNT/A 140-200 U or placebo	PECM (100-150 U), TM (40-60 U) / according to anatomical landmarks	Improvement in MAS, PROM, DAS for hygiene and Fugl-Meyer Scale No significant changes in FIM; AEs: none treatment-related
Rosales et al. 2012 [53]	RCT, prospective, multi-centre, double-blind, placebo- controlled	n = 163 PS after 2-12 weeks with MAS ≥ 1+ in elbow or wrist joint, Asian ethnicity; MAS, BI, mRS, Functional Motor Assessment Scale scores, PROM, AROM	ABO-BoNT/A 500 U and unstructured rehabilitation programme or placebo and unstructured rehabilitation programme	BB, BR, FCR, FCU, FDP, FDS, FPL / NA	Significant improvement in MAS at all time points (24 weeks), improvement in PROM and active finger movements (hand closed) at weeks 4, 8, and 12; no significant changes in BI, mRS, Functional Motor Assessment scores; AEs: 48 (57%) in ABO-BoNT/A and 36 (43%) in placebo group
Gracies et al. 2015 [54]	RCT, prospective, multi-centre, double-blind, placebo-controlled	n = 243 PS or PTBI – over 6 months, MAS in the PTMG ≥ 2 PGA of treatment response using a 9-point scale, DAS in principal target domain (hygiene, dressing, limb position, pain)	E1: ABO-BoNT/A 500 U E2: ABO-BoNT/A 1,000 U or placebo	PTMG among elbow, wrist, or finger flexors, and into at least two additional muscle groups from elbow, wrist, or finger flexors or shoulder extensors ES guidance	MAS score reduction in PTMG in E1 and E2 groups; superiority in PGA; no significant improvements in DAS; AEs: treatment related in 2 (2%), 6 (7%), and 7 (9%) pts in placebo, E1 and E2 groups, respectively (most commonly mild muscle weakness). All AEs – mild or moderate
Elovic et al. 2016 [55]	RCT, prospective, multi-centre, double-blind, placebo-controlled	n = 317 PS – over 3 months with flexed elbow, flexed wrist, and clenched fist with AS ≥ 2 on at each site and a clinical need for a total dose of 400 U of INCO-BoNT/A; AS of PTMG, Investigator's Global Impression of Change using a 7-point balanced Likert scale; DAS in principal target domain (hygiene, dressing, limb position, pain)	INCO-BoNT/A 400 U or placebo	1 PTMG: flexed elbow – 200 U or flexed wrist – 150 U or clenched fist – 100 U and other muscle groups - investigators decided dose and number of injection sites per muscle within predefined ranges EMG and/or ES guidance	Improvements in PTMG in AS, superiority in Investigator's Global Impression of Change, functional improvements in DAS; AEs: 47 of 210 subjects. AE of special interest in 7 subjects (3.3%), most commonly dry mouth (4 subjects)
Rosales et al. 2018 [56]	RCT, prospective multi-centre, double-blind, placebo-controlled	n = 42 PS – 2–12 weeks with MAS ≥ 2; time between UL injection, MAS, UL active motor function, time to reach re-injection criteria, global assessment of change	ABO-BoNT/A 500 U or placebo	PTMG (most commonly – elbow flexors) / NA	Increased time to re-injection, prolonged MAS improvements AEs: 23 adverse events in 12 patients; mostly mild-to-moderate intensity

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Table 6 cont. Selected studies on BoNT/A in treatment of upper limb spasticity

References	Study design	Patient characteristics and outcome measures	BoNT-A and dose (U)	Muscles injected/ /njection guide	Efficacy outcome/ /adverse events
Abo et al. 2020 [57]	RCT, prospective, multi-centre, double-blind, placebo-controlled, dose ranging	n = 131 PS with MAS scores at least 3 in elbow and at least 2 in wrist or fingers; MAS for elbow, wrist, fingers, thumb. DAS in principal target domain (limb position, dressing, hygiene, pain), CGI	ONA-BoNT/A 400 U (240U in forearm and 160 U in elbow flexors) or single treatment of ONA-BoNT/A (240 U in forearm and placebo in elbow flexors)	FCR, FCU, FDP, FDS, FP, ADDP additional injection: BB, B, BR; anatomical landmarks	Forearm MAS reduction in ONA-BoNT/A and forearm only group; elbow flexors greater MAS reduction. Improvement in DAS, Investigator's CGI – similar in both groups
Lindsay et al. 2020 [58]	RCT, prospective, single-centre, double-blind, placebo-controlled	n = 93 PS after 6 weeks, with spasticity and ARAT grasp score ≤ 2; EMG, Tardieu scale, PROM, ARAT	ONA-BoNT/A 160 U or placebo	B, BB, FDS, FDP, FCU, FCR ES or US guidance	Spasticity reduction in ONA-BoNT/A group with significant difference between weeks 2 and 12 (elbow) and weeks 2 and 6 (wrist); slower development of contracture, PROM higher in E group. No differences in ARAT between groups

RCT — randomised controlled trial; PS — post stroke; MAS — modified Ashworth scale; PROM — passive range of motion; BI — Barthel Index, Goal Attainment Scaling; BB — biceps brachii; FCR — flexor carpi radialis; FCU — flexor carpi ulnaris; FDS — flexor digitorum superficialis; FDP — flexor digitorum profundus; AE — adverse event; AS — Ashworth Scale; DAS — Disability Assessment Scale; FPL — flexor pollicis longus; ADDP — adductor pollicis; NA — not applicable; FIM — functional independence measure; SF-36 — 36-Item Short-Form Health Survey; E1/E2/E3 — experimental groups; EMG — electromyography; pts — patients; AQoL — Assessment of Quality of Life scale; VAS — visual analogue scale; HADs — Hospital Anxiety and Depression Rating Scale; MMAS — Modified Motor Assessment Scale; BR — brachialis; B-R — brachio-radialis; TRIC — triceps; FPB — flexor pollicis brevis; ES — electrostimulation; OPP — opponens pollicis; PT — pronator teres; PQ — pronator quadratus; CGI — Clinical Global Impression; ADL — activities of daily living; WMFT — Wolf Motor Function Test; AROM — active range of motion; SIS — Stroke Impact Scale; PECM — pectoralis major; TM — teres major; mRS — modified Rankin Score; PTBI — post traumatic brain injury; PGA — Physician Global Assessment; PTMG — primary target muscle group; UL — upper limb; ARAT — Action Research Arm Test; US — ultrasound

(*m. rectus femoris, m. hamstrings, m. adductor magnus, m. adductor longus, m. adductor brevis, m. gracillis, m. gluteus maximus*).

There is no recommendation for treatment of focal lower limb spasticity in the INCO-BoNT/A SPC.

The only study that provides findings on the conversion ratio (ABO-BoNT/A *vs.* ONA-BoNT/A) for lower limb muscles was performed in a group of healthy volunteers [61]. A double-blind, randomised, dose-escalation study assessed the electrophysiological response of *extensor digitorum brevis* muscle after BoNT/A injection. Dose response curves for 1–20 U of ABO-BoNT/A and ONA-BoNT/A showed an initial rapid decrease in compound muscle action potential (CMAP) at doses ranging from 1 to 6 U, although this decrease was lower at higher concentrations. Statistical modelling predicted that, at the lower concentration, a mean decrease in CMAP to 73% of baseline value would be achieved with 1 U of ONA-BoNT/A. For a comparable effect, 1.57 U of ABO-BoNT/A would be required. The authors concluded that a dose ratio equivalence of 3:1, tested in control clinical trials, would be within the statistical error limits of the model [61].

There are no studies comparing head-to-head the effectiveness and safety profile of different BoNT/A formulations in the treatment of adult LLS. But there have been nine randomised controlled trials (RCTs) evaluating the effectiveness of different preparations of BoNT/A in reducing ankle plantar-flexor spasticity [62–70]. These may indirectly show what doses were used to achieve statistically meaningful effects. However, seeking a conversion ratio based on such a comparison is inappropriate. Detailed descriptions of pivotal studies of both ONA- and ABO-BoNT/A in LLS are set out in Table 7.

The doses tested were established at the beginning of most studies, and ranged from 500 up to 1,500 U of ABO- and up to 400 U of ONA-BoNT/A. Adverse events in treatment groups were usually more frequent when compared to a placebo, but either not clinically relevant or not medication-related. In one study, in approximately 20% of patients a significant reduction of muscle tone was noticed up to week 16 [63].

There has been no RCT evaluating INCO-BoNT/A in the treatment of LLS. An open-label study assessed 71 patients with stroke-related ankle plantar-flexor muscles spasticity treated with a single injection of INCO-BoNT/A at a maximum total dose of 180 U for a change in MAS, frequency of daily spasm, and passive ankle dorsiflexion grade of motion. A significant reduction in MAS and improvement in other evaluated parameters at 30 days was reported (MAS t0 = 3.9 ± 0.6; t1 = 2.5 ± 1.0; p = 0.00) and also at 90 days (MAS t0 = 3.9 ± 0.6; t1 = 3.0 ± 1.0; p = 0.00) of follow-up. During the study, only 11% of patients experienced treatment-emergent, but reversible, adverse events [71].

It is difficult to weigh up the similarities and differences between available studies concerning different BoNT/A medications efficacy in the treatment of LLS in adults. These studies shared no common endpoints except for MAS of the ankle plantar flexor muscles [62–70]. All available studies confirm a beneficial effect in reducing MAS score in patients treated with BoNT/A. The scheme of BoNT/A injection differed between the studies with hamstrings being injected, if needed, in the Wein study [62]. In all studies, except for that by Pittock et al. [64], selected muscles were targeted using ES, EMG or US guidance.

Table 7. Selected studies on BoNT/A in treatment of spasticity of ankle plantar flexor muscles

References	Study design	Patient characteristics and outcome measures	BoNT/A and dose (U)	Muscles injected/ injection guide	Efficacy outcome/ adverse events
Pittock et al. 2003 [64]	RCT, double-blind, dose-ranging, placebo-controlled	n = 234 MAS for ankle plantar flexor, 2MWT, step length, stepping rate, RMA, PROM of ankle, subjective assessment of pain in knee, leg, ankle, foot	3 doses of abo-BoNT/A: 1st group (59 pts): 500 U; 2nd group (60 pts): 1,000 U; 3rd group (60 pts): 1,500 U	GM, GL, SOL; anatomical landmarks	MAS score reduction throughout study period in all groups; greatest improvements in MAS score in 3rd group; AEs: 130 adverse events recorded by 68 out of 234 pts (10 pts receiving abo-BoNT/A considered severe AE and related to treatment: pharyngitis, dysphagia, headache, somnolence, dizziness, pain, asthenia, abnormal gait)
Mancini et al. 2005 [68]	RCT, double-blind, dose-ranging	n = 45 MAS and MRC of spastic foot, gait assessment, Achilles tendon clonus, VAS for gait function and pain	3 doses of ONA-BoNT/A: 1st group (15pts): 167 U; 2nd group (15pts): 322 U; 3rd group (15pts): 540 U	GM, GL, TP, SOL; EMG guidance	Reduction of MAS score in all 3 groups; AEs: in 3rd group (prolonged weakness of treated limb, flu-like syndrome, oedema of injected limb)
Kaji et al. 2010 [65]	RCT, double-blind, placebo-controlled, single cycle	n = 120 MAS for ankle plantar-flexor muscles, gait pattern, speed of gait, CGI	300 U ONA-BoNT/A; placebo	SOL, GM, GL, TP; EMG or ES guidance	Significant improvement in MAS and CGI (investigator). No significant differences in gait patterns and speed; AEs: 7 pts (myalgia)
Gracies et al. 2017 [63]	Single-cycle multicentre, RCT, double-blind, placebo-controlled	n = 331 MAS for ankle plantar-flexor muscles, comfortable barefoot walking speed, PGA	1,000 U and 1,500 U of ABO-BoNT/A; placebo	SOL, GM, GL; ES guidance	Consistent efficacy in MAS for 1,500 U AEs: falls, pain in extremities, muscle weakness
Wein et al. 2018 [62]	Multicentre, RCT, double-blind, placebo-controlled	n = 447 MAS for ankle plantar-flexor muscles, CGI, GAS, pain scale	ONA-BoNT/A (≤ 400 U); placebo	SOL, GM, GL, TP, others (FDL, FDB, FHL, EH, RF)* EMG and US guidance	Significantly improved MAS, CGI, and GAS scores *vs.* placebo AE: 39pts (injection site pain, injection site mass, muscular weakness)

*maximum permitted dose in optional muscles, to a total additional dose of ≤ 100 U during double-blind phase; SOL — soleus; GM — gastrocnemius medial head; GL — gastrocnemius lateral head; TP — tibialis posterior; FDL — flexor digitorum longus; FDB — flexor digitorum brevis; FHL — flexor hallucis longus; EH — extensor hallucis; RF — rectus femoris; PGA — physician global assessment; 2MWT — 2-min walking test; RMA — Rivermead Motor Assessment; PADFM — passive ankle dorsiflexion grade of motion; SFS — spasm frequency scale; AE — investigator-determined treatment-related adverse events

The presented studies reported that amounts of ONA-BoNT/A (range 300-400 U), ABO-BoNT/A (500-1,500 U) and 180 U of INCO-BoNT/A were effective and safe.

Conclusions

- The comparative study was performed in lower limb muscles of healthy volunteers without spasticity, using an electrophysiological method of assessment
- It is challenging to establish the comparative potencies and the equivalence ratio between ABO-BoNT/A, INCO-BoNT/A, and ONA-BoNT/A in the treatment of LLS limb spasticity, as doses were adapted in almost all studies and based on diverse protocols, with no head-to-head designs.

Recommendations and guidelines

In 2009, the US Food and Drug Administration (FDA) established non-proprietary names for the BoNT/A preparations manufactured by Allergan (onabotulinumtoxin A), Ipsen (abobotulinumtoxin A), and Merz (incobotulinumtoxin A). This decision reflected the opinion that individual BoNT/A brands should not be treated as interchangeable due to different purification methods and differences in the final product of purification, different ways of assessing activity, as well as different units in which activity is expressed [72, 73]. Non-proprietary names were also intended to prevent possible errors resulting from the use of the same abbreviations for BoNT/A products supplied to the market by different manufacturers.

Dystonia

Practice guidelines for the BoNT/A treatment of movement disorders were published for the first time by the American Academy of Neurology (AAN) in 2008 [74]. This document summarised the available studies on the use of BoNT/A, /B in the treatment of BS, CD, HFS, limb and laryngeal dystonia, tics and essential tremor.

Botulinum toxin type-A was assigned a level A recommendation only for the treatment of CD. This was based on the results of seven Class I studies (two with ONA-BoNT/A, two with ABO-BoNT/A, and three with type B toxin). Level B recommendation was assigned for the treatment of BS (two Class II studies with Botox), focal upper limb dystonia (one Class I study with ABO-BoNT/A and three Class II studies with ONA-BoNT/A), laryngeal dystonia (one ONA-BoNT/A Class I study) and essential tremor (two Class II studies with ONA-BoNT/A).

The guidelines on the diagnosis and treatment of primary dystonias published by the European Federation of Neurological Societies (EFNS) in 2011 were less detailed, and all marketed formulations of BoNT/A were considered as the same class [75]. The main recommendations considered BoNT/A as a first-line treatment for primary cranial (excluding oromandibular), writer's cramp and CD (level A) [75].

Updated AAN practice guidelines for the BoNT/A treatment of BS, CD, adult spasticity and headache were published in 2016 (76). The authors noted that there are important differences from a clinical point of view between BoNT/A preparations, including potency and duration of action. Therefore, in the updated document, the efficacy and safety of each preparation was evaluated separately. This approach resulted in a reduction in the level of recommendation in individual indications. Only ABO-BoNT/A obtained a level A recommendation for treatment of CD (two Class I studies). Both ONA-BoNT/A (one Class I and one Class II study) and INCO-BoNT/A (one Class I study) were assigned level B. Moreover, the AAN noted that the results of one (Class I) comparative study showed that ABO- and ONA-BoNT/A are probably equally effective in treating CD. ONA-BoNT/A (two Class II studies) and INCO-BoNT/A (one Class I study) were considered to be probably effective (Level B) in BS, and ABO-BoNT/A was assigned a level C recommendation (one Class II study) in this indication. According to comparative (two Class I and one Class II) studies, ONA- and INCO-BoNT/A are equivalent in efficacy in treating BS, while ABO- and ONA-BoNT/A are possibly equivalent (one Class II study) [76].

Spasticity in adults

The first report of the Therapeutics and Technology Assessment Subcommittee of the AAN on the treatment of spasticity with BoNT/A was published in 2008 [74]. The conclusion was that BoNT/A is effective in the treatment of ULS in adults (level A). This was based on six Class I studies including ABO-BoNT/A and four Class I studies with the use of ONA-BoNT/A. The therapy was also considered effective in LLS (two Class I studies of ABO- and one Class I study of Ona-BoNT/A). Botulinum toxin injections were found to be effective for reducing muscle tone and increasing the range of motion in affected limbs, and probably effective in improving active function (level B, one Class I study of ABO-BoNT/A). There were no specific recommendations regarding the differences between products [74].

A European Consensus on the use of BoNT/A in spasticity resulting from the collaboration of 28 experts from 16 countries was published in 2009 [77]. The authors based their conclusions on the results of 21 randomised clinical trials (12 in upper limbs, seven in lower limbs and two in mixed upper and lower limbs) as well as on the results of one meta-analysis. At that time, only ONA- and ABO-BoNT/A data were available, and the maximum recommended single doses for these preparations were 600 U and 1,500 U, respectively.

The main conclusion was that BoNT/A significantly reduced muscle tone and improved passive function in adult subjects with spasticity. The authors also attempted to take a position on the issues that were not answered directly by the results of controlled studies in spasticity. The unwanted spread of toxin from the site of injection is a potential cause of side effects related to weakness of adjacent and distant muscles. From a clinical point of view, the low migration potential is a desirable feature that reduces the risk of side effects, something especially important in spasticity where high doses of drugs are used. ABO- and ONA-BoNT/A migration potentials were not compared in spasticity studies. However, the results of studies in hyperhidrosis and CD showed that ONA- administration was associated with less migration than in the case of ABO-BoNT/A. The contributors to the Consensus clearly expressed their negative opinion on the conversion in clinical practice of doses of BoNT/A preparations supplied by various manufacturers [77]. This was best expressed by Aoki et al.: "It is important that clinicians are familiar with the characteristics and dosages of each preparation they use, and do not try to convert or extrapolate from one preparation to another." [78].

The updated 2016 AAN practice guidelines concluded that all three commercially available BoNT/A formulations are effective in ULS (level A). The data confirmed that they are effective in reducing muscle tension and improving passive function. ABO- and ONA-BoNT/A were also recommended (level A) for the treatment of LLS. In the case of INCO-BoNT/A, data on its effectiveness in lower limb spasticity was considered insufficient [79].

Conclusions

- No published recommendations have suggested any conversion ratios between dosages of specific BoNT/A formulations. Even so, when suggesting that two preparations are equal in terms of efficacy, this means that a significant

treatment effect has been achieved in a Class I or II study for a specific indication
— It is impossible to compare the specific doses used and translate them into the ratio between them.

Summary

Having reviewed all studies using BoNT/A different preparations for CD, BS, HFS and ULS and LLS, despite there being a number of direct comparative studies, there is still no definitive evidence on clear ratios between preparations.

We therefore conclude that despite the similar molecular mechanisms of different BoNT/A preparations, in terms of basic and clinical studies they should be considered to be distinct medications. All should be used in accordance with their individual SPC. The ongoing clinical trials with new (DAXI or PRA-BoNT/A) formulations will make this discussion even more difficult and complex.

We have not mentioned so far differences in the potency of neutralising antibodies (NAB) formation. Preparations may differ in terms of this potency, and switching the treatment from one to another preparation, as suggested by Hefter et al., may be helpful. During the 48-week period of INCO-BoNT/A treatment, NAB titres in patients with previously ineffective treatment with the use of other preparations decreased in 32.2%, did not change in 45.2%, and increased in only 22.6% of patients. Thus, repeated treatment with a low dose of 200 U INCO-BoNT/A over 48 weeks provided a beneficial clinical long-term effect [80]. This gives rise to a new perspective regarding the problem of switching between these medications in clinical practice.

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REVIEW ARTICLE

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LEADING TOPIC

Safety and efficacy of botulinum toxin type-A preparations in cerebral palsy — an evidence-based review

Marcin Bonikowski[1], Jarosław Sławek[2]

[1]Mazovian Neuropsychiatry Centre, Limited Liability Company, Neuro Rehabilitation Department, Movement Analysis Lab., Zagorze, Poland
[2]Division of Neurological and Psychiatric Nursing, Faculty of Health Sciences, Medical University of Gdansk, Poland; Department of Neurology and Stroke, St. Adalbert Hospital, Gdansk, Poland

ABSTRACT

The introduction of botulinum toxin more than 25 years ago for the management of paediatric lower and upper limb hypertonia has been a major advance. BoNT-A as a part of multimodal treatment supports motor development and improves function disturbed by spasticity or hypertonia.

The aim of this paper was to compare the efficacy and safety of three major BoNT-A preparations present on the market: abo-, inco-, and onaobotulinumtoxinA in the treatment of children with cerebral palsy. Based on an analysis of the available literature, all three preparations have been established to reduce hypertonia in the upper and lower extremities, with some conflicting evidence regarding function. There were no differences in treatment safety, with a low incidence of adverse events which were mostly temporary and mild. Any form of universal conversion ratio between all preparations is not recommended.

Key words: botulinum toxin, cerebral palsy

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Introduction

Cerebral palsy (CP) has been described as: "a group of permanent disorders of the development of movement and posture causing activity limitations, which are attributed to nonprogressive disturbances in the developing foetal or infant brain" [1].

CP is the main cause of disability among children and adolescents [2]. The majority of children with CP are affected by some form of hypertonia, of which spasticity is the most common [3]. Untreated spasticity leads to the development of contractures and bone deformities [4]. Other reasons for treating spasticity include improving mobility, facilitating the use of orthoses, improving posture and hand function, reducing pain from muscle spasms, and easing patient care/hygiene [5].

Over the past three decades, botulinum toxin type-A (BoNT-A) has become established as an important treatment modality for hypertonia in children with CP. After Koman et al. reported the first use of OnaBoNT-A in the treatment of spasticity associated with CP [6], the results of small-group studies that were published in the early 1990s showed that both OnaBoNT-A and AboBoNT-A were effective in the treatment of calf muscle spasticity resulting in tiptoeing [7, 8]. Over the following years, efficacy in the treatment of other muscles such as hamstrings or adductors has been presented [9, 10].

The biggest breakthrough in the BoNT-A therapy of children with CP was the introduction of multi-level injections as part of a multimodal rehabilitation process which includes physiotherapy and orthoses among a range of other treatments. Such an integrated approach brings measurable results and changes the natural course of the disease [11, 12]. Subsequent years saw a rapid increase in the number of publications. In 2010, the American Academy of Neurology and Child Neurology Society published a Practice Parameter evaluating evidence from 148 studies; 15 studies encompassing the treatment of 573 patients rose to the highest Class 1 level, and five studies rose to the Class 2 level [13]. Since then, a considerable amount of evidence has been published on this subject. Placebo controlled (PC) double blinded (DB) RCTs have shown significant improvements in different measures compared to placebo without major differences between toxin brands (Tab. 1). In 2019, the

Address for correspondence: Marcin Bonikowski, Mazovian Neuropsychiatry Centre, Limited Liability Company, Neuro Rehabilitation Department, Movement Analysis Lab., 05-462 Zagorze, Poland, e-mail: martinbonikowski@gmail.com

Table 1. Randomised clinical trials (RCT), double blind (DB), single blind (SB), placebo controlled (PC), multicentre (MC), single centre (SC)

References	Study design/ /number of groups/duration of observation (weeks)/number of treatments	Patient characteristics/ /number of assessed/ /outcome measures 1. primary 2. secondary	BoNT-A brand and dose (U/kg)	Muscles injected/ injection guide	Efficacy outcomes (only significant)/adverse events
Koman et al. 1994 [8]	RCT; DB; PC: SC, MI/6 weeks/2/2 (second after 2 weeks)	n = 12; PRS, ROM, Biodex Isokinetic Dynamometry	OnaBoNT-A/2–4	GST/manual palpation	PRS, ROM, no statistical analysis/AE-3 pts treated and 6 pts placebo arm
Sutherland et al.1999 [14]	RCT; DB; PC; SC/2/8 weeks/2 (second after 4 weeks)	n = 19; 3D, EMG, ROM	OnaBoNT-A/2–4	ND	Ankle kinematics/ROM/ AE-no
Koman et al. 2000 [15]	RCT; DB; PC, MC/2/12 weeks/2 (second after 4 weeks)	n = 108; 1. PRS, .ROM, AROM, H-reflex, Blood serum antibodies	OnaBoNT-A/4–8/ repeated after 4 weeks	GST/manual palpation	PRS, AROM/AE-12 pts treated and 3 pts placebo arm
Ubhi et al. 2000 [16]	RCT; DB; PC; SC/2/12 weeks/1	n = 40; 1.2D 2.2D, ROM, GMFM	AboBoNT-A/15–25	GST, SOL, HMST, manual palpation	Ankle kinematics, GMFM AE-6 pts treated and 1 pt placebo arm
Baker et al. 2002 [17]	RCT; DB; PC; MC/4/16 weeks/1	n = 124; 1. MTS 2. ROM, GMFM	AboBoNT-A/10–30	GSC/manual palpation	ROM, MTS/AE 123/94 pts treated and 20/31pts placebo arm, 24% related to treatment
Kanovsky et al. 2004 [18]	RCT; DB; PC; MC/2/16 weeks/1	n = 52; 1/2D; GMFM,	AboBoNT-A/ 30	GSC/manual palpation	Ankle kinematics/ AE- 30/10 pts treated and 33/13 pts placebo arm
Ackman et al. 2005 [19]	RCT; SB; PC; MC/3/ BTX-A/BTX-A+C/ PL+ C/56 /3	n = 34; 1/3D; 2/ROM, MAS, strength	OnaBoNT-A/4–8	GSC/ND	ROM, MAS, 3D, strength – only BTX-A + GR/AE-3 pts treated and 6 pts placebo arm
Mall et al. 2000 [10]	RCT; DB; PC; MC/2/12 weeks/1	n = 57; 1. Knee to knee distance 2. ROM, MAS, GMFM, GAS	AboBoNT-A/30	ADD, HMST/ND	Knee to knee distance, MAS, GAS, AE 9 pts treated and 3 pts placebo arm
Bjornson et al. 2007 [20]	RCT; DB; PC; SC/2/24 weeks/1	n = 33; 1.Spasticity/GMFM66 /88 2.AS, ROM, EMG, E.C.I., strength, GMFM, GAS, COPM	OnaBoNT-A/12	GST/ES	ROM/AE - 6 pts pain at injection site
Moore et al. 2008 [21]	RCT; DB; PC; SC/2/2 years/every 3 months if clinically indicated	n = 124; 1. GMFM, PEDI	AboBoNT-A/10–30	GSC/manual palpation	No differences in long term follow-up/AE-208 in 29 pts treated and 200 in 27 pts placebo arm
Delgado et al. 2016 [22]	RCT; DB; PC; MC/3/12	n = 228; 1/MAS; 2/PGA, GAS, MTS)	AboBoNT-A/10–30	GST+SOL/USG	MAS, PGA, MTS, GAS, AE – 144 pts. 2% treatment related
Corry et al. 1997 [23]	RCT; DB; PC; SC/2/12weeks/1	n = 14; 1/MAS; 2/ROM, MTS, G&R	OnaBoNT-A/4–7 AboBoNT-A/8–9	BB, BR, FCR, FCU, FDS, FDP, FPL, PT/anatomical landmarks	MAS, ROM, G&R AE-2pts
Koman et al. 2013 [24]	RCT; DB; PC; MC/2/27 weeks/1	n = 73; 1/UERS, MA, HC, MHC	OnaBoNT-A/ 1.4–12.5	Shoulder, arm, forearm, hand without spec; anatomical landmarks, USG	ROM (wrist only), MA AE-5pts
Ferrari et al. 2014 [25]	RCT; DB; PC; MC/2/24 weeks/1	n = 27 MAS, GAS, AHA, PEDI, AK	OnaBoNT-A/total dose < 300 U	PT, FCU, FCR, ADP, OPP, BB, PM, FDS, FDS, SSc/USG	GAS, AHA AE-1pt

ES — electrostim; C — serial casting; GAS — Goal Attainment Scaling; GMFM — Gross Motor Function Measure; MAS — Modified Ashworth Scale; PRS — Physicians Rating Scale; ROM — Range of Motion; MTS — Modified Tardieu Scale; 3D — three-dimensional gait analysis; 2D — video gait analysis; PGA — Physician's Global Assessment; G&R — grasp and release score; UERS — upper extremity rating scale; ND — no data; QUEST — Quality of Upper Extremity Skill Test; PEDI — Paediatric Evaluation of Disability Inventory; AK — ABILHAND-Kids; AE — adverse events; pts — patients

Cochrane review of BoNT-A treatment of lower limb spasticity in children by Blumetti et al. [26] included 31 randomised controlled trials assessing 1,508 participants. Studies compared BoNT-A in lower limb muscles to usual care or physiotherapy (PT) (14 studies), placebo or sham (12 studies), serial casting (four studies), or orthoses (one study). 20 studies used OnaBoNT-A and eight studies used AboBoNT-A.

The authors concluded that children receiving BoNT-A injections tended to have improved gait pattern, ROM, satisfaction with the outcome of treatment, and muscle tone, compared to their usual programme of care or PT, or a placebo. The quality of the evidence was very low for the comparison of BoNT-A versus usual care or physiotherapy; moderate for the comparison of BoNT-A versus placebo; moderate and low for the comparison of BoNT-A versus plaster casts; and very low for the comparison of BoNT-A versus orthoses. The authors did not mention any differences between different brands of toxins.

In 2020, Farag et al. [27] published a systematic review of RCTs of BoNT-A treatment of upper limb spasticity in children with CP. 15 RCTs with a total of 499 participants were analysed. 12 studies used OnaBoNT-A, and two used OnaBoNT-A and AboBoNT-A. The authors found evidence to support the use of BoNT-A as an adjunctive treatment to other modalities such as regular PT and occupational therapy (OT) with regard to the reduction of spasticity. Evidence to support its use as an adjunctive treatment to improve upper limb function or quality of life was insufficient. Any differences between brands of toxins were not reported.

In 2012, Pin et al. [28] published a systematic review of the efficacy of BoNT-A in non-ambulant children with severe CP: 19 studies were included. Indications for treatment were pain reduction, maintaining hip integrity, achieving functional changes, and goal attainment. A high percentage of participants in the studies showed positive changes. But most of the studies were of weak-to-moderate methodological quality. The authors did not analyse brands of toxins used. BoNT-A is compared to other treatment modalities in most studies, but in clinical practice it is used as a complement to them. For this reason, the evaluation of its effectiveness as an adjunctive therapy seems interesting. In a review based on a 'traffic light' scheme, Novak et al. assessed 247 articles and 398 intervention outcomes [29]. Interventions were classified with recommendations: green indicating "do it", yellow "probably do it", yellow "probably do not do it", and red "clearly do not do it". 14% (54 /398) of interventions achieved the level of green. Among them were: BoNT-A + OT for UE motor goals achievement (1–3 RCT), BoNT-A for tone reduction (UE + LE) (> 15 RCT), and BoNT + Casting for ROM (contractures) (4–15 RCT). BoNT-A + PT for mobility (4–15 RCT), BoNT-A + PT for tone reduction, BoNT-A for ROM and Prevention of Hip Displacement (1–3 RCT), and BoNT-A + Hip Brace for Prevention of Hip Displacement (1–3 RCT) were rated yellow among 66% (264/398) of interventions.

From the very beginning of BoNT-A's use in paediatrics, the safety of treatment has been evaluated. The reported RCTs and analyses showed no differences between BoNT-A and placebo for adverse events (AEs). A systematic review of 20 randomised studies of botulinum toxin A, enrolling 882 participants, reported 35 different AEs. [30]. 17 studies used OnaBoNT-A and four studies used AboBoNT-A. According to the authors, botulinum toxin type-A use was related to respiratory tract infection, bronchitis, pharyngytis, asthma, muscle weakness, urinary incontinence, falls, seizures, fever and unspecified pain. The authors concluded that botulinum toxin type-A has a good safety profile during the first months of use. However, the demonstration of a relationship between BoNT treatment and common childhood diseases and other common diseases in the population of children with CP may raise doubts. An interesting single centre report from 356 patients and 1,382 injection sessions indicated the overall rate of AEs for BoNT-A as being 3.3% for the sessions and 8.7% for the patients [31]. Both OnaBoNT-A and AboBoNT-A were injected. The data indicated that repeated BoNT-A injections were safe; AE were described as mild and were not associated with BoNT-A dose or brand. AE reactions were associated with GMFCS level and presence of epilepsy, but were mostly mild even for severely affected patients.

The largest study on the efficacy and safety of AboBoNT-A treatment of children with CP is the retrospective study by Bakheit et al. [32]. Among 758 patients (1,594 sessions), the AE rate was 7%. However, in the group that received drug doses higher than 1,000 U / session or 30 U/kg body weight, this percentage was 22%. In a meta-analysis of the safety of OnaBoNT-A, 1,447 treated subjects were compared to a 914-strong control group [33]. The incidence of AE was approximately 25% in patients treated with OnaBoNT-A, and 15% in the control group. The authors found a significantly higher incidence only for focal weakness in the treatment group.

Interesting from the point of view of this review are studies in which both OnaBoNT-A and AboBoNT-A were used [9, 23, 34, 35] and according to the authors preparations were used depending on availability. There were no differences between the preparations in terms of efficacy and safety, but none of the studies compared them directly. Two other papers have described the transition from OnaBoNT-A to AboBoNT-A for economic or administrative reasons [36, 37]. The authors found no differences in the efficacy or safety of the treatment. Tedroff et al. used a fixed 1:2 conversion ratio of OnaBoNT-A to AboBoNT-A. Dursun et al. based dosing decisions on the child's individual presentation at that time. Carraro et al. [38] analysed the safety profile of IncoBoNT-A compared to OnaBoNT-A (ratio 1:1) in the treatment of lower limb spasticity. The authors found no significant difference in frequency and type of AE. León-Valenzuela et al. looked at treatment safety of IncoBoNT-A with dose increase [39]. 69 children, mean age (SD) 8.3 (3.9) years, received IncoBoNT-A injections up to a maximum total dose of 600 U, 24 U/kg body weight.

191 injections were administered, with a dosing interval of 6.0 (1.7) months. The mean (SD) total IncoBoNT-A dose increased from 191.7 (126.2) U at cycle 1 to 368.0 (170.1) U) at cycle 6. 74 AEs (37.5% of injections) were reported, the most frequent being injection pain (93.2% of AEs). 36.8% of participants were classified at GMFCS levels IV and V, without any safety concerns.

In recent years, manufacturer-sponsored, multicentre, international, Phase 3, RCTs have been conducted to assess the efficacy and safety of AboBoNT-A, OnaBoNT-A and IncoBoNT-A in lower and upper limb therapy.

Until this article was published, only the results of the research on AboBoNT-A have been published as full articles; the results of the research on IncoBoNT-A and OnaBoNT-A have only been published as abstracts. In DB RCT and open-label (OL) extension studies (NCT01249417/ NCT01251380), 241 ambulatory children aged 2–17 with dynamic equinus were randomised to treatment with AboBoNT-A (10 or 15 U/kg/leg) or placebo injected into the gastrocsoleus. All children received AboBoNT-A in the OL phase. In DB RCT, treatment-related AEs (TRAE) were evenly distributed, with the highest rate (9%) in the placebo group. [22]. Repeated injections of AboBoNT-A in an open label study were generally well tolerated, with the number of patients experiencing TRAE varying from 16 in cycle 1 to 1 in cycle 4 . In both studies, the majority of TRAE were related to injection procedure and injection site pain was the most frequent. Significantly higher decreases of muscle hypertonia and spasticity (MAS, MTS), goal achievement (GAS), and overall global clinical impression (PGA) were demonstrated for the treatment groups [22, 40, 41]. In the double-blind phase, AboBoNT-A significantly improved observational gait scale (OGS) total scores versus placebo at week 4, and continued to improve gait throughout the OL phase [42]. Importantly, a long-term therapeutic effect was demonstrated: 74% of children treated did not require retreatment before week 16 or later, with 17.7% of patients not requiring retreatment before week 28 [40]. In DB, a repeat-cycle study (NCT02106351) saw 210 children, mean age (SD) 9y (4y 5mo), receive 2 U/kg, 8 U/kg, or 16 U/kg AboBoNT-A injections into UE alongside a home-exercise therapy programme. All children received 8 U/kg or 16 U/kg in cycles 2 to 4. At week 6 of cycle 1, children in the 8 U/kg or 16 U/kg groups had significantly lower MAS scores versus the 2 U/kg group. There were no differences in GAS and PGA between groups. Therapeutic benefits were sustained during cycles 2 to 4. Muscular weakness was the only TRAE reported in at least one child/ /group [43]. In DB RCT (NCT0193411) 241 ambulatory children (aged 2–17) with dynamic equinus were treated with three different doses (16, 12, 4 U/kg BW) of IncoBoNT-A in two subsequent cycles. Overall, improvements in Ashworth Scale (AS) were observed in all IncoBoNT-A treatment groups at week 4, without statistically significant differences. There were also no significant differences in re-injection time (cycle 2) [44]. From that group, 124 patients entered an open-label extension study (NCT01905683) and, together with 246 newly recruited patients (total 370), received up to four cycles of multilevel injections in LE and combined LE/UE muscles, with doses up to 20 U/kg (500 U) of IncoBoNT-A.

The results showed a consistent improvement in plantar flexor hypertonia (AS) over long-term treatment [45]. The results of a similar to the previous PC DB RCT with OL extension study (NCT02002884), but focusing on UE spasticity, were recently published [46]. In the MP, 350 patients aged 7.3 (4.4) years received 8, 6, 2 U/kg BW of IncoBoNT-A into upper limb, with additional lower-limb injections up to 20 U/kg BW followed by three further injection cycles in OL extension study. In the DB, AS scores for the UE main clinical pattern improved significantly from baseline to week 4, with a significantly greater improvement in the 8-U/kg versus the 2-U/kg dose group. Improvements were observed in all treated UE and LE clinical patterns and across all OL cycles.

In analysis of pooled safety data from the three abovementioned LE and UE IncoBoNT-A studies, the authors reported 2% of patients experienced AEs possibly related to the treatment [47]. In DB PC RCT (NCT01603628), OnaBoNT-A 8 U/kg/leg, 4 U/kg/leg, or placebo was injected into ankle plantar flexors of 384 patients OnaBoNT-A significantly decreased spasticity at weeks 4 and 6; it decreased by 1.1 (8 U/kg) and 1.0 (4 U/kg); OnaBoNT-A 8 U/kg significantly improved Clinical Global Impression (CGI) and improved measures of gait versus placebo [48]. Both OnaBoNT-A groups significantly improved active and passive GAS. Moreover, the authors presented gait improvement measured by Edinburgh Visual Gait (EVG) score in the subset of patients. Dose 8 U/kg demonstrated statistical significance vs placebo at week 8 in the total score and select individual items (associated with foot stance and swing) [49].

As in previous studies, AboBoNT-A presented a good safety profile. Rates of patients reporting ≥ 1 AEs were similar across treatment groups. In DB PC RCT study (NCT01603602), 235 children (mean age 7.9 years; range 2–16) were injected with OnaBoNT-A 6 U/kg/side, 3 U/kg/side, or placebo into UE muscles; patients also received occupational therapy. Toxin groups demonstrated significant reductions of hypertonia and spasticity (MAS and MTS) compared to placebo, but did not differ significantly in mean CGI. Only the 6 U/kg group demonstrated significant improvement in GAS passive goals at week 12 but not in active goals. OnaBoNT-A was well tolerated in both treatment groups, with no safety concerns [50].

To conclude, data from multicentre studies showing the efficacy and safety of BoNT treatment in almost 2,000 children with different hypertonia distributions, functional and health statuses could provide the final proof.

Moreover, the authors presented a sustained effect of treatment not only in reducing hypertonia (MAS) but also in improving body function and activity. Interestingly, the dose ratio for higher dose groups in LE studies was 1.9/1/1 for

Abo/Inco/Ona BoNT-A respectively. The differences in duration of response need further analysis.

Summary

Based on the presented studies, we conclude that BoNT-A is safe in spasticity treatment in the majority of children with CP.

In clinical practice, BoNT-A treatment should always be addressed to the patient for whom the reduction of hypertonia has the potential to provide a meaningful benefit in active function, hip integrity, comfort, or care. It is obligatory to use BoNT-A in conjunction with other treatment modalities such as OT, PT, orthotics or casting.

There are no major differences between Abo, Inco and OnaBoNT-A both in PC DB RCT and observational studies. The low number of comparative studies does not provide evidence on exchange ratios.

From the clinician's point of view, different preparations of BoNT-A should be considered as distinct medications. All should be used while respecting individual country's relavent SPCs.

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RESEARCH PAPER

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LEADING TOPIC

Spasticity in practice (SPACE): an international non-interventional study of botulinum neurotoxin type-A in treatment-naïve subjects with spasticity

Julian Harriss[1], Nicolas Roche[2], Carlos Cantú-Brito[3], Svetlana Khatkova[4], Patrik Säterö[5], Susanne Heitmann[6], Olivier Simon[7], Christine Kliebe-Frisch[8], Georg Comes[8], Wolfgang H. Jost[9, 10]

[1]IRMA: Independent Rehabilitation Medicine Assessment, London, United Kingdom
[2]Hôpital Raymond Poincaré, Garches, France
[3]Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico
[4]Federal State Hospital for Treatment and Rehabilitation, Ministry of Health, Moscow, Russia
[5]Sahlgrenska Universitetssjukhuset/Högsbo, Göteborg, Sweden
[6]DKD HELIOS clinic Wiesbaden, Wiesbaden, Germany
[7]formerly of Merz Pharmaceuticals GmbH, Frankfurt am Main, Germany
[8]Merz Pharmaceuticals GmbH, Frankfurt am Main, Germany
[9]Parkinson-Klinik Ortenau, Wolfach, Germany
[10]University of Freiburg, Freiburg/Breisgau, Germany

ABSTRACT

Aim of the study. SPACE, a prospective, non-interventional, open-label, multinational study, investigated physicians' and subjects' assessment of safety, efficacy, and health-related quality of life (HRQoL) following botulinum neurotoxin type-A (BoNT-A) treatment to understand real-world clinical usage for the management of focal and multifocal spasticity.

Clinical rationale for the study. Treatment guidelines recommend the use of BoNT-A for the management of spasticity in adults. This study assessed how physicians use BoNT-A therapy in real-world clinical practice, and provided evidence on long-term safety and efficacy over a period of up to 2 years.

Materials and methods. BoNT treatment-naïve adults with spasticity of any aetiology received any BoNT-A formulation at their physician's discretion, and were observed for ≤ 8 treatment cycles (≤ 2 years). Daily practice information, physician's global assessments of tolerability and efficacy, and HRQoL were documented. Incidences of adverse drug reactions or all adverse events were documented for non-Mexican subjects and for Mexican subjects, respectively, due to protocol differences based on local regulatory requirements.

Results. A total of 701 subjects were enrolled (safety population; nine countries). Physicians rated the tolerability of BoNT-A as 'very good' or 'good' for 88.2–97.4% of subjects throughout the study (subject numbers declined throughout this non-interventional study). Adverse drug reactions were reported for 16/600 (2.7%) of the non-Mexican subjects, with two considered to be 'definitely related' to treatment (injection-site haematoma, n = 1; botulism, n = 1). For 687 subjects, efficacy was rated 'very good' or 'good' by most physicians and subjects. Improvements in HRQoL were observed.

Conclusions and clinical implications. Throughout this 2-year study, BoNT-A treatment was generally well-tolerated, effective, and associated with an improved HRQoL. This study makes a valuable contribution to the broader understanding of how physicians use BoNT-A therapy to manage spasticity in real-world clinical practice.

Key words: botulinum neurotoxin A, rehabilitation, muscle spasticity, quality of life

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Address for correspondence: Dr Julian Harriss. IRMA, 10 Oakway, Bromley, BR2 0LJ, United Kingdom, e-mail: jharriss@doctors.org.uk

Introduction

European and US treatment guidelines and consensus statements recommend intramuscular botulinum neurotoxin type-A (BoNT-A) injections for the management of spasticity in adults [1–4]. At the time when this study was being conducted, three BoNT-A formulations were commercially available in North America and Europe: incobotulinumtoxinA (Xeomin®; Merz Pharmaceuticals GmbH, Frankfurt am Main, Germany) [5, 6], onabotulinumtoxinA (Botox®; Allergan Inc., Irvine, CA, USA) [7, 8], and abobotulinumtoxinA (Dysport®; Ipsen Ltd, Boulogne-Billancourt, France) [9, 10]. Multiple controlled clinical trials have demonstrated the safety and efficacy of repeated BoNT-A injections for focal and multifocal spasticity [11–20]. However, less data exist regarding the long-term safety and efficacy outcomes in real-world clinical practice in subjects with spasticity [21–24].

The SPAsticity in PractiCE (SPACE) study is one of the most extensive non-interventional studies of BoNT-A in spasticity to date, enrolling subjects with spasticity of any aetiology and allowing the treatment of upper- and lower-limb spasticity simultaneously, according to the local approval status of the BoNT-A formulation and clinical setting in participating countries. The study was designed to investigate physicians' and subjects' assessment of safety, efficacy, and health-related quality of life (HRQoL) following BoNT-A treatment of treatment-naïve subjects in routine clinical practice, by collecting data on subjects' disease course and treatments, the treating physicians, and their treatment preferences.

Clinical rationale for the study

With a paucity of data on the long-term safety and efficacy outcomes related to everyday use of BoNT-A in subjects with spasticity, the primary objective of this study was to investigate physicians' and subjects' assessment of safety, efficacy, and HRQoL in treatment-naïve subjects with multifocal spasticity who received BoNT-A in routine, real-world clinical practice over a treatment period of ≤ 2 years.

Materials and methods

Study design and participants

SPACE was a prospective, non-interventional, open-label, multicentre study conducted in nine countries: Canada, France, Germany, Italy, Mexico, Russia, Spain, Sweden, and the UK. Subjects ≥ 18 years of age were eligible if they had spasticity of any aetiology requiring BoNT-A injections and had never previously received BoNT-A or -B for any indication. Subjects were also required to have sufficient understanding of the primary local language to complete the study questionnaires and provide informed consent. Subjects already participating in an interventional study, or who were planning to participate in a study involving BoNT-A treatment, were ineligible.

Subjects could receive treatment for ≤ 2 years with any BoNT-A product available in their country, i.e. incobotulinumtoxinA, onabotulinumtoxinA or abobotulinumtoxinA, according to the local product approval status and the individual subject's needs, at the treating physician's discretion. Therefore, the visit schedule comprised ≤ 8 injection visits (treatment cycles) at intervals > 3 months, plus a final visit with no injection in subjects who returned for assessment at the end of the study. Doses (total and per-muscle), injection sites, injection techniques, and treatment intervals were determined by each physician based on clinical need.

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and in compliance with local regulatory requirements. Study documents were reviewed and approved by Ethics Committees and regulatory authorities according to local requirements in the participating countries. Subjects had to provide written informed consent, in the local language, for the use of their data or, if unable to sign the consent form, could consent verbally in the presence of a witness. The study protocol was registered with the Verband Forschender Pharma-Unternehmen Deutschland (the Association of Pharmaceutical Research Companies of Germany), https://www.vfa.de/de/arzneimittel-forschung/datenbanken-zu-arzneimitteln/nisdb/nis-details/_533.

Daily practice information

Information was captured on participating subjects, including history and current spasticity status (e.g. aetiology, topography, patterns of spasticity), details of each BoNT-A treatment (BoNT-A formulation used, muscles treated, injection sites/muscle, assessment scales used, injection guidance [e.g. electromyography with or without electrostimulation, ultrasound]), and concomitant treatment.

Data were also collected on treating physicians, including their medical speciality, years in clinical practice, previous experience with BoNT-A, and opinions on dosages.

Safety

Physicians rated each subject's tolerability of the medication at the end of each treatment cycle (i.e. at the next injection visit) on a 4-point scale from 1 (very good) to 4 (poor).

The incidence of adverse drug reactions (ADRs, defined as adverse events [AEs] for which a causal relationship to treatment cannot be excluded) was reported for all subjects enrolled, including subjects with no record of the BoNT-A product administered at the first injection, but for whom product data had been recorded at subsequent injections. In Mexico, due to local regulatory requirements, the incidence of all AEs (serious and non-serious, related or not), including ADRs, was recorded using a specific ADR/AE reporting form. As non-related AEs were recorded in addition to ADRs in Mexico, these were analysed separately from ADRs in non-Mexican countries.

Global assessment of efficacy

Physicians could document treatment efficacy using various impairment- or function-based scales (e.g. Ashworth Scale, Tardieu Scale, Rivermead Scale, Functional Ambulation Classification Scale). However, in this diverse, multinational study population, efficacy assessments were not consistently performed by all physicians in routine clinical practice. Therefore, global assessments of efficacy relevant to real-world clinical practice were assessed, and are reported here.

Physicians and subjects rated the efficacy of each treatment at the end of each treatment cycle (i.e. at the next injection visit) on a 4-point scale from 1 (very good) to 4 (poor). Responders were subjects with a score ≤ 3 (at least moderate efficacy).

HRQoL

HRQoL was assessed using the EuroQoL 5-dimension questionnaire (EQ-5D) visual analogue scale (VAS) [25], completed by the subjects at their study centres during each injection visit and at home 4 weeks post injection (i.e. during the assumed peak effect of treatment [26]). Subjects rated their current state of health on a quantitative scale from 0 (the worst imaginable) to 100 (the best imaginable).

Subjects also selected the statement that best described their state of health on that day using the five dimensions of the EQ-5D descriptive system (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), and completed the 12-item Short-Form (SF-12) Health Survey to describe their perceived state of health (see Supplemental Methods).

Statistical analysis

Study data were summarised using descriptive statistics. All subjects enrolled were analysed for safety. All subjects with an available date of written informed consent and recorded information about the BoNT-A product administered at the first injection were analysed for efficacy and HRQoL. Subjects with no reported BoNT-A product at their first injection, who could not therefore be assigned to a treatment group (incobotulinumtoxinA, onabotulinumtoxinA, or abobotulinumtoxinA), were excluded from the efficacy and HRQoL analyses. Missing values were not imputed, and all analyses were conducted on observed cases.

Two post-hoc analyses were performed. One assessed differences in the proportion of non-Mexican subjects with ≥ 1 ADR or serious ADR (SADR) between treatment groups using Fisher's exact test. Another post-hoc analysis assessed change from Visit 1 (baseline) in EQ-5D VAS score using the Wilcoxon signed rank test; in this analysis, data following a switch between treatment groups was excluded.

Results

Daily practice information

Subjects

A total of 701 subjects were evaluated for safety; efficacy and HRQoL outcomes were assessed in 687 subjects with an available date of written consent and reported BoNT-A product administered at the first injection (Supplemental Fig. 1). Subjects' mean (standard deviation [SD]) age was 55.0 (15.5) years, and 61.3% were male (Tab. 1). The median (range) time since onset of spastic symptoms was 2.0 (0–79) years. Most participants had post-stroke spasticity and paresis most commonly presented as hemiplegia. At least one relevant concomitant medication was documented for 36.8% of subjects, among which antithrombotic agents (15.6%), muscle relaxants (13.4%), and lipid-modifying agents (13.0%) were the most frequently documented. At least one concomitant therapy was documented in 23.7% of subjects, with physiotherapy (20.7%) and occupational therapy (12.7%) the most frequently documented.

Overall, 205/701 (29.2%) subjects formally discontinued from the study prematurely, including four with no reported BoNT-A product at their first injection (Supplemental Fig. 1). The main reasons for discontinuation were: loss to follow-up (74/701, 10.6%), lack of efficacy (28/701, 4.0%), and another undocumented reason (79/701, 11.3%). The proportion of subjects attending at each injection visit also decreased throughout the study (Supplemental Tab. 1), although reasons were not documented.

The median (interquartile range; IQR) injection interval ranged from 3.5 (3.0–4.6) months at Visit 2 to 3.2 (3.0–3.7) months at Visit 8, with 22.8 (21.4–26.3) months between the first and last injections. The most frequently injected upper-limb muscles at Visit 1 were the flexor digitorum superficialis, biceps brachii, and flexor digitorum profundus (Supplemental Fig. 2a). The most frequently injected lower-limb muscles were the gastrocnemius caput mediale, soleus, gastrocnemius caput laterale, and tibialis posterior (Supplemental Fig. 2c). These remained among the most frequently injected muscles at Visit 8 (Supplemental Fig. 2b and d).

The median (IQR) total incobotulinumtoxinA, onabotulinumtoxinA, and abobotulinumtoxinA doses administered at Visit 1 were 30 (20, 50) U, 50 (40, 75) U, and 125 (100, 200) U. Median doses administered into the most frequently injected muscles at Visit 1 are summarised in Table 1. The treating physician performed the BoNT-A injection for most subjects (67.9% of those with data recorded; 411/605) at Visit 1.

For 40.5% of subjects with data recorded, injections were administered without the use of guidance techniques at Visit 1 (47.6%, 19.0%, and 37.5% with incobotulinumtoxinA, onabotulinumtoxinA, and abobotulinumtoxinA, respectively). Electrostimulation was used in 18.6% (17.4%, 23.9%, and 16.3%, respectively), electromyography in 14.8% (12.4%, 17.6%, and

Table 1. Subject baseline demographics and characteristics

Characteristic	IncobotulinumtoxinA n = 465	OnabotulinumtoxinA n = 142	AbobotulinumtoxinA n = 80	Study population n = 687
Male sex, n (%)	283 (60.9)	83 (58.5)	55 (68.8)	421 (61.3)
Age, years; mean (SD)	54.6 (15.6)	55.6 (15.3)	56.2 (15.3)	55.0 (15.5)
BMI, kg/m^2; mean (SD)	25.8 (5.1)	25.6 (5.7)	25.7 (4.6)	25.7 (5.1)
Time since spasticity-causing event, years; median (range)	2.0 (0–63)	2.0 (0–52)	2.0 (0–55)	2.0 (0–63)
Time since onset of spastic symptoms, years; median (range)	2.0 (0–59)	2.0 (0–51)	2.0 (0–79)	2.0 (0–79)
Aetiology of spasticity, n (%)[a]				
Stroke	310 (66.7)	85 (59.9)	49 (61.3)	444 (64.6)
Brain injury	33 (7.1)	4 (2.8)	4 (5.0)	41 (6.0)
Multiple sclerosis	36 (7.7)	19 (13.4)	9 (11.3)	64 (9.3)
Spinal-cord injury	19 (4.1)	8 (5.6)	3 (3.8)	30 (4.4)
Cerebral palsy	10 (2.2)	4 (2.8)	4 (5.0)	18 (2.6)
Other	48 (10.3)	18 (12.7)	11 (13.8)	77 (11.2)
Missing	2 (0.4)	0	0	2 (0.3)
Topographical distribution of paresis, n (%)				
Hemiplegia	377 (81.1)	106 (74.6)	58 (72.5)	541 (78.7)
Diplegia	44 (9.5)	23 (16.2)	12 (15.0)	79 (11.5)
Quadriplegia	41 (8.8)	9 (6.3)	8 (10.0)	58 (8.4)
Missing	3 (0.6)	4 (2.8)	2 (2.5)	9 (1.3)
BoNT-A dose in most frequently injected muscles at Visit 1, median (IQR)				
Overall, median (IQR) [n]	30 (20, 50) [2,899]	50 (40, 75) [676]	125 (100, 200) [476]	NA
Upper limb				NA
Flexor digitorum superficialis; L, R	30 (25, 50), 30 (25, 50)	55 (40, 77.5), 60 (50, 75)	175 (100, 250), 150 (100, 200)	
Biceps brachii: L, R	60 (40, 75), 50 (40, 75)	50 (50, 75), 55 (50, 77.5)	225 (150, 300), 150 (100, 200)	
Flexor digitorum profundus: L, R	30 (20, 40), 25 (20, 40)	50 (50, 70), 50 (50, 60)	150 (100, 200), 100 (50, 200)	
Lower limb				NA
Gastrocnemius caput mediale; L, R	50 (40, 55), 50 (35, 50)	50 (40, 75), 50 (40, 75)	150 (100, 250), 125 (100, 150)	
Soleus; L, R	50 (40, 70), 50 (50, 75)	60 (50, 85), 70 (50, 80)	200 (150, 200), 150 (125, 200)	
Gastrocnemius caput laterale; L, R	50 (40, 50), 50 (35, 50)	50 (40, 75), 50 (40, 75)	100 (80, 125), 125 (50, 150)	

[a]Multiple entries were possible. Percentages based on total subject populations
BMI — body mass index; BoNT-A — botulinum neurotoxin type-A; IQR — interquartile range; L — left; n — number of observations; N — total number of subjects; NA — not applicable; R — right; SD — standard deviation; U — units

23.8%, respectively), and ultrasound in 13.6% (14.6%, 11.3%, and 12.5%, respectively) of subjects.

Physicians

Of the 171 participating physicians, 54 (31.6%) were from Germany, 33 (19.3%) from France, 28 (16.4%) from Italy, 14 (8.2%) from the UK, 11 (6.4%) from Russia, 11 (6.4%) from Spain, 10 (5.8%) from Canada, seven (4.1%) from Mexico, and three (1.8%) from Sweden. Most were neurologists (47.4%) or physiatrists (28.1%). The physicians had a mean (SD) of 15.7 (8.7) years of experience in medical practice and a mean (SD) of 9.2 (5.8) years of experience with BoNT injections; 59.1% stated that they would like to inject higher doses of BoNT-A than permitted by current product labelling. The mean (SD; IQR) higher doses these physicians would like to inject were incobotulinumtoxinA 651.8 U (191.6; 600–800), onabotulinumtoxinA 640.3 U (170.4; 500–800), and abobotulinumtoxinA 1,751.9 U (844.2; 1,500–2,000).

Safety

Safety analyses were performed for all 701 subjects across the entire study duration (≤ 2 years). The tolerability of all BoNT-A formulations was rated as 'very good' or 'good' by

Table 2. Frequency of non-Mexican subjects with ADRs

System organ class	Incobotulinum-toxinA n = 369	Onabotulinum-toxinA n = 142	Abobotulinum-toxinA n = 75	Total n = 600
Subjects with ≥ 1 ADR, n (%)	11 (3.0)	3 (2.1)	2 (2.7)	16 (2.7)
General disorders and administration-site conditions	3 (0.8)	1 (0.7)	1 (1.3)	5 (0.8)
Nervous system disorders	4 (1.1)	1 (0.7)	0 (0.0)	5 (0.8)
Gastrointestinal disorders	1 (0.3)	0 (0.0)	1 (1.3)	2 (0.3)
Infections and infestations	1 (0.3)	0 (0.0)	1 (1.3)	2 (0.3)
Eye disorders	0 (0.0)	0 (0.0)	1 (1.3)	1 (0.2)
Injury, poisoning, and procedural complications	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.2)
Investigations	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.2)
Musculoskeletal and connective tissue disorders	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.2)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.2)
Psychiatric disorders	0 (0.0)	0 (0.0)	1 (1.3)	1 (0.2)
Respiratory, thoracic, and mediastinal disorders	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.2)

Data shown for non-Mexican subject population, where incidence of ADRs was documented. In Mexico, the incidences of ADRs and all other AEs, regardless of their relationship with the study treatment, were recorded. Total population includes those with no reported injection in first treatment cycle. Medical terms are as per the Medical Dictionary for Regulatory Activities version 16.0
ADR — adverse drug reaction; AE — adverse event; n — number of subjects; N — total number of subjects

physicians for the large majority of subjects (88.2–97.4%) throughout the study (Supplemental Fig. 3).

In most countries, the incidence of ADRs was recorded except in Mexico, where non-related AEs were recorded in addition to ADRs. Therefore, safety outcomes for Mexican (n = 101) and non-Mexican (n = 600) subjects were analysed separately. Among the 600 non-Mexican subjects, over the entire duration of the study, there were only 27 ADRs reported by 16 subjects (Tab. 2). The most frequent system organ classes affected were 'general disorders and administration site conditions' and 'nervous system disorders'. The proportion of subjects with ADRs was similar across the BoNT-A treatment groups (Tab. 2), and post-hoc analysis did not reveal a significant difference ($p \geq 0.7666$ for comparisons between treatment groups).

For 8/600 (1.3%) non-Mexican subjects, at least one ADR was considered 'unlikely to be related', for 2/600 (0.3%) 'possibly related', for 4/600 (0.7%) 'probably related', and for 2/600 (0.3%) 'definitely related' to the study medication. The ADRs considered 'definitely related' to the study medication were injection-site haematoma (n = 1) and botulism (n = 1) that was further described as asthenia, generalised weakness, and a decrease in the activities of daily living.

SADRs were reported for eight subjects; in four subjects these were classed as 'nervous system disorders'. All reported SADRs were considered 'unlikely to be related' to BoNT-A treatment. SADRs included abdominal pain, anxiety, astrocytoma, bipolar disorder, cerebrovascular accident, chronic obstructive pulmonary disease (COPD), death, epilepsy, fall, hemiparesis, hemiplegia, patella fracture, radius fracture, and subarachnoid haemorrhage. The percentage of subjects with SADRs was similar across the three treatment groups (incobotulinumtoxinA, 5/369 subjects [1.4%]; onabotulinumtoxinA, 2/142 subjects [1.4%]; abobotulinumtoxinA, 1/75 subjects [1.3%]), and post-hoc analysis did not reveal significant differences (all $p = 1.000$).

Within the Mexican subject population, 17/101 subjects (16.8%) experienced an AE without causal relationship; most events were classed as 'infections and infestations' (n = 6) or 'cardiac disorders' (n = 5). One subject experienced two ADRs (urinary tract infection and lower respiratory tract infection) that were both classed as SADRs; however, the relationship to the study treatment was considered 'not assessable'. ADRs/AEs were recorded as serious in 14/17 subjects, with most classed as 'cardiac disorders' (n = 5), 'infections and infestations' (n = 5), or 'respiratory, thoracic, and mediastinal disorders' (n = 3). A small cluster of serious cases of pneumonia (n = 6 subjects) was observed.

Nine subjects died while participating in the study (one subject in the non-Mexican population and eight in the Mexican population; Supplemental Tab. 2). These subjects had received BoNT-A doses of 40–620 U for the treatment of upper- and lower-limb spasticity. Deaths occurred between 10 days and 7–8 months after treatment. All eight Mexican subjects who died had poor health and multiple comorbidities, including high blood pressure, type 2 diabetes mellitus, COPD, heart disease, HIV infection, and cancer, which were strong confounding factors. In all cases, the cause of death was considered to be unrelated to BoNT-A treatment.

Global assessment of efficacy

At all visits, most subjects in all three treatment groups were classed as responders according to the physicians' and the subjects' global assessment of efficacy. At Visit 2 following the first treatment cycle, for those with available data

treated with incobotulinumtoxinA, onabotulinumtoxinA, and abobotulinumtoxinA, physician-assessed response rates were 95.5% (359/376 subjects), 91.3% (95/104 subjects), and 98.4% (63/64 subjects), respectively. Similarly, subject-assessed response rates were 92.9% (353/380 subjects), 86.5% (96/111 subjects), and 93.7% (59/63 subjects), respectively.

Although the number of subjects with global efficacy assessment data reduced substantially from Visit 2 to the final visit, both physician-assessed and subject-assessed response rates in the recorded data remained high. Among subjects treated with incobotulinumtoxinA, onabotulinumtoxinA, and abobotulinumtoxinA, physician-assessed response rates at the final visit were 97.4% (147/151 subjects), 87.0% (20/23 subjects), and 100% (18/18 subjects), respectively; with similar subject-assessed response rates of 97.4% (149/153 subjects), 81.8% (18/22 subjects), and 100% (18/18 subjects), respectively.

At Visit 2 and at the final visit, most physicians and subjects rated the efficacy of BoNT-A as 'very good' or 'good', regardless of BoNT-A formulation. However, these ratings were recorded for fewer subjects at the final visit (Fig. 1).

HRQoL

Treatment with all three BoNT-A formulations was associated with an improvement in HRQoL from injection Visit 1 (baseline), as measured on the EQ-5D VAS (Fig. 2). In subjects receiving incobotulinumtoxinA, onabotulinumtoxinA, and abobotulinumtoxinA, respectively, the mean (SD) EQ-5D VAS score was 53.4 (18.66), 56.1 (20.32), and 52.6 (18.75) at injection Visit 1, and 71.1 (20.35), 65.7 (18.52), and 67.0 (15.64) at the final visit.

A post-hoc analysis of the change in EQ-5D VAS score from injection Visit 1 revealed statistically significant improvements for pooled data across all formulations, and for incobotulinumtoxinA ($p < 0.0001$ from Visit 1 at each subsequent visit). For onabotulinumtoxinA and abobotulinumtoxinA, statistical significance was less consistent. In those receiving incobotulinumtoxinA, onabotulinumtoxinA, and abobotulinumtoxinA, respectively, the mean (SD) change in EQ-5D VAS score was 6.2 (16.19), 3.2 (16.49), and 2.4 (17.33) at Visit 2, and 18.6 (20.13) 5.9 (16.57), and 18.2 (19.65) at the final visit.

In general, compared to Visit 2, the percentage of subjects reporting their condition as 'normal (no problems)' increased, and those reporting 'severe impairment (extreme problems)' decreased with all three BoNT-A formulations across all dimensions of the EQ-5D at the final visit (Supplemental Fig. 4). Also, from Visit 1 until 4 weeks post injection, subjects treated with incobotulinumtoxinA showed improvements in mean composite SF-12 physical and mental health scores, with less data available for meaningful analysis in onabotulinumtoxinA- and abobotulinumtoxinA-treated subjects (Supplemental Tab. 3).

Discussion

This non-interventional study investigated how BoNT-A is used to treat spasticity in treatment-naïve subjects in routine clinical practice settings in nine countries worldwide during up to eight treatment cycles, for up to 2 years. Over the entire study duration, the incidence of ADRs was low, and the rate was similar across all three BoNT-A treatment groups. Of the 16/600 non-Mexican subjects reporting ADRs, two subjects had ADRs considered by the treating physician to be 'definitely related' to BoNT-A treatment, but of a non-serious nature; however, half of the subjects had ADRs that, while a causal relationship to treatment could not be ruled out, were assessed by the treating physician as 'unlikely to be related' to BoNT-A treatment, including all reported SADRs. Eight of nine deaths reported during the study occurred in Mexican subjects. In all cases, these subjects had a history of poor health, the deaths were deemed to be unrelated to BoNT-A treatment, and multiple co-morbidities and strong confounding factors were present.

Physicians were able to document treatment efficacy using various impairment or function-based scales (e.g. Ashworth Scale, Tardieu Scale, Rivermead Scale, Functional Ambulation Classification Scale). However, many of these assessments are of academic value and are not performed in routine clinical practice, or only performed occasionally. For this reason, and to alleviate the potential effects of multinational differences in approval status for BoNT-A dose and indication, efficacy was evaluated using global assessments of more relevance to real-world clinical practice.

Global assessments of efficacy and tolerability showed that BoNT-A spasticity treatment was effective and well-tolerated, confirming the positive findings from previous clinical studies of BoNT-A injections for spasticity treatment, including randomised controlled trials [11–20]. No formal statistical analyses of the data were conducted; however, there did not appear to be any major differences in efficacy between BoNT-A formulations. Most subjects and physicians rated the efficacy of the first and last treatments as 'very good' or 'good' in all three BoNT-A treatment groups, with no noticeable reduction in perceived benefit with repeated treatment over time. Also, assessment of HRQoL, based on EQ-5D VAS, suggested that BoNT-A treatment improved HRQoL for the duration of the study, i.e. up to 2 years. However, when considering the apparent gradual increase in HRQoL scores over time, the effects of selection bias, resulting from the diminishing analysis population, should be taken into account.

It is worth underlining that physicians were given complete freedom to choose the BoNT-A formulation, dose and interval between injections, diagnostic and treatment procedures, and concomitant medications for each subject. The majority of participating physicians (59.1%) stated that they would like to inject higher doses of BoNT-A than is permitted by current product labelling, suggesting that many felt that current

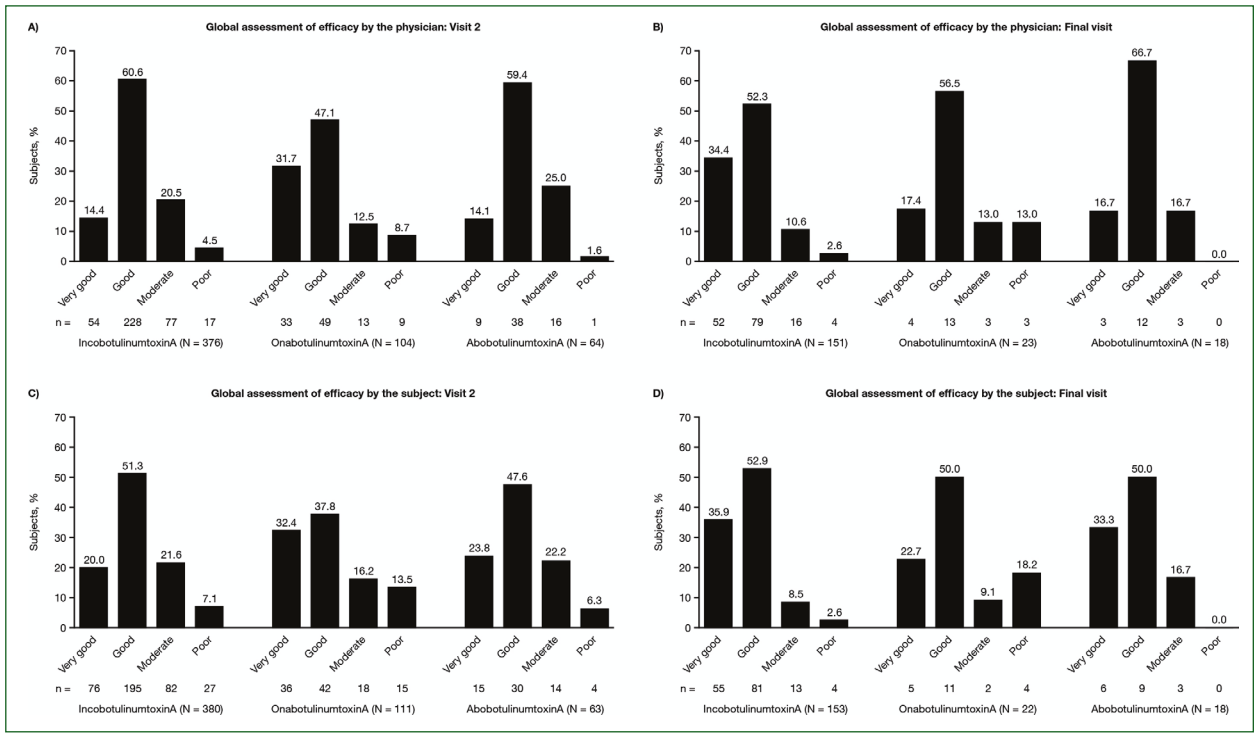

Figure 1. Proportion of subjects with very good, good, moderate, or poor global assessment of efficacy ratings according to physician at A) Visit 2 (evaluation of treatment cycle 1) and B) final visit[a] (evaluation of treatment cycle 8), and according to subject at C) Visit 2 and D) final visit[a]

[a]Final visit occurred at end of study, subjects did not receive an injection at this point and only those who returned for assessment were included in analysis

Percentages are based on non-missing values; N — total number of subjects assessed

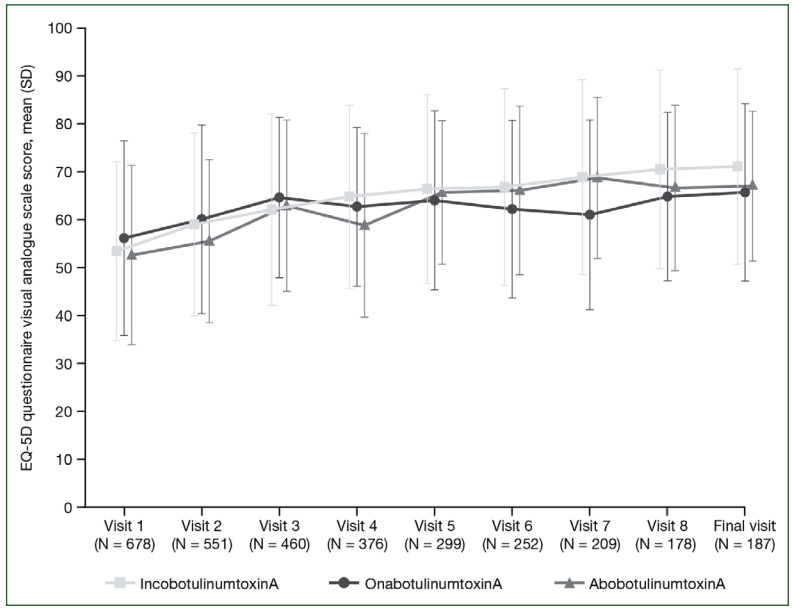

Figure 2. Mean (SD) HRQoL (EQ-5D visual analogue scale score)

Final visit occurred at end of study, subjects did not receive an injection at this point and only those who returned for assessment were included in analysis

EQ-5D — EuroQoL 5-dimensions; HRQoL — health-related quality of life

maximum dose recommendations might be too restrictive for some subjects' needs (see relevant prescribing information for details of current indicated doses of BoNT-A products [5–10]). This is consistent with a survey reporting that a physician-estimated 24.6% of individuals could benefit from higher doses of BoNT-A, and that lifting dosing and interval restrictions could improve therapy outcomes and treatment satisfaction [27]. A prospective, dose-titration study investigated the safety and efficacy of escalating incobotulinumtoxinA doses in subjects with upper- and lower-limb spasticity [20]. IncobotulinumtoxinA doses up to 800 U were well tolerated and allowed the treatment of a greater number of muscles and clinical patterns in a single treatment cycle, which may alleviate physicians' requirements to prioritise clinical patterns for treatment.

The strengths of this study include the large population (n = 701 for the safety analysis) from nine countries worldwide, the long duration (up to 2 years), and the fact that all participating subjects were treatment-naïve at study entry.

However, the representation of routine clinical practice across nine countries with different licenced indications and recommendations could also be viewed as a limitation. Further limitations include the lack of subject-reported safety information, and the gradual attrition of subject information and the resulting convenience sampling at later treatment cycles. Such attrition may seem discordant with the reported efficacy; additional studies are needed to investigate the factors contributing to treatment discontinuation in those who experience efficacy with BoNT-A. Although not reported in this study, reasons for attrition in such non-interventional studies can include subjects being lost to follow-up, either because they do not return for treatment or because the physician no longer documents the data, as well as when subjects experience treatment dissatisfaction, or indeed improvement in their symptoms, and do not require further treatment.

Conclusion

These results support the routine use of BoNT-A therapy in adults with spasticity. Throughout this 2-year real-world study, BoNT-A treatment was well tolerated, effective, and associated with an improved HRQoL.

Clinical implications/future directions

The results of the SPACE study make a valuable contribution to the broader understanding of how physicians use BoNT-A therapy to manage spasticity in real-world clinical practice. Further studies are required to investigate any correlations in practice and outcomes across the participating countries, including the effects of guidance techniques known to influence the efficacy of BoNT treatment [28].

Furthermore, research would be welcomed that brings clinicians closer to a consensus about objective outcome measures which could be used to capture the diverse range of benefits in subjects with spasticity, including the evaluation of goal attainment and functional improvements included in previous trials [20, 24, 29].

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LEADING TOPIC

Dose per muscle in cervical dystonia: pooled data from seven movement disorder centres

Wolfgang H. Jost[1], Artur Drużdż[2], Sanjay Pandey[3], Bo Biering-Sørensen[4], Alexandre Kreisler[5], Laurent Tatu[6], Christian F. Altmann[1], Jarosław Sławek[7,8]

[1]Parkinson-Klinik Ortenau, Wolfach, Germany
[2]Department of Neurology, Municipal Hospital in Poznan, Poznan, Poland
[3]Department of Neurology, Govind Ballabh Pant Institute of Postgraduate Medical Education and Research, JLN Marg, New Delhi, India
[4]Movement Disorder Clinic, Department of Neurology, Rigshospitalet, Copenhagen, Denmark
[5]Service de Neurologie et Pathologie du Mouvement, CHRU de Lille, France
[6]Department of Neuromuscular Diseases and Department of Anatomy, CHRU Besançon, University of Franche-Comté, Besançon, France
[7]Division of Neurological and Psychiatric Nursing, Faculty of Health Sciences, Medical University of Gdansk, Poland;
[8]Department of Neurology and Stroke, St. Adalbert Hospital, Gdansk, Poland

ABSTRACT

Aim of the study. Botulinum neurotoxin type-A (BoNT/A) injections are the established treatment in cervical dystonia (CD). But clinical practice regarding the choice of muscles into which injections are made varies between centres. Until now, there have been no dose-per-muscle recommendations based on 'searching the dose' clinical trial data.

Clinical rationale for study. We therefore examined the dosages under real world conditions at seven international movement disorders centres, using an identical clinical approach.

Results. We examined 305 patients with CD (55.6 ± 13.2 years, 204 female). The most commonly injected muscles were the splenius capitis (84.9%), sternocleidomastoid (80.3%), trapezius (59.7%), levator scapulae (49.8%), semispinalis capitis (39%), and obliquus capitis inferior (36.7%). The mean total dose per treatment session with aboBoNT/A was 652.5 (SD = 285.5), with onaBoNT/A it was 159.5 (SD = 62.4), and with incoBoNT/A it was 173.4 (SD = 99.2) units. The doses injected into each muscle in the ona- or incoBoNT/A groups were between 19.7 and 48.2 units, with the highest dose for the splenius capitis with 49.2 ± 26.0 units. The doses in the aboBoNT/A group were between 69.6 and 146.4 units, and the highest dose being injected into the splenius capitis (139.6 ± 80.7 units).

Conclusions and clinical implications. In clinical trials the doses per muscle are based on an arbitrary decision. In our study, the doses were lower than in other studies, which may be due to the number of muscles per session, the use of ultrasound guidance (and therefore more precise injections), as well as the use of the Col-Cap concept. Our results exemplify everyday practice, and may help as the basis for recommendations and further investigations.

Key words: torticollis, cervical dystonia, Col-Cap concept, botulinum toxin, sternocleidomastoideus muscle, splenius capitis muscle

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Address for correspondence: Wolfgang Jost, Parkinson-Klinik Ortenau, Kreuzbergstr. 12 Str., 77709 Wolfach, Germany, e-mail: w.jost@parkinson-klinik.de

Introduction

The choice of muscles for injections in cervical dystonia (CD) varies between centres, and is based both on different concepts and on personal experience. There are no generally accepted dose recommendations based on dose-finding studies. However, a few studies have shown the dose per muscle used in a randomised and open (observational) manner [1–3]. In the summary of products characteristics (SPC) of all botulinum neurotoxin-A products (BoNT/A) there are only indicated maximal recommended doses. For some products, specific muscles are mentioned but without specified dose recommendations (SPC Botox®, SPC Dysport®, SPC Xeomin®). Therefore, the standard dose recommendations are mostly based on pivotal clinical trials and personal experience [4, 5]. The majority of studies in CD were performed many years ago. In 2009, a new concept (the Col-Cap) was introduced, expanding not only the number of CD patterns, but also the number of muscles to be injected [6, 7].

The aim of our study was to look for effective doses per muscle used in everyday clinical practice in different centres using a similar treatment regime. As a data basis for further studies, we therefore analysed pooled data on usually-chosen dosages per muscle in a larger collective study in previously injected patients with established muscle patterns.

Materials and methods

Between 1 January and 30 June 2019, we examined retrospectively in seven centres specialized in movement disorders, 311 consecutive patients with CD, who were being already successfully treated (with a moderate or good response clinically determined by patient and physician) for at least three times. Consecutive patients were included if they had idiopathic CD, with pronounced symptoms interfering with their daily activities, and who had been admitted at least three months after their previous BoNT/A treatment, the effect of which had worn off. Six patients were excluded from our study because of incomplete data, thus resulting in a sample size n = 305. The centres involved were: Besançon (France), Copenhagen (Denmark), Gdansk (Poland), Lille (France), New Delhi (India), Poznan (Poland), and Wolfach (Germany). All investigators were specialists in movement disorders with long-term experience with BoNT/A treatment in CD (at least 15 years each). All injections were performed by investigators trained in the use of ultrasonography guidance (US). The therapeutic approach (treatment regime) across all centres was uniform and based on the Col-Cap concept [6]. BoNT/A was diluted according to the SPC recommendations: ona- and incoBoNT/A vials containing 100 units were reconstituted with 2ml, and aboBoNT/A vials with 300 and 500 units with 1.5 ml and 2.5 ml of 0.9% NaCl respectively.

Patients were excluded if at least a moderate effect of previous BoNT/A injections had not been obtained and if the co-morbidities (e.g. severe depression) could influence the overall subjective assessment of the results. Concomitant use of neuroleptics was forbidden, and other causes of CD (suggesting symptomatic or pseudodystonic origin) were excluded.

Results

305 patients with CD (mean age 55.6 ± 13.2 years, range 21–90, 204 female) were injected and assessed.

The most common primary form of CD in our group was torticaput (49%) and the second most common was laterocaput (16.7%). All other subtypes afflicted less than 10% of our study population. Pure forms were observed in 16.3% of patients only. Torticaput was combined in 46% with laterocaput, and in 20.7% with retrocaput. Laterocaput was combined mainly with torticaput (45.1%), laterocollis (33.2%) or retrocaput (23.5%). Shift forms were found in 14.7%. On average, patients had 2.51 (± SD 1.09) subtypes each, and tremor was observed in 55.6% [5, 8].

The most commonly injected muscles were the splenius capitis (84.9%), sternocleidomastoid (80.3%), trapezius (59.7%), levator scapulae (49.8%), semispinalis capitis (39%), and obliquus capitis inferior (36.7%) respectively. 154 patients received onabotulinumtoxinA (onaBoNT/A), 53 patients incobotulinumtoxinA (incoBoNT/A), and 98 abobotulinumtoxinA (aboBoNT/A). The mean total dose for a treatment session with aboBoNT/A was 652.5 (SD = 285.5) units, for ona- 159.5 (SD = 62.4) units, and for incoBoNT/A 173.4 (SD = 99.2) units respectively. The doses injected into each muscle are set out in Table 1. The doses injected into each muscle in the ona- or incoBoNT/A groups were between 19.7 and 49.2 units. The highest dose was injected into the splenius capitis, 49.2 ± 26.0 units, with the highest total dose per session being 130 units. The lowest doses were chosen for both semispinalis muscles.

The doses in the aboBoNT/A group were between 75.4 and 139.6 units (Tab. 1B). The highest dose was injected into the splenius capitis with 139.6 ± 80.7 units, with the highest dose of 400 units total per session. The lowest doses were chosen for semispinalis cervicis, longissimus (cervicis and/or capitis) and medial scalene muscles.

Discussion

Although BoNT/A injections are the therapy of choice for CD, the dose per muscle is an unresolved problem [7, 9]. Both total dose per session and per muscle were pre-established at study design in clinical trials and incorporated into published recommendations [1, 2]. SPCs are mostly focused on maximal total dose (SPC Botox®, SPC Dysport®, SPC Xeomin®). Recently published versions of SPC do not include the specific doses per muscle, and only aboBoNT/A SPC recommends for head tilt 150 units to sternocleidomatoid muscle (SCM) and 350 units to splenius capitis (SC).

Table 1A. Dose per muscle of abobotulinumtoxinA

Muscle	SCM	SM	LS	SsCap	SsCer	SCap	SCer	OCI	Trap	Long
Mean	117.9	87.5	135.8	111.4	102.1	139.6	75.4	117.3	123.4	87.3
SD	40.1	36.8	50.8	63.4	73.9	80.7	47.5	43.6	47.7	35.7
MAX	200	175	250	380	400	400	200	200	250	160
MIN	40	20	40	40	10	25	25	40	40	25
N	77	18	59	45	28	82	11	44	74	15
Proportion	78.6%	18.4%	60.2%	45.9%	28.6%	83.7%	11.2%	44.9%	75.5%	15.3%

All others: Mean = 87.3; SD = 54.6; MAX = 240; MIN = 30; N = 13; Proportion = 13.3%

Table 1B. Dose per muscle of inco-BoNT/A

Muscle	SCM	SM	LS	SsCap	SsCer	SCap	SCer	OCI	Trap	Long
Mean	34.7	28.8	39.0	30.7	31.3	36.8	65.0	31.7	33.0	27.0
SD	15.2	16.5	17.9	15.2	14.3	21.2	49.5	20.9	13.3	10.6
MAX	70	50	80	70	50	100	100	90	60	40
MIN	15	10	15	10	10	10	30	5	10	10
N	43	4	34	15	8	43	2	23	35	10
Proportion	81.1%	7.6%	64.2%	28.3%	15.1%	81.1%	3.8%	43.4%	66.0%	18.9%

All others: Mean = 23.3; SD = 15.3; MAX = 40; MIN = 10; N = 3; Proportion = 5.7%

Table 1C. Dose per muscle of ona-BoNT/A

Muscle	SCM	SM	LS	SsCap	SsCer	SCap	SCer	OCI	Trap	Long
Mean	40.8	24.3	32.8	19.7	18.0	49.2	13.3	20.6	29.2	20.5
SD	15.5	5.8	12.3	13.2	8.5	26.0	4.8	11.4	13.2	9.9
MAX	80	30	70	100	40	130	20	50	100	40
MIN	7.5	10	10	7.5	5	10	5	7.5	10	5
N	125	14	59	59	37	134	9	45	73	27
Proportion	81.2%	9.1%	38.3%	38.3%	24.0%	87.0%	5.8%	29.2%	47.4%	17.5%

All other: Mean = 22.5; SD = 16.1; MAX = 90; MIN = 7.5; N = 47; Proportion = 30.5%
SCM — sternocleidomastoideus; SM — scalenus muscles; LS — levator scapulae; SsCap — semispinalis capitis; SsCer — semispinalis cervicis; SCap — splenius capitis; SCer — splenius cervicis; OCI — obliquus capitis inferior; Trap — trapezius; Long — longissimus; N — number of muscles injected

Regarding only the main double-blind, placebo-controlled, randomised studies: in a majority of them the number of injection sites per muscle and the volume/dose injected into each muscle were determined at the discretion of the investigator [10–13].

In an early study by Poewe et al., aboBoNT/A was injected into only two muscles: SCM and SC [total doses of 250, 500, or 1,000 units divided among them and related to Toronto Western Spasmodic Torticollis Score (TWSTRS) result] [14].

Another early study, by Wissel et al., specified the range of doses per muscles of aboBoNT/A used: SCM: 100-200 units, SC 250–350 units, trapezius (Trap) 100-200 units and levator scapulae (LS) 100–200 units. The total maximum allowed dose per patient was 500 units. This reflects only the methodology of this trial, but does not show the actual dosages used per muscle in clinical practice [15].

In a more recent study by Poewe et al., the authors listed the injected muscles (LS, Trap, SCM, SC, scalene medius, semispinalis capitis and longissimus), but did not reveal the injected doses [16].

Figures regarding the dose per muscle in open label studies (more closely resembling our group of patients) are also scarce. Camargo et al. observed 28 patients with CD treated for seven years with BoNT/A and they reported doses consecutively injected into each muscle: SCM 15–75 units, Trap 30–100 units, SC 15–50 units, LS 15–50 units, and paravertebral muscles 15–50 units (doses were calculated for onaBoNT/A, but different preparations were used over the course of the seven years). This group was small (n = 28) and doses were not assigned to a specific BoNT/A product for the whole follow up [2].

Bentivoglio et al. reported in a long term (at least six consecutive injections) open study of aboBoNT/A in CD the doses used for injected muscles: SCM, Trap, SM, SC, and LS. Mean dose (and SD plus range) for each muscle were: 110.0 ± 44.9 (40–200) units for SCM, 231.4 ± 158.3 (60–500) units for Trap, 74.8 ± 47.7 (40–180) units for SM, 157.1 ± 111.1 (60–400) units for SC, and 118.7 ± 57.9 (60–300) units for LS. Nevertheless, the authors used the standard CD classification (as used in the pre-Col-Cap era). The most frequent dystonic patterns identified were torticollis and laterocollis, accounting for

Table 2. Comparison between doses recommended in position statement of group of experts (1, 7) and mean doses used in our study (shown in bold; we selected more commonly used muscles)

Muscle	ona/incoBoNT/A (units, range)	aboBoNT/A (units, range)	onaBoNT/A (units, SD)	incoBoNT/A (units, SD)	aboBoNT/A (units, SD)
Sternocleidomastoid	20–50	40–120	**40.8 (15.5)**	**34.7 (15.2)**	**117.9 (40.1)**
Splenius capitis	40–100	100–350	**49.2 (26.0)**	**36.8 (21.2)**	**139.6 (80.7)**
Trapezius	25–100	60–300	**29.2 (13.2)**	**33.0 (13.3)**	**123.4 (47.7)**
Levator scapulae	20–100	60–200	**32.8 (12.3)**	**39.0 (17.9)**	**135.8 (50.8)**
Semispinalis capitis	20–100	60–300	**19.7 (13.2)**	**30.7 (15.2)**	**111.4 (63.4)**
Splenius cervicis	20–60	60–140	**13.3 (4.8)**	**65.0 (49.5)**	**75.4 (47.5)**
Semispinalis cervicis	20–60	60–140	**18.0 (8.5)**	**31.3 (14.3)**	**102.1 (73.9)**
Obliquus capitis	10–20	60–200	**20.6 (11.4)**	**31.7 (20.9)**	**117.3 (43.6)**

78.7% and 78.5% of all the treatments respectively, followed by dystonic tremor (37.9%) and shoulder elevation (14.4%). Mixed patterns were a combination of torticollis and laterocollis (28.9%) and torticollis with dystonic tremor (5.6%) [1].

In our earlier publication regarding a cohort of 305 patients with CD, we demonstrated that the most frequently injected muscle was the SC (83%), followed by SCM (79.1%) and Trap (58.5%). But less frequently injected muscles were also treated: LS, semispinalis capitis (SScap), and OCI in 38.2%, 48.7% and 35.3% of patients respectively [17]. The most common pattern of CD was torticaput (49%) followed by laterocaput (16.7%). Pure forms were observed in 16.3% of patients only [5]. These 'new' muscles (i.e. those rarely included in clinical trials, such as OCI) gained more awareness when the Col-Cap concept was introduced by Reichel at al. [6]. The doses chosen in our international cohort study are based on this relatively new approach. To the best of our knowledge, this has not been studied in such a large cohort previously.

The doses we used in our cohort are lower than in other studies with aboBoNT/A [1, 14, 15]. This may indirectly reflect the common use of US guidance in our practice which may result in more precise injections and may lower the dose per muscle. In all randomised and double-blind clinical studies published so far, US has not been used as the guidance technique [10–13]. The doses per muscle are lower for some muscles in our cohort compared to the recommendations of experts [4] – see Table 2.

The 'ideal' dose per muscle remains unknown because it has never been formally studied in a scientific manner. Nevertheless, the dose per muscle (after proper identification of dystonia pattern using the Col-Cap concept) could be crucial to effective treatment.

Our study, featuring a large cohort of 305 patients, reflects real life practice in movement disorder clinics using the same treatment regime across continents, and shows the doses identified as being 'effective' (all patients were treated previously with at least moderate/good response). It can potentially help as an overview for injectors going into the field of CD treatment.

We are aware that the use of ultrasound guidance is not yet available at some centres, and that others use other methods such as EMG guidance. Although this might influence the injection of some rare muscles, it should not significantly impair the fundamental results and implications of our study.

Conclusions

Our study shows, for the first time, the doses per muscle used in CD patients in real life practice using the Col-Cap concept, including muscles not previously injected.

The doses per muscle were lower than in other studies, which may be the result of both the Col-Cap concept and the use of (presumably more precise) US-guided injections.

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Prevalence of cognitive impairment in acute ischaemic stroke and use of Alberta Stroke Programme Early CT Score (ASPECTS) for early prediction of post-stroke cognitive impairment

Ahmed Esmael, Mohammed Elsherief, Khaled Eltoukhy

Neurology Department, Faculty of Medicine, Mansoura University, Dakahlia, Egypt

ABSTRACT

Aim of the study. This study aims to assess the prevalence of post-stroke cognitive impairment, and to evaluate the correlation of ASPECTS with impaired cognition.

Materials and methods. 150 patients presenting with acute middle cerebral artery territory ischaemic stroke were included in this study. Risk factors of ischaemic stroke and the initial NIHSS were determined. An initial and a follow-up non-contrast CT brain were carried out after seven days which were assessed by ASPECTS. The prevalence of cognitive impairment was determined by MoCA during the follow up of patients after three months. Correlations of ASPECTS, NIHSS and MoCA were done by Spearman correlation. Multivariate logistic regression analysis was carried out for the independent variables of cognitive impairment.

Results. The prevalence of post-stroke cognitive impairment in this study, according to the threshold for cognitive impairment with a MoCA score of 25 or less, was 25.3% (38 patients). Significant positive correlations between ASPECTS and total MoCA test domains were found ($r = 0.73$ and $p = 0.002$). Logistic regression analysis demonstrated that the independent factors associated with cognitive impairment were older age, certain domains of the MoCA test like executive functions, memory, attention, language, NIHSS, HTN, and ASPECTS.

Conclusions and clinical implications. There is a prevalence of cognitive impairment in about 25% of patients after three months of follow-up in cases with acute ischaemic stroke. ASPECTS is directly correlated with cognitive impairment, and may be considered as a biomarker of post-stroke cognitive impairment.

Key words: stroke, Alberta Stroke Programme Early CT Score, National Institutes of Health Stroke Scale, cognitive impairment

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Introduction

Stroke is the third leading cause of death, and is considered to be an important cause of disability and impaired cognition [1, 2]. Post-stroke cognitive impairment is a common but neglected sequel compared to other neurological deficits [3]. Different domains of cognition, such as attention, concentration, memory, language, and executive functions may be affected in stroke survivors [4].

Up to 50% of all cases with ischaemic stroke show diminished or below-average performance of cognitive functions. Impaired processing speed, attention and working memory are frequently affected [5]. Also, a high proportion of stroke survivors have cognitive impairment within three months after stroke, as found in the study by Nys et al. [6]. Although the prevalence of post-stroke cognitive impairment is high according to previous studies, it appears that the frequency of post-stroke cognitive decline in stroke survivors may have been underestimated [7, 8].

The evaluation of cognitive functions by classic neuropsychological methods during an acute stroke is very difficult due to factors that cause the misinterpretation of test results, such as the severity of the patient's condition, apathy, depression,

Address for correspondence: Ahmed Esmael, Neurology Department, Mansoura Faculty of medicine, Mansoura University, Mansoura 35516, Dakahlia, Egypt, e-mail: deltaneuro@mans.edu.eg

and anxiety disorders [9]. So, specific and ideal biomarkers to predict the development of post-stroke cognitive impairment are needed to reflect the severity of its course and effectiveness of treatment [10, 11]. The Alberta Stroke Programme Early Computed Tomography Score (ASPECTS) has been widely used to determine the extent of early ischaemic changes in brain imaging for acute stroke [12].

Clinical rationale for study

The aim of our study differs from that of other studies in that ASPECTS has been used to predict cognitive impairment resulting from acute ischaemic stroke.

Materials and methods

Participants and inclusion/exclusion criteria

This study was approved by the local ethics committee Institutional Research Board (IRB) and all patients provided written consent. 150 patients with acute ischaemic stroke (AIS) were admitted to our neurology department between October 2017 and March 2019; 79 males and 71 females were included in this study and admitted to the Convalescent Care Unit. The 150 had all experienced the first attack of acute MCA territory infarction within two days from the onset and were aged 18 years and older. Acute ischaemic stroke (AIS) was defined as a rapidly developing neurological deficit with an obvious known onset, plus an initial CT brain with no proof of ICH. Exclusion criteria were previous stroke, presence of anterior cerebral artery infarction, posterior cerebral artery infarction, and venous infarction. We also excluded patients with previous neuropsychiatric diseases or who had been prescribed drugs that impair cognition. In addition, severe cases with NIHSS > 25, and cases where MoCA could not be assessed, were excluded.

Classification and patient subgroups

Patients were classified into two groups according to their MoCA score three months after the onset of AIS. The first group, the 'cognitively impaired', had a MoCA score of 25 or less. The second group, the 'cognitively preserved', had a MoCA score of 26 or more.

Clinical and radiological diagnosis

A history of vascular risk factors was obtained for each patient. Complete general and neurological examinations were carried out. All patients underwent CT examinations by 16-multi-slice GE, (Optima 520, China). Initial non-contrast CT brain was done for all cases at the onset and a follow-up CT brain was done after seven days. For all patients, the CT images were obtained in an axial plane, 5 mm sections from the base to the vertex. Imaging parameters were: 120 kVp, 320 mA, FOV of 195 mm, 1s/rotation, and table speed of 15mm/rotation.

Images were analysed independently by neuroradiologists. Assessment of brain CT was done by ASPECTS. An ASPECTS score was calculated for each patient. Brain CT images were assessed for proof of localised parenchymal hypo-attenuation, loss of differentiation between grey and white matter, and if there was effacement of sulci. ASPECTS is a reliable method for the evaluation of ischaemic stroke that utilises a 10-point scoring system, with M1, M2, M3, M4, M5, M6, I: insula, IC: internal capsule, L: lentiform, and C: caudate representing those 10 points. A score of 10 means a normal CT scan. One point is subtracted for each affected area on the brain CT. So, a score of 0 indicates widespread ischaemia affecting the MCA territory (Fig. 1) [13]. Patients were classified into two subgroups, the first group comprising those with better ASPECTS ranging from 10-8, and the second group comprising those with worse ASPECTS ranging from 0-7.

Cognitive assessment

To assess cognitive functions, we used the Montreal Cognitive Assessment (MoCA) in its Arabic form for our study participants [14]. This scale evaluates different domains of cognition such as attention, orientation, memory, language, visuo-constructional capacity, and executive functions. MoCA is a 30-point test where a score of 25 or below is considered to demonstrate abnormal impaired cognition [15]. Patients were classified into two groups according to their MoCA score three months after the onset of AIS. The first group, the 'cognitively impaired', had a MoCA score of 25 or less. The second group, the 'cognitively preserved' had a MoCA score of 26 or more. Potocnik et al. determined that the optimal cut-off value for impaired cognition is ≤ 25 points, with high sensitivity (81%) and specificity (70%) [16].

Statistical analysis

Quantitative data was prescribed as interquartile and median range and comparison was done by Mann–Whitney U test. Nominal data was presented as numbers and percentages and compared by the χ^2 test.

In order to reveal possible correlations between cognitive impairment and ALBERTA, the Pearson correlation analysis was used. Multivariate logistic regression analysis was carried out for the independent variables of cognitive impairment such as age, ASPECTS, and MoCA domains.

Results

Thirty-eight (25.3%) ischaemic stroke patients showed impaired cognitive functions, while 112 patients (74.7%) had preserved cognition. Patients with impaired cognitive functions were older ($p = 0.001$) with no significant sex difference ($p = 0.71$) (Tab. 1).

Patients with impaired cognitive functions compared to patients with preserved cognition were associated with a significantly higher incidence of hypertension ($p = 0.001$), but there was no significant difference between the two groups regarding DM, smoking, IHD, AF, or hyperlipidemia.

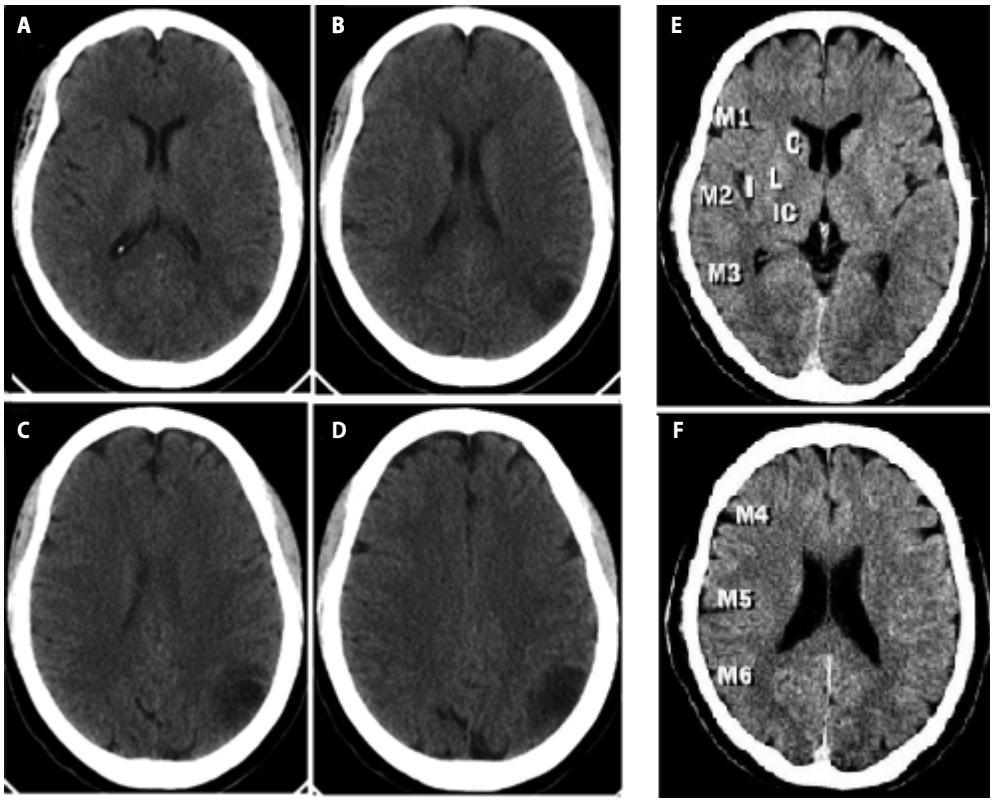

Figure 1. **A–D** sequential axial non-contrast CT images of brain reveal hypodense area of infarction at left posterior parietal region (M3 and M6 regions); ASPECTS = 8. **E–F** sequential axial non-contrast CT images of brain reveal ganglionic and supraganglionic levels and ASPECTS scoring: one point is subtracted for each affected area on brain CT

In addition, there was a significantly higher initial NIHSS in patients with impaired cognitive functions compared to patients with preserved cognition (19.32 ± 5.74 *vs.* 12.34 ± 6.69 and p = 0.001). Moreover, cognitively impaired patients were associated with more severe and moderate NIHSS scores compared to cognitively preserved patients (p = 0.002) (Tab. 1).

There was a clear significant impairment in the domains of language, attention, memory, and executive functions (p < 0.005). On the other hand, the domains of visual-spatial ability, naming, and orientation were slightly decreased in cognitively impaired patients (Tab. 1).

Also, there was a strong positive correlation between ASPECTS and total MoCA test (r = 0.73 and p = 0.002), as shown in Figure 2.

Regarding hemispheric dominance, cases with dominant hemisphere infarction demonstrated significantly lower MoCA scores compared to cases with non-dominant hemispheric infarction (22.36 ± 5.42 *vs.* 23 ± 3.92, p = 0.029), as demonstrated in Figure 3.

Finally, logistic regression analysis demonstrated the independent factors associated with cognitive impairment to be older age (OR 2.42, p < 0.001), followed by certain domains of the MoCA test like executive functions, memory, attention, and language (OR 2.11, p = 0.001, OR 2.1, p = 0.001, OR 2.06, p = 0.004, and OR 2.09, p = 0.002 respectively), and NIHSS and HTN (OR 2.1, p = 0.001 and OR 2.03, p = 0.006 respectively). Also, although to a lesser extent, ASPECTS was associated with cognitive impairment (OR 2.01, p = 0.005) (Tab. 2).

Discussion

Our study had two goals: (1) to identify the prevalence of cognitive impairment in AIS, and (2) to assess if there is a correlation between ASPECTS and cognitive outcomes after three months.

Post-stroke impaired cognition occurs frequently, its prevalence ranging from 20–80% with differences between countries, races, and diagnostic criteria. The risk of post-stroke impaired cognition is related to both demographic factors like age, education, and occupation, and vascular factors [17].

Acute ischaemic stroke (AIS) requires a rapid evaluation of clinical and radiological findings. The ability to distinguish an acute infarct by CT is helpful in confirming the diagnosis and the analysis of acute stroke [18]. CT has the advantage of being a simple technique that leaves enough time for early treatment and fast intervention where needed. Baseline ASPECTS is a reliable predictor of prognosis in patients with AIS [19]. ASPECTS is increasingly being integrated into the decision-making process for intervention in patients with AIS [20].

Table 1. Patients with cognitive impairment compared to patients with preserved cognition

	Impaired cognition	Preserved cognition	P value
Number	38 (25.3%)	112 (74.7%)	
Age (y) mean ± SD	68.5 ± 7.12	60.23 ± 7.61	0.001*
Age < 60 N (%)	13	71	0.002*
Age > 60 N (%)	25	41	
Gender (male)	21 (55.2%)	58 (51.8%)	0.71
Hypertension	30 (79.8%)	56 (50%)	0.001*
DM	11 (29%)	28 (25%)	0.63
Smoking	15 (39.5%)	37 (33%)	0.47
Hyperlipidemia	7 (18.4%)	16 (14.3%)	0.54
AF	7 (18.4%)	18 (16%)	0.73
IHD	4 (10.5%)	11 (9.2%)	0.9
Initial NIHSS mean ± SD	19.32 ± 5.74	12.34 ± 6.69	0.001
Mild (0–5)	9	61	0.002
Moderate (6–15)	13	29	
Severe (≥ 16)	16	22	
MoCA test scores			
Visuo-spatial ability	3.18 ± 1.23	3.4 ± 0.89	0.39
Naming	2.25 ± 0.91	2.58 ± 0.72	0.21
Executive functions	2.28 ± 1.29	3.7 ± 0.95	p < 0.001
Attention	4.51 ± 1.28	5.93 ± 0.96	0.004
Language	3.41 ± 1.02	4.42 ± 1.12	0.002
Memory	2.82 ± 1.41	4.19 ± 1.11	p < 0.001
Orientation	5.82 ± 0.39	6.49 ± 0.34	0.11
Total MoCA score	21.72 ± 2.93	26.02 ± 3.21	p < 0.001
ASPECTS	5.23 ± 3.95	8.54 ± 1.44	p = 0.005

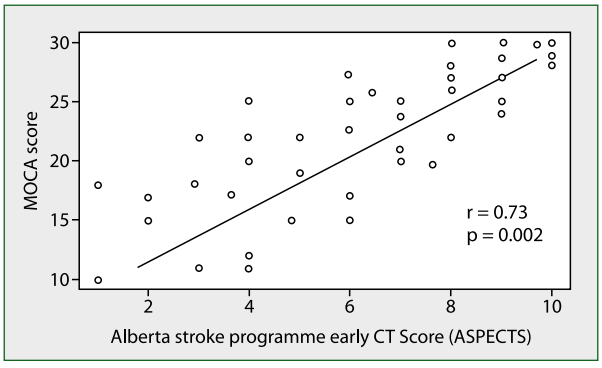

Figure 2. Correlation of ASPECTS against MoCA score

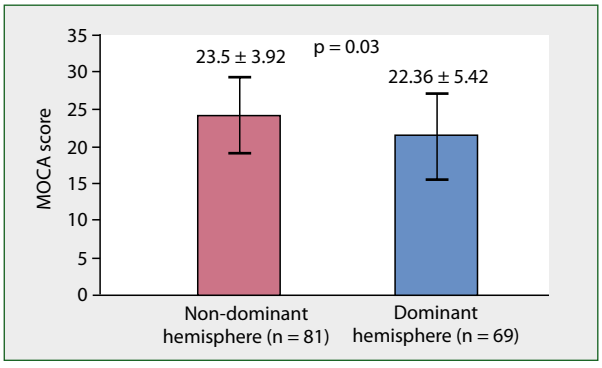

Figure 3. Relationship of laterality of infarction and cognition

Prevalence of post-stroke cognitive impairment

The prevalence of post-stroke CI in previous studies ranged from 7.5–72% [21–24]. In the present study, the prevalence of cognitive impairment was 25.3%, similar to the percentage found in previous studies. The varying prevalence in previous studies might be due to differences in the setting of a study, different age groups, and different assessment scales and biomarkers used to diagnose cognitive impairment.

For example, a study by Liman et al. reported 11.8% cognitive impairment three years after stroke [25]. Douiri et al. reported 24% cognitive impairment three months from onset [26], and Knopman et al. reported 10.9% cognitive impairment

Table 2. Independent factors highly associated with cognitive impairment

Variables	O R	95% CI	P
Age	2.42	1.87–3.12	p < 0.001
HTN	2.03	1.37–2.67	0.005
NIHSS	2.1	1.51–2.73	0.001
ASPECTS	2.01	1.39–2.64	p = 0.005
Executive functions	2.11	1.53–2.79	p = 0.001
Attention	2.06	1.43–2.68	p = 0.004
Language	2.09	1.46–2.71	p = 0.002
Memory	2.1	1.45–2.75	p = 0.001

[27]. The difference in the prevalence of impaired cognition in our study compared to the other studies was due to the scale used which was MoCA; previous studies used MMSE with a cut-off score of < 24 to indicate impaired cognition. Although MMSE is sensitive in diagnosing dementia, it is insensitive in diagnosing early dementia or mild cognitive impairment [28, 29].

Risk factors of AIS and cognitive impairment

In our study, the common risk factors for stroke were hypertension, smoking, DM, AF, hyperlipidemia, and ischaemic heart disease. These findings are more or less similar to the studies by Amelia et al. and Mahdi et al. [30, 31]. Moreover, recent studies agree with our results regarding the traditional risk factors such as hypertension, diabetes, dyslipidemia, and smoking that can account for 60-80% of strokes [32–34].

Patients with impaired cognitive functions compared to patients with preserved cognition were older (p = 0.001) and showed a significantly higher incidence of hypertension (p = 0.001), but there was no significant difference between the two groups regarding sex, DM, smoking, IHD, AF, or hyperlipidemia. Also, the study by Goldstein et al. on stroke survivors with high blood pressure found impaired cognitive function, especially in the performance of tasks requiring rapid responses and expressive language [35]. The literature has explained the role of vascular risk factors and the mechanism of impaired cognition [36, 37], and the interaction of vascular risk factors with ischaemic stroke [38].

Infections are known to increase the risk of stroke. Also, infection in stroke patients is a common inpatient complication. On top of the fact that infection can lead to cerebral stroke, stroke also induces suppression of immunity which increases the chance of infection and adversely influences cognitive outcomes in patients with stroke, all serving to increase the risk of cognitive impairment following stroke [39, 40].

Correlations of ASPECTS, NIHSS, and laterality of infarction with cognition

We found a significant positive correlation between the neurocognitive test domains (executive functions, attention, memory, and language) and ASPECTS (p < 0.05). Cognitively impaired patients were associated with more severe and moderate NIHSS scores compared to cognitively preserved patients. Similarly, analysing the results of Sivakumar et al. by Spearman correlation indicated that NIHSS scores were significantly correlated with MoCA scores at baseline (r = -0.52; p = 0.02) and at day 30 (r = -0.51; p = 0.04) [41]. We also detected that cases of ischaemic stroke with dominant hemispheric infarction showed lower scores on the MoCA test. These results were similar to the findings of Chan et al., who found that poor performance of dominant cerebral hemisphere ischaemic stroke cases on the MoCA test probably indicates the reliance of the MoCA test sub-items on both receptive and expressive language abilities beside verbal memory capacities, which commonly affect the dominant cerebral hemisphere in stroke [42].

Factors associated with cognitive impairment in ischaemic stroke

Finally, logistic regression analysis showed that the independent factors associated with impaired cognition in ischaemic stroke were older age, hypertension, NIHSS, and certain domains of the MoCA test like executive functions, memory, attention, and language (p < 0.005). To a lesser extent, ASPECTS was associated with cognitive impairment (p < 0.01).

The management of impaired cognition following stroke will include anti-dementia medications and therapeutic measures for cerebrovascular diseases. As impaired cognition following stroke is attributed to cerebral lesions caused by ischaemic injury, it seems likely that an improved ischaemic injury could ameliorate cognitive improvement. There is increasing evidence that managing vascular risk factors related to stroke could decrease the risk of post-stroke cognitive impairment [43].

A combination of antiplatelet treatment and clopidogrel therapy should be considered in cases with cerebral ischaemic stroke for the prevention of recurrent stroke with subsequent cognitive impairment [44].

Clinical implications/future directions

We conclude that the prevalence of cognitive impairment is about 25% in acute ischaemic stroke patients after three months of follow-up. ASPECTS is directly correlated with cognitive impairment via a positive correlation with the results of neuropsychological testing (MoCA), and may be useful in anticipating post-stroke cognitive impairment. Also, early diagnosis or the anticipation of future impaired cognition following ischaemic stroke will be of therapeutic importance. Both the long-term follow-up of patients and the assessment of their cognitive functions, together with the medications that improve cognition, are advised.

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Validation of the Polish version of the Unified Dyskinesia Rating Scale (UDysRS)

Joanna Siuda[1]*, Magdalena Boczarska-Jedynak[2]*, Sławomir Budrewicz[3], Jarosław Dulski[4,5], Monika Figura[6], Urszula Fiszer[7], Agata Gajos[8], Agnieszka Gorzkowska[9]*, Ewa Koziorowska-Gawron[3], Dariusz Koziorowski[6], Anna Krygowska-Wajs[10], Monika Rudzińska-Bar[11], Jarosław Sławek[4,5], Mateusz Toś[1], Magdalena Wójcik-Pędziwiatr[11], Jeffery Lin[12], Sheng Luo[13], Pablo Martinez-Martin[14], Glenn T. Stebbins[15], Christopher G. Goetz[15], the Polish UDysRS Validation Task Force**, Grzegorz Opala[1]

[1]Department of Neurology, Faculty of Medical Sciences in Katowice, Medical University of Silesia, Katowice, Poland
[2]Department of Neurology and Regenerative Medicine, Health Institute dr Boczarska-Jedynak, Oświęcim, Poland
[3]Department of Neurology, Wroclaw Medical University, Wroclaw, Poland
[4]Department of Neurological and Psychiatric Nursing, Faculty of Health Sciences, Medical University of Gdansk, Gdansk, Poland
[5]Department of Neurology and Stroke, St. Adalbert Hospital, Gdansk, Poland
[6]Department of Neurology, Faculty of Health Sciences, Medical University of Warsaw, Warsaw, Poland
[7]Department of Neurology and Epileptology, Centre of Postgraduate Medical Education, Orłowski Hospital, Warsaw, Poland
[8]Department of Extrapyramidal Diseases, Medical University of Łódź, Łódź, Poland
[9]Department of Neurorehabilitation, Faculty of Medical Sciences in Katowice, Medical University of Silesia, Katowice, Poland
[10]Department of Neurology, Jagiellonian University, Collegium Medicum, Krakow, Poland
[11]Department of Neurology, Faculty of Medicine and Health Sciences, Andrzej Frycz Modrzewski Krakow University, Krakow, Poland
[12]Department of Biostatistics, Gilead Sciences, Inc., Foster City, California, United States
[13]Department of Biostatistics and Bioinformatics, Duke University, Durham, North Carolina, United States
[14]Centre for Networked Biomedical Research in Neurodegenerative Diseases (CIBERNED), Carlos III Institute of Health, Madrid, Spain
[15]Department of Neurological Sciences, Rush University Medical Centre, Chicago, Illinois, United States
[16]Department of Neurology, John Paul II Specialised Hospital, Krakow, Poland

ABSTRACT

Background. In 2008, the Movement Disorders Society published the Unified Dyskinesia Rating Scale (UDysRS). This has become the established tool for assessing the severity and disability associated with dyskinesia in patients with Parkinson's Disease (PD). We translated and validated the Polish version of the UDysRS, explored its dimensionality, and compared it to the Spanish version, which is the Reference Standard for UDysRS translations.

Materials and methods. The UDysRS was translated into Polish by a team led by JS and GO. The back-translation, completed by colleagues fluent in both Polish and English who were not involved in the original translation, was reviewed and approved by the Executive Committee of the MDS Rating Scales Programme. Then the translated version of the UDysRS underwent cognitive pretesting, and the translation was modified based on the results. The approved version was considered to be the Official Working Document of the Polish UDysRS and was tested on 250 Polish PD patients recruited at movement disorder centres. Data was compared to the Reference Standard used for validating UDysRS translations.

Address for correspondence: Joanna Siuda, Department of Neurology, Faculty of Medical Sciences in Katowice, Medical University of Silesia, Katowice, Poland, e-mail: jsiuda@sum.edu.pl

*translation/back-translation team members
**Task Force members in alphabetical order: Andrzej Bogucki[8], Piotr Janik[6], Magdalena Koszewicz[3], Marta Leńska-Mieciek[7], Małgorzata Michałowska[7], Marta Piaścik-Gromada[7], Katarzyna Potasz-Kulikowska[10], Marek Śmiłowski[1]*, Anna Wasilewska[16]

Results. The overall factor structure of the Polish version was consistent with that of the Reference Standard version, as evidenced by the high Confirmatory Fit Index score (CFI = 0.98). The Polish UDysRS was thus confirmed to share a common factor structure with the Reference Standard.

Conclusions. The Official Polish UDysRS translation is recommended for use in clinical and research settings. Worldwide use of uniform rating measures offers a common ground to study similarities and differences in disease manifestations and progression across cultures.

Key words: Parkinson's Disease, dyskinesia, validation, translation, rating scales, UDysRS

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Introduction

In advanced Parkinson's Disease (PD), among many disabling symptoms (motor fluctuations, autonomic dysfunction, cognitive and psychiatric disorders), drug-induced dyskinesia (DID) is one of the most difficult to manage [1–4]. It is important to recognise and objectively assess the severity of DID in PD [5].

In this regard, the International Parkinson and Movement Disorder Society (MDS) in 2008 published a comprehensive rating tool of dyskinesia in PD: the Unified Dyskinesia Rating Scale (UDysRS). Today, the UDysRS is commonly used to assess dyskinesia severity and associated disability. UDysRS combines patient-based assessments of dyskinesia with objective evaluations of disability and impairment from dyskinesias, and it has been clinimetrically validated [6].

The UDysRS is composed of four parts:

- Part 1: *ON Dyskinesia* — measures the subjective impact of ON dyskinesia on everyday activities. The first item, on time spent with ON dyskinesia, is assessed by a trained rater (Part 1 A), whereas the remaining 10 items (Part 1 B) are self-rated by the patient and/or given from the caregiver's perspective (11 items, giving a maximum of 44 points);
- Part 2: *OFF Dystonia* — evaluates the burden caused by OFF dystonia. The first item, on time spent with OFF dystonia, is evaluated by a trained rater (Part 2 A), and the remaining three items (Part 2 B) are information from the patient and/or the caregiver's perspective (four items, giving a maximum of 16 points);
- Part 3: *Impairment* — objectively assesses dyskinesia severity, anatomical distribution over seven body regions, and type (i.e. choreic and/or dystonic) based on four activities observed during a clinical life examination or video recorded (seven items, giving a maximum of 28 points);
- Part 4: *Disability* — examines the disability associated with dyskinesia on four representative tasks, including communication, drinking, dressing, and ambulation (four items, giving a maximum of 16 points).

To enhance the uniform administration of the UDysRS, the MDS Rating Scales Programme sets a specific protocol to designate successful translation of non-English versions [7].

We aimed to translate and validate a Polish version of the UDysRS scale, and to compare it to the Spanish language version, which is the established Reference Standard for UDysRS translations [8].

Below, we present a scale translation and clinimetric testing results of the Polish version of the UDysRS.

Materials and methods

The participants were 250 PD patients recruited from the neurology departments in ten sites across Poland (two in Katowice, two in Krakow, one in Wroclaw, three in Warsaw, one in Gdansk, and one in Lodz). At each site, experienced Polish-speaking movement disorder specialists were recruited to examine native Polish-speaking PD patients with different distributions and severities of dyskinesia. All patients participated voluntarily and gave written informed consent prior to the study. Anonymised data, without patient names or medical record numbers, was transferred to the analytic team via a secure website. The Reference Standard for UDysRS translations is the Spanish language version of the scale, validated previously on 253 native Spanish-speaking PD patients [8]. This data available from the MDS Translation Committee was used for comparative analysis of the UDysRS according to the MDS-established Protocol for official non-English language translations.

Procedure

The MDS Rating Scales Programme has prepared a well-defined protocol, with objective criteria for translation and validation of non-English versions of the MDS-UPDRS and UDysRS in order to have an 'official' MDS translation in a foreign language [7].

There is a four-step process involved in developing an officially approved translation of these scales: (1) translation and independent back-translation; (2) cognitive pretesting to establish that the translation is clear, comfortably administered by native-speaker raters, and understood by native-speaker patients; (3) field testing in the native language using a large sample of PD patients; and (4) statistical analyses including validity testing and factor analysis. This process was previously used by our team in a successful validation of thevPolish version of the MDS-UPDRS [9].

Translation of UDysRS

This Polish version validation was performed as follows: firstly, the UDysRS was translated into Polish by a team of Polish speakers who were not only fluent in English but were also physicians and specialists in movement disorders. This team was led by Dr. Joanna Siuda and Prof. Grzegorz Opala. This was then back-translated into English by colleagues fluent in both English and Polish who had not been involved in the original translation. Finally, it was reviewed by a team of American experts led by Profs. Christopher Goetz and Glenn Stebbins (of the Executive Translation Programme Committee, ETPC) who had been involved in the development of the original English language version [6].

Cognitive pretesting

Cognitive pretesting is a qualitative approach to assessing task difficulty for examiner and respondent, respondent interest, attention span, discomfort, and comprehension [10].

Where there were observed differences between the back-translated Polish version and the English version, items were selected for cognitive pretesting along with questions that were identified during cognitive pretesting of the English version.

The question topics included in cognitive pretesting were: Instructions to Raters and Instructions to Patients; Time Spent with Dyskinesia; Chewing and Swallowing; Exciting or Emotional Settings; Effects of Spasms or Cramps Separate from Pain on Activities; Objective Impairment Ratings; and Objective Disability Ratings.

Based on the results of the initial cognitive pretesting, other round(s) of translation and back translation and cognitive pretesting may be required. Once cognitive pretesting responses were taken into account, the version was modified into the final translation that was approved by the ETPC.

Factor analysis

To conduct the factor analysis of the UDysRS, we omitted Questions 1 (time of ON dyskinesia) and 12 (time of OFF dystonia) and considered these items as descriptive indices rather than measures of impairment or disability. To maximise the accuracy of these time indices, we added three clarifying statements to ensure harmonisation of the time-based questions with the patient/caregiver questionnaire and interview items: In the initial instructions to the full scale, we alert the rater to review the patient questionnaire after completion to ensure that, if item scores indicate the presence of dyskinesia or dystonia over the past week, the time-based items also reflect their occurrence (rating 1, 2, 3, or 4 but not 0).

At the end of each questionnaire section (ON dyskinesia and OFF dystonia), the same alert is inserted.

M-plus Version 7.4 was used to carry out the confirmatory and exploratory factor analyses as the variables are categorical [11]. We used the weighted least squares (WLSMV) approach to factor estimation that minimises the weighted sum of squared differences between observed and estimated correlation matrices. To assist in the interpretation of factors, we used an orthogonal VARIMAX rotation that constrains the factors to be uncorrelated.

The sample size for the translation study was based on the need for 7–10 subjects per item of the questionnaire in order to perform the tasks needed to validate the instrument [12].

Because there are 26 items on the UDysRS, a sample of at least 250 was required. The investigators obtained approval from the human subjects prior to data collection. Deidentified data (with no patient names or medical record numbers) was transferred to the analytic team via a secure website.

Primary analysis

As the primary analysis, we conducted a confirmatory factor analysis (CFA), comparing the Polish data to the Reference Standard data [13,14]. We determined whether the factor structure for the Spanish language UDysRS, which served as the Reference Standard, could be confirmed in the data collected using the Polish translation. This was the primary question of interest. We evaluated the CFA results based on the Comparative Fit Index (CFI). To confirm a good fit between the Polish and the Reference Standard UDysRS, we required that the CFI was 0.90 or greater. Mean and variance adjusted weighted least square (WLSMV) estimator was used to confirm model fit.

We also used the root mean square error of approximation (RMSEA) to check the goodness of fit. This is a population-based index that relies on noncentral $\chi 2$ distribution, which is the distribution of the fitting function when the fit of the model is not perfect.

Secondary analysis

As a secondary analysis, we conducted an exploratory factor analysis (EFA) to explore the underlying factor structure for the Polish language translation, without constraint of a prespecified factor structure, using a weighted least squares (WLSMV) approach. We used a scree plot to choose the number of factors retained for UDysRS. *The subjective scree test* is a scatter plot of eigenvalues plotted against their ranks with respect to magnitude, to extract as many factors as there are eigenvalues that fall before the last large drop (i.e. an 'elbow' shape) in the plot [15]. Once the factors were chosen, an item was retained in a factor if the factor loading for the item was 0.40 or greater. To assist interpretation of the factors, an orthogonal CF-VARIMAX rotation was used which set the factors to be uncorrelated.

Ethics

All patients gave written consent to participate. The anonymised patient data was transferred to the US team for analysis via a secure website. The programme for validation of the UDysRS Polish version was approved for all sites by the Ethics Committee of the Medical University of Silesia in Katowice (KNW/0022/KB/121/14).

Results

Baseline characteristics

The demographic characteristics of the Polish patients are set out in Table 1. The Polish dataset included 250 native Polish-speaking Parkinson's Disease patients with dyskinesia who were examined using the UDysRS. Table 2 sets out the distributions of answers to each question.

Cronbach's alpha index and correlation analysis

The overall raw and standardised Cronbach's coefficient alpha was 0.938 and 0.94, respectively, indicating that the Polish UDysRS was reliable. Table 3 sets out the correlation between each question and the total score. Examination of the correlation of individual items to the total score revealed lower correlations for items 14 and 15.

Cognitive pretesting

Three examiners and 10 patients with Parkinson's Disease were interviewed using a structured cognitive pretesting manual. On the first round of cognitive pretesting, a few minor issues were identified for the instructions for the raters and for one definition provided to the patients. Slight modifications were made to the translation based on this feedback, and a second round of cognitive pretesting was requested with a new set of five patients. No problems were identified on the second round of testing by either patients or raters, so the translated scale was approved as the Official Working Document of the Polish UDysRS for testing in a larger group of patients with PD.

Primary analysis: Confirmatory Factor Analysis (CFA)

M plus performs listwise deletion of cases with any missing data. That is, any case with one or more missing data points is omitted entirely from analyses. Thus, the sample size in factor analysis is 250. The Comparative Fit Index (CFI), compared to the Reference Standard factor structure, was 0.954, and root mean square error of approximation was 0.115. Our pre-specified criterion was a CFI of 0.90 or greater.

Hence, we concluded that the pre-specified Reference Standard factor structure was confirmed in the Polish dataset.

Secondary analysis: Exploratory Factor Analysis (EFA)

Table 4 shows the results of Exploratory Factor Analysis for all patients of the Reference Standard and Polish UDysRS without the items for *Time Spent with On Dyskinesia,* and *Time Spent with Off Dystonia*. The scree plots are given in Figure 1. From these we extracted three factors. The factor structure of Polish UDysRS is quite consistent with that of Reference Standard UDysRS.

EFA analysis for the Polish UDysRS dataset differed from the EFA of the Reference Standard dataset in some areas. Two of the 24 items loaded on different factors in the two scales. In contrast to the Reference Standard UDysRS, *Exciting situations* loaded in the Polish version on factor 3, instead of factor 1. *Dystonia pain severity* loaded on factor 2 in the Polish version, and on factor 3 in the Reference Standard. *Ambulation* did not load on any of the factors in the Polish version, but originally loaded on factor 2 in the Reference Standard. *Communication*

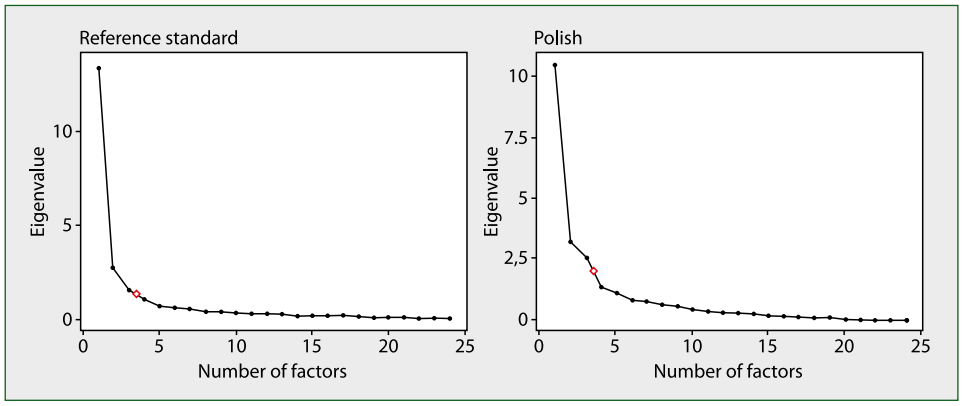

Figure 1. Scree plots for reference standard and Polish exploratory factor analyses

Table 1. Demographic characteristics of study population

Number of PD patients		Male*		Age** (years)		PD duration*** (years)		DID duration**** (years)	
	N	N	%	Mean	SD	Mean	SD	Mean	SD
Reference standard	253	122	48.2	69.2	10.5	12.5	6.8	4.9	4.6
Polish	250	135	59	74.6	13.9	12.1	6	4.2	3

*Data available for 229, **221, ***180, and ****171 subjects in Polish PD population; PD — Parkinson's Disease; DID — drug induced dyskinesia; SD — standard deviation

Table 2. Distribution of UDysRS responses

Time dyskinesia	Reference standard		Polish			Reference standard		Polish	
	Freq	Percent	Freq	Percent	Speech	Freq	Percent	Freq	Percent
0	45	17.79	5	2	0	92	36.36	105	42
1	56	22.13	101	40.4	1	99	39.13	81	32.4
2	55	21.74	83	33.2	2	52	20.55	52	20.8
3	37	14.62	43	17.2	3	8	3.16	9	3.6
4	60	23.72	18	7.2	4	2	0.79	3	1.2
Total	253	100	250	100	Total	253	100	250	100
Chewing /swallowing	**Freq**	**Percent**	**Freq**	**Percent**	**Eating tasks**	**Freq**	**Percent**	**Freq**	**Percent**
0	117	46.25	118	47.2	0	84	33.2	73	29.2
1	84	33.2	88	35.2	1	83	32.81	81	32.4
2	37	14.62	32	12.8	2	65	25.69	56	22.4
3	14	5.53	10	4	3	18	7.11	26	10.4
4	1	0.4	2	0.8	4	3	1.19	14	5.6
Total	253	100	250	100	Total	253	100	250	100
Dressing	**Freq**	**Percent**	**Freq**	**Percent**	**Hygiene**	**Freq**	**Percent**	**Freq**	**Percent**
0	73	28.85	52	20.8	0	86	33.99	57	22.8
1	71	28.06	88	35.2	1	81	32.02	88	35.2
2	74	29.25	67	26.8	2	59	23.32	68	27.2
3	25	9.88	32	12.8	3	20	7.91	24	9.6
4	8	3.16	11	4.4	4	7	2.77	13	5.2
Total	251	99.21	250	100	Total	253	100	250	100
Handwriting	**Freq**	**Percent**	**Freq**	**Percent**	**Doing hobbies/ /activities**	**Freq**	**Percent**	**Freq**	**Percent**
0	80	31.62	56	22.4	0	75	29.64	66	26.4
1	65	25.69	74	29.6	1	80	31.62	74	29.6
2	59	23.32	61	24.4	2	57	22.53	70	28
3	38	15.02	42	16.8	3	29	11.46	28	11.2
4	8	3.16	17	6.8	4	12	4.74	12	4.8
Total	250	98.81	250	100	Total	253	100	250	100
Walking/balance	**Freq**	**Percent**	**Freq**	**Percent**	**Public/social**	**Freq**	**Percent**	**Freq**	**Percent**
0	69	27.27	46	18.4	0	67	26.48	21	8.4
1	74	29.25	73	29.2	1	84	33.2	54	21.6
2	68	26.88	80	32	2	62	24.51	88	35.2
3	31	12.25	40	16	3	34	13.44	67	26.8
4	11	4.35	11	4.4	4	6	2.37	20	8
Total	253	100	250	100	Total	253	100	250	100
Exciting situations	**Freq**	**Percent**	**Freq**	**Percent**	**Time off dystonia**	**Freq**	**Percent**	**Freq**	**Percent**
0	72	28.46	22	8.8	0	125	49.41	78	31.2
1	83	32.81	59	23.6	1	45	17.79	67	26.8
2	59	23.32	82	32.8	2	27	10.67	55	22
3	36	14.23	64	25.6	3	15	5.93	25	10
4	2	0.79	23	9.2	4	40	15.81	25	10
Total	252	99.6	250	100	Total	252	99.6	250	100

→

Table 2 cont. Distribution of UDysRS responses

Dystonia effects on activities	Reference standard		Polish			Reference standard		Polish	
	Freq	Percent	Freq	Percent	Effect of pain from dystonia	Freq	Percent	Freq	Percent
0	128	50.59	92	36.8	0	151	59.68	118	47.2
1	45	17.79	60	24	1	34	13.44	51	20.4
2	31	12.25	58	23.2	2	29	11.46	39	15.6
3	29	11.46	26	10.4	3	29	11.46	32	12.8
4	20	7.91	14	5.6	4	9	3.56	10	4
Total	253	100	250	100	Total	252	99.6	250	100
Dystonia pain severity	**Freq**	**Percent**	**Freq**	**Percent**	**Face**	**Freq**	**Percent**	**Freq**	**Percent**
0	147	58.1	111	44.4	0	122	48.22	134	53.6
1	21	8.3	52	20.8	1	73	28.85	51	20.4
2	41	16.21	44	17.6	2	48	18.97	43	17.2
3	37	14.62	35	14	3	9	3.56	14	5.6
4	6	2.37	8	3.2	4	1	0.4	8	3.2
Total	252	99.6	250	100	Total	253	100	250	100
Neck	**Freq**	**Percent**	**Freq**	**Percent**	**Right hand/ /arm/shoulder**	**Freq**	**Percent**	**Freq**	**Percent**
0	109	43.08	100	40	0	90	35.57	54	21.6
1	64	25.3	58	23.2	1	58	22.92	66	26.4
2	62	24.51	65	26	2	67	26.48	79	31.6
3	17	6.72	18	7.2	3	33	13.04	37	14.8
4	1	0.4	9	3.6	4	5	1.98	14	5.6
Total	253	100	250	100	Total	253	100	250	100
Left hand/arm/ /shoulder	**Freq**	**Percent**	**Freq**	**Percent**	**Trunk**	**Freq**	**Percent**	**Freq**	**Percent**
0	100	39.53	56	22.4	0	92	36.36	66	26.4
1	59	23.32	61	24.4	1	55	21.74	79	31.6
2	66	26.09	78	31.2	2	65	25.69	75	30
3	25	9.88	46	18.4	3	40	15.81	25	10
4	2	0.79	9	3.6	4	1	0.4	5	2
Total	252	99.6	250	100	Total	253	100	250	100
Right foot/leg/ /hip	**Freq**	**Percent**	**Freq**	**Percent**	**Left foot/leg/hip**	**Freq**	**Percent**	**Freq**	**Percent**
0	88	34.78	76	30.4	0	109	43.08	68	27.2
1	67	26.48	68	27.2	1	57	22.53	60	24
2	69	27.27	65	26	2	61	24.11	83	33.2
3	25	9.88	28	11.2	3	22	8.7	21	8.4
4	4	1.58	13	5.2	4	4	1.58	18	7.2
Total	253	100	250	100	Total	253	100	250	100
Communication	**Freq**	**Percent**	**Freq**	**Percent**	**Drinking**	**Freq**	**Percent**	**Freq**	**Percent**
0	72	28.46	114	45.6	0	81	32.02	70	28
1	129	50.99	89	35.6	1	109	43.08	88	35.2
2	44	17.39	38	15.2	2	50	19.76	56	22.4
3	7	2.77	8	3.2	3	11	4.35	22	8.8
4	1	0.4	1	0.4	4	2	0.79	14	5.6
Total	253	100	250	100	Total	253	100	250	100

→

Table 2 cont. Distribution of UDysRS responses

Dressing (objective)	Reference standard		Polish			Reference standard		Polish	
	Freq	Percent	Freq	Percent	Ambulation	Freq	Percent	Freq	Percent
0	59	23.32	64	25.6	0	54	21.34	35	14
1	76	30.04	71	28.4	1	99	39.13	86	34.4
2	80	31.62	67	26.8	2	69	27.27	81	32.4
3	28	11.07	30	12	3	29	11.46	36	14.4
4	10	3.95	18	7.2	4	2	0.79	12	4.8
Total	253	100	250	100	Total	253	100	250	100

Table 3. Item-to-total correlations and Cronbach's alpha with deleted items

Deleted variables	Cronbach Coefficient Alpha with Deleted Variable*			
	Raw variables		Standardised variables	
	Correlation** with total	Alpha	Correlation with total	Alpha
Q1	0.560	0.940	0.563	0.941
Q2	0.565	0.940	0.575	0.941
Q3	0.623	0.940	0.630	0.941
Q4	0.724	0.938	0.731	0.939
Q5	0.752	0.938	0.756	0.939
Q6	0.760	0.938	0.761	0.939
Q7	0.743	0.938	0.746	0.939
Q8	0.770	0.938	0.774	0.938
Q9	0.650	0.939	0.652	0.940
Q10	0.618	0.940	0.620	0.941
Q11	0.585	0.940	0.590	0.941
Q12	0.493	0.941	0.483	0.942
Q13	0.550	0.940	0.536	0.942
Q14	0.373	0.943	0.360	0.944
Q15	0.396	0.943	0.383	0.944
Q16	0.481	0.941	0.487	0.942
Q17	0.478	0.941	0.479	0.942
Q18	0.608	0.940	0.609	0.941
Q19	0.567	0.940	0.569	0.941
Q20	0.540	0.940	0.541	0.942
Q21	0.618	0.940	0.619	0.941
Q22	0.546	0.941	0.547	0.942
Q23	0.550	0.940	0.551	0.942
Q24	0.736	0.938	0.738	0.939
Q25	0.754	0.938	0.756	0.939
Q26	0.698	0.939	0.696	0.940

Cronbach coefficient alpha is a measure of squared correlation between observed scores and true scores
*What Cronbach coefficient alpha would be if that variable were deleted
**Correlation between individual item and sum of remaining items

Table 4. Exploratory Factor Analysis (EFA)

Factor	Item	Item factor loading	
		Reference standard (n = 246)	Polish (n = 250)
Factor 1	Speech	0.698	0.555
	Chewing/swallowing	0.749	0.822
	Eating	0.800	0.825
	Dressing	0.861	0.875
	Hygiene	0.825	0.773
	Handwriting	0.780	0.862
	Doing hobbies/activities	0.728	0.798
	Walking/balance	0.731	0.827
	Public/social	0.686	0.752
	Exciting situations	0.718	NA
	Right hand/arm/shoulder	0.412	NA
	Drinking	0.441	0.479
	Dressing (objective)	0.415	0.421
	Communication	NA	0.473
Factor 2	Chewing/swallowing	0.411	NA
	Walking/balance	0.401	NA
	Public/social	0.462	NA
	Face	0.717	0.638
	Neck	0.752	0.785
	Right hand/arm/shoulder	0.701	0.739
	Left hand/arm/shoulder	0.663	0.629
	Trunk	0.769	0.703
	Right foot/leg/hip	0.711	0.682
	Left foot/leg/hip	0.741	0.728
	Communication	0.775	0.704
	Drinking	0.755	0.756
	Dressing (objective)	0.739	0.662
	Ambulation	0.729	NA
	Dystonia pain severity	NA	0.591
Factor 3	Dystonia effects on activities	0.883	0.978
	Effect of pain from dystonia	0.971	0.966
	Dystonia pain severity	0.945	NA
	Exciting situations	NA	0.663

CFI = 0.942; RMSEA = 0.109; NA — implies that listed item did not load on factor indicated

loaded in factors 1 and 2 in the Polish version, but only in factor 2 in the Spanish version. Inversely, *Right hand/arm/shoulder* objective assessment of dyskinesia severity loaded on factors 1 and 2 in the Reference Standard, but only in factor 2 in the Polish version. Three items (*Chewing/swallowing, Walking/balance, Public/social*) loaded in factors 1 and 2 in the Reference Standard, but only in factor 1 in the Polish UDysRS version. Two items (*Drinking* and *Dressing*) loaded on more than one factor in both language versions.

Discussion

The Movement Disorders Society Rating Scales Programme leads the global translation effort of different assessment scales including the UDysRS. Currently, this programme includes 14 non-English validated editions of the UDysRS.

The original English version was clinimetrically evaluated to establish internal consistency and inter-rater reliability, but the small sample size of the English version precluded a comprehensive analysis of factor structure.

Because of this limitation, we could not compare the resultant structure from the present study with that of the original English version.

Therefore we instead compared our results to the Spanish version of the UDysRS. This was the first large-scale clinimetric analysis of this instrument, and is now recognised as the Reference Standard for UDysRS translations.

In agreement with the Reference Standard, the Polish version of the UDysRS demonstrated a clear factor structure, with three factors related to ON dyskinesia, OFF dystonia, and patient perceptions of the functional effects of dyskinesia. The overall factor structure of the Polish version was consistent with that of the Reference Standard. Exploratory factor analysis, where variability from sample to sample is expected, identified isolated, subtle item differences of factor structure between the Polish and the Reference Standard UDysRS.

We are aware that this study has some limitations related to potential sample selection bias.

The data comes from high reference neurology clinics specialising in movement disorders, and as such does not represent the general Polish PD patient population. However, this is a minor issue because neurologists at specialist centres are the most likely group to be using this scale for their research.

Conclusions and clinical implications

The Polish UDysRS was confirmed to share a common factor structure with the Reference Standard. Therefore, this version was designated to be the Official Polish version of the UDysRS, and will be available from the MDS website (https://www.movementdisorders.org/MDS-Files1/Education/Rating-Scales).

In order to establish the UDysRS as the international 'gold standard' tool for the clinical assessment of dyskinesia in advanced Parkinson's Disease, fully tested non-English translations must be available for worldwide research programmes.

As such, having a validated Polish version of the scale will provide opportunities for Polish centres to contribute data from Polish-speaking individuals in large multicentre studies and clinical trials evaluating dyskinesia in PD patients.

Moreover, having the previously published validation of Polish translation of the MDS-UPDRS, plus now the validated Polish UDysRS version, allows movement disorders specialists in Poland to be fully equipped with two scales important in the objective assessment of moderate and severe Parkinson's Disease.

We believe that these tools will be useful in everyday clinical practice, especially in hospitals, where advanced treatment options (DBS surgery and infusion therapies) are available.

Worldwide use of the same rating measures (in appropriate translations) enhances international communication and offers a common ground on which to study similarities and differences in disease manifestations, progression, and disabilities across cultures.

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Clinical features of neurological patients with coronavirus 2019: an observational study of one centre

Justyna Zielińska-Turek[1], Anna Jasińska[1], Jolanta Kołakowska[2], Joanna Szadurska[1], Dariusz A. Kosior[3, 4], Małgorzata Dorobek[1]

[1]Department of Neurology, Central Clinical Hospital of the Ministry of Internal Affairs and Administration, Warsaw, Poland
[2]Department of Cardiac Rehabilitation, Central Clinical Hospital of the Ministry of Internal Affairs and Administration, Warsaw, Poland
[3]Department of Cardiology and Hypertension, Central Clinical Hospital of the Ministry of Internal Affairs and Administration, Warsaw, Poland
[4]Faculty of Medicine, Collegium Medicum, Cardinal Stefan Wyszynski University, Warsaw, Poland

ABSTRACT

Background. Since the emergence of coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 (Severe acute respiratory syndrome coronavirus 2) in Wuhan, China, it has been extensively studied by many scientists. Susceptibility to SARS-CoV-2 infection is shown by people of all ages, especially those with different comorbidities. Our goal was to describe the clinical characteristics, treatment, course, and outcome of COVID-19 in patients with pre-existing neurological disorders.

Materials and methods. We retrospectively studied 70 patients with COVID-19 and previous neurological diseases who were treated in the Central Clinical Hospital of the Ministry of the Interior and Administration from 16 March to 15 June 2020. Demographic data, symptoms, image data, laboratory results, treatment methods and results, clinical signs and symptoms of patients hospitalised due to CNS diseases with COVID-19 were collected.

Results. The average age of hospitalised patients was 72, and the majority (63%) were women (44/70). The most common neurological disease was dementia, which was present in almost a third of patients (30.76%), followed by ischaemic stroke (24.61%). Chest imaging showed the presence of interstitial changes in 47% (33) of patients. Laboratory tests revealed increased total blood cells, increased levels of C-reactive protein, procalcitonin, D-dimers, liver indicator markers and IL-6 in the most severely affected patients. The treatment of patients was focused on monitoring their clinical condition, and supporting respiratory inefficiency with passive oxygen therapy and mechanical ventilation. According to the guidelines of the Hospital Therapeutic Committee, pharmacological treatment (Arechin®, Kaletra®) was introduced in cases without contraindications. In patients with moderate COVID-19, antimalarial or antiviral agents were applied (78%). 30% of our observed patients died during the hospitalisation.

Conclusions. We studied a select group of patients (elderly, with comorbidities, and moderate or severe COVID-19 course). Pre-existing neurological disorders were additionally associated with a poorer prognosis and a high fatality rate (30%). Dementia and CNS vascular disorder were the most frequent pre-existing neurological conditions. The neurological symptoms of COVID-19 were various. We observed impaired consciousness, dizziness, headache, nausea, myalgia, psychomotor agitation and slowness, delirium, and psychoses. Further analysis is needed to elucidate the incidence of COVID-19 neurological complications.

Key words: coronavirus, COVID-19, SARS-CoV-2, dementia, stroke

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Address for correspondence: Justyna Zielińska-Turek, Department of Neurology, Central Clinical Hospital of the Ministry of Internal Affairs and Administration, Wołoska 137 Str., 02-507 Warsaw, Poland, e-mail: jzturek@gmail.com

Introduction

Coronavirus disease 2019 (COVID-19) led to a global pandemic within just a few months of the first outbreak in humans in the city of Wuhan, China in December 2019 [1].

As yet, no concise recommendations based on randomised clinical trials for the management of patients with COVID-19 have been proposed. Therefore the procedure for infected patients remains a challenge. Patients with COVID-19 may present multi-organ insufficiency, including central nervous system involvement. The treatment is complicated by the fact that patients, especially the elderly, may have multiple comorbidities.

The goal of this retrospective study was to present the clinical characteristics, course and outcome of patients with both COVID-19 and coexisting neurological problems.

Materials and methods

Patients

We analysed 70 patients with neurological disorders and diagnosed COVID-19. The patients were hospitalised in the Department of Neurology between 16 March and 15 June 2020 in the Central Clinical Hospital of the Ministry of the Interior and Administration in Warsaw, Poland, a tertiary multispecialty hospital. This hospital was declared a designated infectious disease centre as part of the general healthcare system reorganisation programme in response to the pandemic.

Patients were admitted either directly from the emergency department, outpatient clinics, or external hospitals. The reasons for admission were moderate or severe COVID-19 or SARS-CoV-2-positive patients with other severe concomitant acute or chronic diseases. Infections were confirmed using real time PCR in all patients prior to admission by detecting the genetic material of the SARS-CoV-2 virus in a nasopharyngeal swab. The Modified Early Warning Scale (MEWS) was used to assess the clinical status of the COVID-19 patients (in particular, monitoring of respiratory function), and the widely used Glasgow Coma Scale (GCS) was used to monitor the patient's state of consciousness (Tab. 1).

Collected data

Demographic data, clinical features, infection exposure history, estimated incubation period, signs and symptoms of the disease, computed tomography (CT) or X-ray results, complications, treatment, clinical results and the laboratory results of each patient were obtained from the electronic system of the medical documentation of the Central Clinical Hospital of the Ministry of the Interior and Administration in Warsaw. The date of disease onset, COVID-19 smear, hospital admission, duration of illness, and family history of exposure were recorded. Each patient on admission, and before discharge, had a laboratory test including blood count, serum biochemistry (C-reactive protein, procalcitonin, aspartate aminotransferase, alanine aminotransferase, creatine kinase, creatinine and D-dimer), and IL-6. Patients who required monitoring of laboratory parameters due to deterioration of their clinical status had the necessary procedures performed as appropriate.

Ethics

This study was approved by the Local Ethics Committee of the Central Clinical Hospital of the Ministry of the Interior and Administration (CSK-05/06/2020).

Results

Demographic characteristics of COVID-19 patients

All patients were hospitalised in the CSK MSWiA in Warsaw following its transformation into a COVID-19-dedicated hospital. We included 70 patients in the study group. The average age was 72. The majority of patients were women (65.4%). Fourteen patients were residents of nursing homes. 53 patients were initially hospitalised in other mainly neurological departments outside the CSK MSWiA or were transferred directly from emergency wards after the diagnosis of COVID-19. All these patients had had close contact with confirmed or suspected COVID-19 patients. Only three patients were admitted directly from their homes: their transmission route was unclear. The duration of the disease in all patients was 18 days on average (time from positive RT PCR to obtaining the first negative RT PCR). Four patients had a significantly

Table 1. Modified early warning score (MEWS)

Score	3	2	1	0	1	2	3
Systolic blood pressure	< 70	71–80	81–100	101–199			
Heart rate		< 40	41–50	51–100	101–110	111–129	> 130
Temperature		< 35		35–38.4		> 38.5	
Respiratory rate		< 9		9–14	15–20	21–29	> 30
Level of consciousness				Alert	Voice	Pain	Unresponsive

Contact physician when MEWS score > 4, if oxygen saturation drops < 90% with oxygen treatment, and if you are concerned about the patient's condition

Table 2. Demographics, baseline and symptoms of patients with coronavirus disease 2019 (COVID-19)

Characteristics	
Age (years)	71.68
Sex (M:F)	26:44
Disease duration (days)	18
Symptoms	
Fever, n (%)	32 (45.71%)
Cough	14 (20%)
Fatigue/myalgia	15 (21.42%)
Headache	12 (17.14%)
Expectoration	3 (4.28%)
Nausea/vomiting	7 (10%)
Diarrhoea	6 (8.57%)
Constipation	2 (2.85%)
Dizziness	15 (38.57%)
Dyspnoea	27 (50%)
Chest CT/X-ray	25/45
Unilateral pneumonia	10 (14.28%)
Bilateral pneumonia	27 (40.0%)
Death, n (%)	21 (30.0%)

longer elimination period for coronavirus RNA compared to the others (34, 35, 55 and 66 days). Twenty-one of the hospitalisations were fatal, which gave a mortality rate of 30%.

Clinical characteristics and chest imaging results

In our patients, the most common symptom was fever (59.6%), followed by shortness of breath (50%), cough (25%), muscle pain (19.2%), dizziness (19.2%), headache (17.14%), vomiting (13.5%), diarrhoea (11.5%), and constipation (2%) (Tab. 2). COVID-characteristic abnormalities in the chest tomography (CT) or X-ray (Tab. 2) were observed in most patients. Eight patients had unilateral pneumonia, and 25 (36%) had bilateral pneumonia. Imaging changes included interstitial compaction, 'frosted glass' or 'honeycomb' areas, and exudate.

Sepsis occurred in four patients, and complications of treatment with features of acute pancreatitis was observed in three patients treated with ritonavir/lopinavir (Kaletra®). Among all the patients, we noted four cases of pulmonary embolism. After treatment with low-molecular-weight heparin, the embolic material completely resorbed, which was confirmed by CT angiography of the chest.

Evaluation of laboratory tests

All patients hospitalised in our centre had SARS-CoV-2 infection confirmed by RT-PCR. We noted increased levels of C-reactive protein (CRP), increased alanine aminotransferase (ALT) and asparagine aminotransferase (AST) (Tab. 3). Thirty-two patients had increased D-dimers levels. IL-6 was elevated in 18 patients. All patients who died had significantly

Table 3. Laboratory tests of patients with coronavirus disease 2019 (COVID-19)

Variables	Value
Leucocytes (normal range 4–10 x 10^3 /µL)	9.07 (4.07–28.06)
Thrombocyte (normal range 130–350 x 10^3/µL)	222.25 (98–374)
Haemoglobin (normal range 14–18 g/dL men, 12–16 g/dL women)	12.84 (7–18.5)
C-reactive protein (normal range < 10 mg/L)	52.62 (0.4–191.4)
Aspartate aminotransferase (normal range 5–50 U/L)	39.1 (13–110)
Alanine aminotransferase (normal range 5–50 U/L)	34.1 (8–159)
Creatine kinase (normal range 24–195 IU/L)	293.8 (14–5,089)
Creatine (normal range 0.6–1.3 mg/dL)	1.13 (0.39–8.25)
D-dimer (normal range < 500 mg/L)	2,619 (149–31,128)
IL-6 (normal range < 7 pg/mL)	60.22 (2.02–369)
Procalcitonin (normal range < 15 ng//mL)	0.41 (0.02–4.26)

Table 4. Treatment of neurological patients with coronavirus disease 2019 (COVID-19)

Variables	No (%)
Oxygen therapy	40 (61.53)
Mechanical ventilation	4 (5.71)
Antibiotic treatment	
— Azithromycin	30 (42.85)
— Ceftriaxone	31 (44.28)
Chloroquine	52 (74.28)
Antiviral treatment (lopinavir + ritonavir)	9 (12.85)

higher mean inflammatory parameters in relation to the group of convalescents: CRP (82.50 *vs.* 49.86 mg/L), PCT (1.16 *vs.* 0.48 ng/mL), and IL-6 (184.44 *vs.* 72.4 pg/mL).

Treatment and results

Treatment methods during the SARS-CoV-2 pandemic have changed over time due to the accumulated experience of many researchers worldwide. Initially, all patients who had no contraindications received chloroquine. Patients with pneumonia were additionally administered ceftriaxone and/or azithromycin. Hydrocortisone was the next treatment option given to patients with a moderate or severe course. Patients with inadequate oxygen saturation were administered low and slow flow oxygen supplementation. COVID-19 treatment continued to focus on a symptomatic approach and respiratory support (Tab. 4). Of the 70 patients, 40 received high-flow oxygen therapy, while four underwent mechanical ventilation after being transferred to the Intensive Care Unit. Two of these four died.

Most patients (74.28%) received chloroquine. If signs of pneumonia appeared, azithromycin (30/70) and/or ceftriaxone (31/40) were added. After chloroquine treatment failure, nine

Table 5. Common neurological diseases and co-morbidities of patients with coronavirus disease 2019 (COVID-19)

Neurological disease	No (%)	Other accompanying disease	No (%)
Dementia	22 (31.42)	Arterial hypertension	36 (51.42)
Ischaemic stroke	17 (24.28)	Tumour	18 (25.71)
Ischaemic stroke – subacute phase	11 (15.71)	Tumour – mild	2 (2.85)
Ischaemic stroke – chronic phase	6 (9.23)	Tumour – malignant	16 (22.85)
Malignant tumour CNS	9 (12.85)	Diabetes mellitus	13 (18.57)
Intracerebral haemorrhage	5 (7.14)	Heart failure	13 (18.57)
Craniocerebral trauma	7 (10)	Atrial fibrillation	11 (15.71)
Epilepsy	4 (5.71)	Dyslipidaemia	10 (14.28)
Subarachnoid haemorrhage	3 (4.28)	Renal failure	9 (13.84)
Multiple sclerosis	2 (2.85)	Chronic obstructive pulmonary disease	5 (7.14)
Polyneuropathy	2 (2.85)	Hypothyroidism	5 (7.14)
Myasthenia	1 (1.42)	Prostatic hyperplasia	5 (7.14)
Parkinson's Disease	2 (2.85)	Bronchial asthma	4 (5.71)
Essential tremor	1 (1.42)		

patients received lopinavir in combination with ritonavir. Seven of these nine patients died, and three demonstrated early complications in the form of biochemical features of pancreatitis. Intravenous glucocorticoids were instituted as adjunctive therapy in brain tumours; other pharmaceuticals were used according to the patient's condition/other comorbidities.

ECG assessment – QTc

We estimated QTc interval in ECG at the beginning of hospitalisation. Prolongation of the QTc interval was observed in 21.4% of patients before introducing chloroquine and/or azithromycin. This prolongation was borderline or connected with a bundle branch block (mainly RBBB) or the presence of a stimulator (QRS > 120 ms), so we did not postpone therapy. During our observation, we noticed a prolongation of QTc interval in all of the previously prolonged QTc cases. In some cases, we stopped therapy with medicines that influenced the duration of the QTc interval. In some, we estimated the QTc interval every day and continued therapy.

Only in 7.1% of patients with correct QTc interval before treatment did we observe a prolongation of the QTc interval during such therapy. The maximal QTc interval in these cases was 480 ms.

We did not observe any serious ventricular arrythmias including torsade de pointes.

Death analysis

In relation to the entire study population, the average age of the patients with a fatal outcome was significantly higher (71.68 *vs.* 81.86; p = 0.012), but the group was still dominated by women. Almost half of the patients (10/21) who died suffered from severe dementia. Six patients were hospitalised with concomitant ischaemic stroke. All of them were admitted outside the thrombolytic/thrombectomy window. The other neurological conditions associated with COVID-19 were: multiple sclerosis (1/21), essential tremor (1/21), and malignant tumour with CNS metastases (3/21). A high percentage of deaths (30%) was associated with comorbidities other than neurological diseases. These comorbidities significantly influenced the course of SARS-CoV-2 infection. Eleven out 21 patients had atrial fibrillation, 6/21 patients had type 2 diabetes, five patients suffered from chronic kidney disease stage 4; one was in stage 5 on dialysis. Hypertension was present in all patients with a fatal outcome.

All patients who died had significantly increased mean inflammatory parameters. Compared to the whole studied group, the following parameters were increased: CRP (80.49 *vs.* 52.62 mg/L), PCT (0.66 *vs.* 0.41 ng/mL), and IL-6 (141.24 *vs.* 60.22 g/mL). Coagulation parameters were also elevated (mean D-dimer 4,367 *vs.* 2,619 µ/L) with normal mean platelet values (215.57 *vs.* 222.25 thousand/µL).

50% of patients whose hospitalisation ended with death had bilateral pneumonia and/or fever (11 *vs.* 22 and 11 *vs.* 22). The abovementioned neurological and non-neurological comorbidities, advanced age, and coexisting SARS-CoV-2 infection all contributed to the high percentage of deaths.

Neurological diseases in patients with COVID-19

All patients hospitalised in our Department were admitted due to SARS-CoV-2 infection and co-existing neurological disease. Fifteen patients admitted to our centre were initially asymptomatic for COVID-19, of whom five developed symptoms of pneumonia.

Dementia was the most common disorder, present in 30.61% of patients (Tab. 5). Patients with dementia were older in relation to the whole study population (78.61 *vs.* 71.68), and all of them had a number of comorbidities that negatively influenced the prognosis.

Fever (12/22), myalgia (5/22), and headache (3/22) were the most common symptoms that accompanied SARS-CoV-2 infection in the dementia group. Fifteen patients developed pneumonia accompanied by dyspnoea.

Ischaemic stroke was the second most frequent disease (16 patients with SARS-CoV-2 infection) (Tab. 5). Ten of them were admitted to the hospital in a subacute phase. None of our patients with ischaemic stroke were admitted to our centre in the therapeutic window, while four patients were transferred after thrombolysis at other centres.

Ischaemic stroke was mainly caused by thrombosis/embolism in intracerebral arteries, in 17 patients. In nine patients, there was coexistence with hypertension, dyslipidaemia, type 2 diabetes, and current smoking. Cardiogenic mechanism of stroke could be suspected in 6/17 patients (arrhythmias, atrial fibrillation). The remaining patients had end-stage renal failure and disseminated neoplastic disease.

The above data may suggest that the coexistence of SARS--CoV-2 infection and stroke was rather accidental, and that infection was not the cause of ischaemic stroke. D-dimer is an important parameter in stroke and COVID-19. D-dimer levels were five times their normal value in patients with both stroke and COVID-19. 7/17 ischaemic stroke patients had fully symptomatic pneumonia which necessitated oxygen supplementation. In six patients, SARS-CoV-2 infection was asymptomatic, and in the remaining patients headache, fever and cough were present.

In one patient with epilepsy, the infection caused cluster seizures. The remaining three patients with chronic epilepsy did not present any seizures during hospitalisation.

Less frequent cases included cerebral haemorrhagic stroke, CNS malignant tumour, and craniocerebral trauma (Tab. 3).

We have not observed any significant impact (e.g. worsening of symptoms) of SARS-CoV-2 infection on the coexisting neurological disorder. The described neurological symptoms resulting from headache, nausea, dizziness and myalgia are related to all viral infections, just as with COVID-19. Nevertheless, in our studied group, these symptoms were mainly present in patients without neurological diseases.

Discussion

Analysis of our patients confirmed the neurological complications of COVID-19 that have been documented in the literature to date [2]. They may involve the central and peripheral nervous systems. We observed ischaemic strokes, haemorrhages and subarachnoid haemorrhages, and epileptic seizures. These findings underline the importance of close neurological monitoring of patients.

The patients with COVID-19 were most commonly hospitalised due to worsening of cognitive function associated with dementia. The severity of these symptoms ranged from headache, dizziness, psychomotor slowness to impaired consciousness. Signs of focal, acute central nervous system involvement was the second most common reason for admission. signs of acute cerebrovascular disease, impaired consciousness to dizziness and headache. Direct infection of CNS (meningitis and encephalitis) with SARS-CoV-2 has been the least frequently reported complication so far. We have not observed direct infection of the central nervous system, which may confirm that this phenomenon is extremely rare [3–5]. However, in the presence of impaired consciousness in the course of e.g. hypocapnia, signs of CNS involvement can be easily missed. These complications require active research and further observation in a larger study group, cerebrospinal fluid assessment and neuroimaging examinations.

We observed that fever was relatively frequent in our patients (45%), while it was present in 20% of patients in other centres [7]. Gastrointestinal symptoms such as nausea and watery diarrhoea were relatively rare and did not exceed 10% of the hospitalised patients. These findings are comparable to other studies [7].

Elevated levels of D-dimers, interleukin-6, ferritin, and lactate dehydrogenase have been documented as part of a cytokine storm in the death rate from COVID-19 [8]. We observed a correlation between the level of the above-mentioned pro-inflammatory markers and the severity of the course of COVID-19. We also noted a direct relationship between the increase of these markers and death. This indicates that the parameters we tested may be considered biomarkers of COVID-19. Similar findings have been reported previously by others [8].

Complications of dementia syndromes

Aggravation of dementia symptoms could be expected. The acute course of COVID-19 may cause complications in the nervous system such as increased cognitive dysfunction, psychosis, psychomotor agitation, depression, and anxiety. Patients with dementia constituted 30% of the studied group. These patients were of advanced age. Considering the severity of the basic disease, COVID-19, and the fact that these patients usually have many comorbidities, this explains the severity of consciousness disorders and delirium [9]. A study conducted by French scientists identified the most common neurological symptoms associated with COVID-19: impairment disturbances of consciousness in 73% of patients, sleep disturbances after discontinuation of sedatives (41%), disorientation (32%), and agitation (9%) [10]. We observed psychomotor agitation only in two patients (2.85%), and wakefulness disturbances after discontinuation of sedatives in approximately 20% of patients.

According to the study of the French ICU, 84% of patients with COVID-19 had abnormalities in neurological examination [11]. Additionally, 15% of patients leaving this department presented symptoms of executive function disorder (concentration and decision-making disturbances, difficulty in controlling behaviour) [11].

Cerebrovascular complications

Cerebrovascular symptoms were much more common in patients with severe SARS-COV-2 infection. They manifested as ischaemic or haemorrhagic stroke. Mao et al. reported that 5.7% of patients with severe COVID-19 developed acute cerebrovascular disease that usually manifested as ischaemic stroke, less commonly as haemorrhagic stroke. [12]. That was also confirmed in our study. Currently, it is believed that the hyperactivation of inflammatory factors is the main cause of clinical deterioration. Hyperactivated neutrophils and macrophages are the source of cytokine storm, which is considered an unfavourable prognostic factor in the disease course [13].

In our analysis, ischaemic stroke was the second most common neurological manifestation, occurring in 15.71% of patients. Four patients underwent thrombolysis in other centres. In the publication by Lodigiani et al., 21% of patients experienced thromboembolic events, including venous thromboembolism, ischaemic stroke, and acute coronary syndrome [14]. The pathomechanism of hypercoagulability in COVID-19 is not entirely understood, but it is believed that an increase of D-dimers may be the cause. In an Italian population of COVID-19 patients with ischaemic stroke, increased levels of D-dimers were noted in 80% of patients. [14]. Similarly, in our group of patients with COVID-19 and stroke, we recorded increased D-dimer in 78% of cases. In addition, as mentioned earlier, the average values of D-dimers in our COVID-19 patients with ischaemic stroke exceeded the norm by up to five times. These values are much higher than those of stroke patients without SARS-CoV-2 infection, and this is believed to be the result of the cytokine storm or hypercoagulable state that occurs in patients with severe COVID-19 [15].

Severe pneumonia in COVID-19 often leads to sepsis-induced hypercoagulability, as evidenced by increased intravascular activation of platelets, increased fibrinogen, and mild prolongation of PT and APTT [16]. Moreover, it is suspected that transient production of antiphospholipid antibodies may play an important role in this mechanism, which is confirmed in the study by Harzallah et al. [17], where almost 45% of patients with confirmed or suspected SARS-CoV-2 infection tested positive for lupus anticoagulants, and five patients had antibodies against cardiolipin or anti-β2-glycoprotein I [17]. In another study by Zhang et al., antiphospholipid antibodies were found in three COVID-19 patients, all of whom had suffered ischaemic strokes in the past [18].

All ischaemic stroke patients hospitalised in our department had multiple comorbidities and potential vascular risk factors, which could result in an unfavourable prognosis, even without coronavirus disease.

Neuromuscular complications

A significant number of patients with neuromuscular diseases are severely physically disabled and may have symptoms of heart, circulatory and/or breathing insufficiency. The course of COVID-19 in these patients may be severe [19].

It has been reported that previously identified human coronaviruses [SARS-CoV-1 and MERS] were associated with Guillain-Barre syndrome [20], but we did not observe acute polyneuropathy.

Among our patients with previously diagnosed neuromuscular diseases (including myasthenia gravis, polyneuropathy), we did not see an exacerbation of the underlying disease resulting from infection. Moreover, none of the patients had respiratory insufficiency or cardiac dysfunction.

Neuromuscular complications due to damage in the course of the applied pharmacotherapy has been already identified [12, 21]. Skeletal muscle injury was defined as muscle pain, elevated serum creatine kinase (CK) (normal value < 170 U/L), ALT, AST, myoglobin. In our research, such complications occurred in 14 patients, but these were only mild and resolved spontaneously.

Epilepsy complications

Four COVID-19 patients in our study were admitted due to epileptic seizures, and one had a complication in the form of cluster seizures. Others had single seizures with good response to pharmacotherapy. According to the publication of Lu et al., in which the authors evaluated 304 COVID-19 patients, none of their patients had symptomatic seizures or status epilepticus [22]. Due to the fact that we still have limited knowledge about the impact of SARS-CoV-2 on epilepsy, and because of polypharmacy, these patients may require increased vigilance and more frequent EEG tests or periodic continuous monitoring in selected cases [23].

Conclusions

We had a selected group of patients. They were elderly, often with comorbidities and moderate or severe COVID-19 course. Additionally, coexisting neurological diseases also significantly contributed to the course of the disease, causing a high fatality rate (30%). In this studied group, dementia and CNS vascular disorders were the most frequent pre-existing neurological conditions. Increased inflammatory parameters were directly associated with more severe course of COVID-19. This may be due to a direct cytopathic effect of the virus, inflammatory response, and/or hypercoagulable state.

Neurological symptoms of COVID-19 are not uncommon. We observed impaired consciousness, dizziness, headache, nausea, myalgia, psychomotor agitation and slowness, delirium, and psychoses. We did not observe direct CNS involvement (encephalitis, encephalopathy), which is increasingly being reported in the literature. Further analysis is needed to elucidate the incidence of COVID-19's neurological complications.

Conflict of interest: *The authors declare that they have no competing interests. The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest*
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Utility of the Polestar N30 low-field MRI system for resecting non-enhancing intra-axial brain lesions

Lior Ungar*, Zion Zibly*, Anton Wohl, Ran Harel, Moshe Hadani, Moshe Attia, Roberto Spiegelmann, Zeev Feldman, Jacob Zaubermann, Nachshon Knoller, Zvi R. Cohen

Department of Neurosurgery, Sheba Medical Centre, Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel

ABSTRACT

Background. To determine the utility of an intraoperative magnetic resonance imaging (iMRI) system, the Polestar N30, for enhancing the resection control of non-enhancing intra-axial brain lesions.

Materials and methods. Seventy-three patients (60 males [83.3%], mean age 37 years) with intra-axial brain lesions underwent resection at Sheba Medical Centre using the Polestar between February 2012 and the end of August 2018. Demographic and imaging data were retrospectively analysed. Thirty-five patients had a non-enhancing lesion (48%).

Results. Complete resection was planned for 60/73 cases after preoperative imaging. Complete resection was achieved in 59/60 (98.3%) cases. After iMRI, additional resection was performed in 24/73 (32.8%) cases, and complete resection was performed in 17/60 (28.8%) cases in which a complete resection was intended. In 6/13 (46%) patients for whom incomplete resection was intended, further resection was performed. The extent of resection was extended mainly for non-enhancing lesions: 16/35 (46%) as opposed to only 8/38 (21%) for enhancing lesions. Further resection was not significantly associated with sex, age, intended resection, recurrence, or affected side. Univariate analysis revealed non-eloquent area, intended complete resection, and enhancing lesions to be predictive factors for complete resection, and non-enhancing lesions and scan time to be predictive factors for an extended resection. Non-enhancement was the only independent factor for extended resection.

Conclusions. The Polestar N30 is useful for evaluating residual non-enhancing intra-axial brain lesions and achieving maximal resection.

Key words: glioma, image guided surgery, MRI, surgical management

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Introduction

The Polestar system (Medtronic, Louisville, CO, USA) is a low-field (0.15 Tesla) intraoperative magnetic resonance imaging (iMRI) system, introduced in 2001 by our group at the Sheba Medical Centre in Tel-Aviv [1]. This system comprises an MRI scanner integrated with an optical tracking system. The system is installed in a conventional radiofrequency-shielded operating room. When the scanner is placed under the operating room table, the magnetic field strength in the surgical field is low, enabling the use of standard surgical equipment.

From 1999 to 2018, a total of 236 patients with intra-axial brain lesions were operated on using three generations of the Polestar iMRI (N10, N20, and N30).

In our previous experience including a cohort of 163 patients operated on between 1999 and 2012 [2], we concluded that non-enhancing lesions were the only independent variable that predicted further resection using the iMRI system. As a result of that study, we changed our policy and almost half of the patients operated on between February 2012 and August 2018 had non-enhancing brain lesions, compared to only one third of the patients in the previous cohort.

Address for correspondence: Zvi R. Cohen, Department of Neurosurgery, Sheba Medical Centre, Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel, e-mail: zvi.cohen@sheba.health.gov.il

*These authors contributed equally to this study

Table 1. Pathology characteristics

Pathology	Number of cases n = 73	Non enhancing n = 35	Enhancing n = 38
AA WHO III	8 (11)	6 (17.1)	2 (5.3)
AO WHO III	12 (16.4)	4 (11.4)	8 (21.1)
Cavernoma	3 (4.1)	0 (0)	3 (7.9)
Demyelinative	1 (1.4)	0 (0)	1 (2.6)
Enhancing glial tumor WHO II	1 (1.4)	0 (0)	1 (2.6)
Ependymoma WHO II	1 (1.4)	0 (0.)	1 (2.6)
Ependymoma WHO III	1 (1.4)	0 (0.)	1 (2.6)
Ganglioglioma WHO I	1 (1.4)	0 (0)	1 (2.6)
GBM WHO IV	5 (6.8)	0 (0)	5 (13.2)
Glioneuronal WHO I	1 (1.4)	0 (0.)	1 (2.6)
Gray matter heterotopia	1 (1.4)	1 (2.9)	0 (0)
HGG WHO III	4 (5.5)	2 (5.7)	2 (5.3)
JPA WHO I	6 (8.2)	0 (0)	6 (15.8)
LGA WHO II	10 (13.7)	10 (28.6)	0 (0)
LGO WHO II	12 (16.4)	11 (31.4)	1 (2.6)
MET	1 (1.4)	0 (0)	1 (2.6)
Neurocytoma WHO I	1 (1.4)	0 (0)	1 (2.6)
PNET WHO IV	1 (1.4)	0 (0)	1 (2.6)
PXA WHO I	2 (2.7)	0 (0)	2 (5.3)
Sub Ependymoma WHO I	1 (1.4)	1 (2.9)	0 (0)
*Grouping pathology			
HGG WHO III–IV	30 (41)	12 (34)	18 (47)
Miscellaneous	21 (29)	2 (6)	19 (50)
LGG WHO II	22 (30)	21 (60)	1 (3) $p < 0.001$

*Grouping pathology: $p < 0.001$; HGG WHO III–IV: AA, AO, Ependymoma III, GBM, HGG;
Miscellaneous: Cavernoma, Demyelinative, Enhncing, Ependymoma II, Ganglioglioma, Glioneuronal I, Gray matter., JPA, MET, Neurocytoma II, PNET, PXA, Subependymoma; LGG WHO II: LGO, LGA

In the current cohort of 73 patients using the third generation Polestar N30, we operated on very few patients with metastasis, and more often on patients with low-grade glioma than on patients with high-grade glioma. In addition, 12/30 patients with a high-grade glioma had non-enhancing lesions (Tab. 1).

For the purpose of the current analysis, our goal was to compare the impact of iMRI for the surgical strategy and course of brain tumour resection in different types of lesions including non-enhancing and enhancing ones.

The survival benefits of extensive resection in patients with high-grade glioma are well established [3–8], whereas a limited number of studies have reported the survival benefits of extensive resection in patients with low-grade gliomas [9–11] A review of the current literature supporting safe, maximal resection for gliomas was recently provided by D'Amico et al. [12].

Based on our new policy and the efforts of the neurosurgical community to define the clinical benefits of safe, maximal tumour resection with respect to symptomatic relief and improved quality of life, progression-free survival and overall survival in patients having low-grade and high-grade glioma with molecular heterogeneity, we evaluated the feasibility of low-field MRI using the Polestar N30 to achieve extended resection with intraoperative neurophysiological monitoring (IONM) when needed, especially for non-enhancing brain lesions (both low-grade and high-grade gliomas), and we discuss its future role in an era of other advanced intraoperative technologies.

Materials and methods

Patients

Surgery was performed in 73 patients with intra-axial lesions using an intraoperative ultra-low-field MRI (Polestar N30, Medtronic) from February 2012 until the end of August 2018, in the Department of Neurosurgery, Sheba Medical Centre, Tel-Aviv, Israel. A total of 8/73 (11.1%) patients underwent an awake craniotomy due to the proximity of the lesion to eloquent speech areas, and 25/73 (34%) patients underwent

resection under motor cortical and/or subcortical stimulation using magnetic resonance-compatible needles (Technomed Europe Medical Accessories, The Netherlands). Twenty-five patients (34%) were operated on for recurrent tumours.

Imaging and surgical methods

Preoperative scans were performed in each patient using the Polestar N30 system in the operating room and then uploaded onto an image-guided navigation system (StealthStation, Medtronic). Resection was performed until the neurosurgeon felt he had achieved maximal resection or until the neurosurgeon felt that neurological stability was at risk. At this time, further intraoperative resection control scans were acquired. If a residual tumour was suspected on the resection control images, the surgeon explored the lesion so as to ascertain whether further resection was required. If the neurosurgeon felt that it was, additional resection control scans were obtained.

The intent of the resection was determined on the basis of preoperative images and functional MRI, and classified as either an intended complete or an incomplete lesion resection. Lesions located adjacent to or in eloquent brain areas, for which we believed an aggressive gross total resection might result in a substantial neurological deficit, were characterised as an intended incomplete resection. For the remaining lesions, the intent was to perform a complete resection. During the resection procedure, control images were obtained and compared to the preoperative iMRI images and the diagnostic images. The success of the resection was categorised as 'a complete resection' if no residual tumour was detected on one or more resection control images, or as an 'incomplete resection' if a residual tumour was observed.

Residual tumour for enhancing lesions was defined as the presence of nodular enhancement on the basis of T1-weighted images with gadolinium. Linear enhancement or a fuzzy enhancing lesion outside the area of the preoperative enhancing lesion was not considered a residual tumour but was instead defined as a complete resection. Residual tumour for non-enhancing lesions was based on the presence of a nodular or bulky lesion on FLAIR (fluid-attenuated inversion recovery) or T2-weighted images. Areas of FLAIR or T2-weighted image abnormality outside the area of the preoperative non-enhancing lesion were considered surgical procedure-induced changes and defined as a complete resection. (Supplemental Fig. 1–3) Diagnostic Flair and T1-weighted images with gadolinium are presented as well (Supplemental Fig. 1E–F) to gain understanding of the character, quality and resolution of the intraoperative scans.

A retrospective analysis of demographic data, diagnostic imaging, and pathology was performed. The data was retrieved from the patient's personal records and from our institute's imaging and pathology database. Additional data, such as the positioning of the patient, number of scans, sessions, and various time parameters, was obtained from the Polestar system database.

Finally, comparisons were made between the two success groups (i.e. complete and incomplete resection) and between cases in which iMRI led to further resection and those in which iMRI did not lead to further resection.

Statistical methods

Data was analysed with SPSS software version 25.0 (SPSS Inc., Chicago, IL, USA). Pathology characteristics according to enhancing/non-enhancing status were presented as frequencies and percentages for categorical variables. Chi-square tests and independent t-tests were performed to compare the two groups: complete/incomplete resection, and 2+ sessions for categorical and continuous variables, respectively. A multivariate analysis (Wald test, logistic regression) was performed, including factors such as age, sex, and enhancement. Hosmer-Lemeshow goodness-of-fit test was performed to assess the overall model. The significance level was set to less than 0.05.

This study was approved by the institutional review board of Sheba Medical Centre.

Results

Histological classification

The pathologies were classified into three groups (Tab. 1): high-grade gliomas (World Health Organisation [WHO] grade III–IV = 30 patients. These 30 comprised 12 anaplastic oligondendrogliomas [WHO III], eight anaplastic astrocytomas [WHO III], four high-grade glioma [WHO III], five glioblastoma multiforme [WHO IV], and one anaplastic ependymoma [WHO III]; low-grade gliomas (WHO II = 22 patients. These 22 comprised 10 low-grade astrocytomas [WHO II] and 12 low-grade oligodendrogliomas [WHO II]), plus various other lesions (21 patients; three cavernous angiomas, one primitive neuroectodermal tumour, six pilocytic astrocytomas, one ependymoma, one demyelinative tumour, one ganglioglioma, one glioneuronal tumour, two pleomorphic xanthoastrocytomas, one central neurocytoma, one grey matter heterotopia, one subependymoma, one metastasis, and one enhancing glial tumour).

Imaging characteristics

Thirty-seven (51%) of the lesions were right-sided, and 36 (49%) were left-sided. The lesions were further divided according to their location: 45 (62%) lesions were frontal, six (8%) were temporal, 10 (14%) were parietal, and the remaining 12 (16%) were located in other areas (insular cortex, cerebellum, intraventricular occipital, or a combination of two lobes). During surgery, 55 (75%) patients with mainly frontal and parietal lesions were positioned with their face upward (head-up position), six (8%) patients with mainly occipital and cerebellar lesions were positioned in the head-down position,

Table 2. Parameters in relation to the outcome

Parameter	Total n = 73	Complete resection n = 60	Incomplete resection n = 13	P value
Male gender	61 (84)	50 (83)	11 (85)	0.910
Age	37 ± 18	37 ± 19	40 ± 13	0.574
Intent to GTR	60 (82)	59 (98)	1 (8)	< 0.001
HGG (WHO III-IV)	30 (41)	22 (37)	8 (61)	
Miscellaneous	21 (29)	20 (33)	1 (8)	
LGG (WHO II)	22 (30)	18 (30)	4 (31)	0.132
Recurrence (yes)	25 (34)	20 (33)	5 (38.5)	0.724
Head position:				
right	7 (10)	5 (8)	2 (15)	
left	5 (7)	3 (5)	2 (15)	
down	6 (8)	6 (10)	0 (0)	0.407
up	55 (75)	46 (77)	9 (69)	
Location:				
frontal	45 (62)	35 (58)	10 (77)	
temporal	5 (8)	6 (10)	0 (0)	
parietal	10 (14)	9 (15)	1 (8)	0.130
other	12 (16)	10 (17)	2 (15)	
Eloquent lesion	29 (40)	20 (33)	9 (69)	
Non-eloquent lesion	44 (60)	40 (67)	4 (31)	0.016
Enhancement	38 (52)	35 (58)	3 (23)	
Non-enhancement	35 (48)	25 (42)	10 (77)	0.021
IONM	25 (34)	18 (30)	7 (54)	0.177
Lesion side:				
right	37 (51)	32 (53)	5 (38.5)	
left	36 (49)	28 (47)	8 (61.5)	0.524
Time of scanning (min)	49 ± 21	47 ± 21	1.00 ± 0.20	0.056

GTR — gross total resection, Eloquent lesion — adjacent to motor and speech centers, IONM — Intraoperative Neurophysiological Monitoring, HGG — High Grade Glioma, LGG — Low Grade Glioma

five (7%) patients were operated on in a left side-up position, and seven (10%) patients were operated on in a right side-up position. Twenty-nine (40%) of the lesions were located in eloquent areas (adjacent to motor and speech centers) and 44 (60%) were located in non-eloquent brain areas.

The radiology parameters were documented for each patient and included 38 contrast-enhancing lesions (52%). The remaining 35 (48%) lesions were non-enhancing lesions.

Resection intent

Among the 73 patients, the surgical intent was to perform complete tumour removal in 60 (82.2%). For the remaining 13 patients, the surgical intent was to perform incomplete tumour removal. Of the 60 cases for which the surgical intent was to perform a complete resection, 59 (98.3%) cases achieved a complete resection. In this subgroup of 59 patients, additional scans were performed in 17/59 (28.8%) to increase the extent of the resection and to achieve complete resection. The surgical intent of the resection significantly correlated with the results ($p < 0.001$; Tab. 2).

Of the 13 patients for whom the surgical intent was incomplete resection, 12 had an incomplete resection and one (7.7%) had a complete resection. No additional scan was performed in this 13th patient, but additional scans were performed in 6/12 (50%) patients to increase the extent of the resection, even though incomplete resection was achieved (Fig. 1).

Benefit of iMRI

73 resections were performed with intent to achieve either complete or incomplete surgical resection. Among these 73 patients, iMRI led to further resection in 24 cases, indicating that iMRI led to a maximal tumour resection in 32.8% of the total cases without consideration of the outcome (complete/ /incomplete removal) (Fig. 1).

In 60 patients, the initial intent was to achieve complete lesion resection. In the remaining 13 patients, the surgical intent was to perform incomplete tumour removal. A complete resection was achieved in 60 patients (59 from the intent to perform complete resection group and one from the intent to perform incomplete resection group). The surgical intent of the resection significantly correlated with the results ($p < 0.001$; Tab. 2).

In 49 (67.2%) of these patients, only two scan sessions were performed: a preoperative image acquisition within the operation room prior to surgery, and an intraoperative resection control image. These 49 patients account for the cases in which the surgeon did not perform additional resection

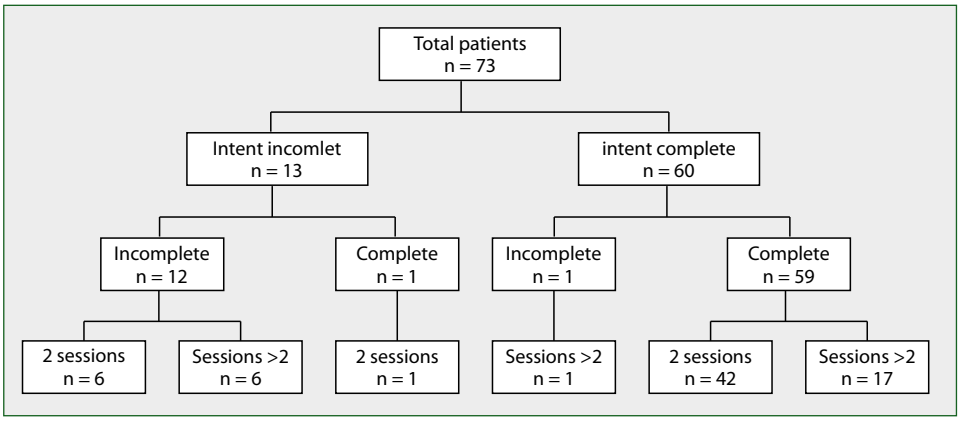

Figure 1. Distribution of cases in relation to intent of resection and number of sessions performed for resection control

after iMRI; 43 patients due to the absence of residual tumour observed on imaging, and six patients on the basis of the surgeon's decision not to proceed with the resection because further resection might compromise neurological function. More than two scan sessions were performed in 24 patients, and additional resection was performed due to the presence of residual tumour that was revealed by the resection control imaging. Complete resection was achieved in 18 of these patients. Thus, iMRI was responsible for 30.5% of the complete resections achieved in our study (in which the intent was to perform complete removal). Of these 24 patients, three imaging sessions were performed in 18 cases, indicating that in the large majority (75%) of cases in which iMRI led to additional resection, two resection control images (a total of three scans, including the preoperative scan) were sufficient to achieve complete resection. In two cases, four sessions were performed, in one case, five sessions, and in one case, six sessions (Tab. 3).

Among the 13 patients for whom the initial intent was to perform an incomplete resection, incomplete tumour removal was achieved in 12 cases. In six of these cases, more than two scan sessions took place, indicating that iMRI led to further surgery to maximise the resection in 46.1% of this group. In one case, iMRI led to complete resection (following two scans), although the original intent was for incomplete resection.

In summary, the Polestar N30 iMRI system maximised the extent of the intra-axial lesion resection in 32.8% of all operations performed in this cohort. Use of the iMRI led to 17 additional complete lesion resections, representing a 40.6% increase in complete lesion resections.

Interestingly, iMRI largely influenced the extent of the resection in cases in which the intent was incomplete resection, and was thus responsible for additional resection in 46.1% of patients in this group (Fig. 1).

Table 2 shows the relation between various parameters examined and the surgical outcome (resection success rates).

Age, sex, and diagnosis had no significant effect on resection success rates. Data regarding radiological characteristics,

Table 3. Distribution of cases in relation to number of iMRI scan sessions. More than 2 sessions indicates cases in which iMRI led to further resection

Number of scan sessions per patient	Number of patients
2	49 (67%)
3	18 (25%)
4	4 (5.4%)
5	1 (1.3%)
6	1 (1.3%)

e.g. enhancing *vs.* non-enhancing lesions, had no effect on the general success of the resection. Frontal lesions and left hemispheric lesions were more frequent in cases resulting in incomplete resection (related to the proximity to eloquent areas), but this difference was not statistically significant. On the other hand, non-eloquent area ($p = 0.016$) and enhancing lesions ($p = 0.02$) were predictive factors for complete resection in univariate analysis (Tab. 2).

Table 4 shows the relation between the various parameters examined and extended resection.

The extent of the resection was expanded mainly for non-enhancing lesions: 16/35 (46%) compared to only 8/38 (21%) of the enhancing lesions.

Univariate analysis performed to compare cases in which additional resections were performed following resection control imaging (24 cases) with patients in which no further resection was performed (13 cases) identified scan time and enhancement to be the only variables that differed significantly between the two groups (Tab. 4).

Patients with non-enhancing lesions more frequently comprised cases in which additional resection was performed and univariate analysis revealed a significantly increased scan time. On the other hand, sex, age, intent of resection, recurrence, diagnosis, patient positioning, and location of the lesion were not significantly different between these two groups.

A multivariate analysis (logistic regression) was performed (Tab. 5), with factors such as age, sex, diagnosis, and enhancement as covariates. Enhancement was the only independent variable. The odds ratio for non-enhancing lesions adjusted for age and sex was 3.1, indicating that there was a three-fold greater probability that a non-enhancing lesion would require more than two sessions to achieve the maximal tumour resection.

Table 4. Parameters in relation to extent of resection

Parameter	2 Sessions n = 49	> 2 Sessions n = 24	P value
Male gender	42 (86)	19 (79)	0.478
Age (years)	36 ± 20	39 ± 13	0.425
Intent to GTR	41 (84)	19 (79)	0.636
Recurrence (yes)	17 (35)	8 (33)	0.908
Lesion side:			
right	22 (45)	15 (62.5)	
left	27 (55)	9 (37.5)	0.099
Location:			
frontal	25 (51)	20 (83)	
temporal	6 (12)	0 (0)	
parietal	9 (18)	1 (4)	
other	9 (18)	3 (12.5)	0.119
Eloquent lesion	18 (37)	11 (46)	
Non-eloquent lesion	31 (63)	13 (54)	0.455
Enhancement	30 (61)	8 (33)	
Non-Enhancement	19 (39)	16 (67)	0.025
IONM	15 (30)	10 (41)	0.157
Head position:			
right	6 (12)	1 (4)	
left	4 (8)	1 (4)	
down	6 (12)	0 (0)	
up	33 (67)	22 (92)	0.060
Complete resection	42 (86)	18 (75)	0.261
Time of scanning (min)	44 ± 21	60 ± 19	0.003
HGG WHO III–IV	19 (39)	11 (46)	
Miscellaneous	17 (35)	4 (17)	
LGG WHO II	13 (26)	9 (37)	0.265

GTR — gross total resection, Eloquent lesion — adjacent to motor and speech centers, IONM — Intraoperative Neurophysiological Monitoring, HGG — High Grade Glioma, LGG — Low Grade Glioma

Scan data and time

Resection control was based on T1-weighted images in 38 (52%) patients and T2-weighted images in 35 (48%) patients. FLAIR sequences were used to assist in determining the success of the resection. In 49 patients, two scan sessions were performed: a preoperative session and a resection control session that did not lead to further resection. The resection control session was performed at the time that the surgeon felt maximal resection had been achieved, or at the point at which the surgeon felt further resection would jeopardise the patient's neurological stability. In 18 patients, three iMRI sessions were performed: one preoperative, a second that led to further resection, and a third followed by no further resection. In four cases, four scan sessions were performed; in one case, five scans were performed; and in one case, six scans were performed. In all cases, no further resection was performed after the last intraoperative scan.

Imaging duration was defined as the sum of all scan durations from all sessions. Surgery overhead was defined as the sum of all session durations, including time spent between scans. This parameter does not include time spent before the first scan for preparing and positioning the device, yet serves as an important indicator of the surgical duration while using the Polestar iMRI system. The mean surgery overhead for cases with two sessions was 44 min. Cases in which further resection was performed (more than two sessions) had a mean surgery overhead of 60 min.

Thus, iMRI extended the surgery time by a mean of 16 min in cases in which resection control images led to additional resection as opposed to cases where the second iMRI session led to the conclusion of the surgery. Scan time was significantly different between these two groups of patients (i.e. two sessions or more than two sessions) in univariate analysis, but was not an independent factor in multivariate analysis.

In summary, univariate analysis revealed that non-eloquent area (p = 0.016) and enhancing lesions (p = 0.02) were predictive factors for complete resection (Tab. 2). Univariate analysis revealed that non-enhancing lesions and scan time were predictive factors for extended resection (Tab. 4), but the only independent factor for extended resection, as demonstrated in a Wald multivariate analysis, was non-enhancement (Tab. 5).

Table 5. Independent predictors of extended resection in a multivariate Wald test analysis. Variable(s) entered: age, gender, non-enhancement

Independent variables	B	S.E.	Wald	P value	Exp (B)	95% CI for Exp (B)	
						Lower	Upper
Constant	1.616	0.685	5.57	0.018	0.199		
Age (years)	0.005	0.015	0.107	0.744	1.005	0.976	1.035
Non-enhancement	1.157	0.537	4.636	0.031	3.181	1.109	9.122
Gender	0.597	0.681	0.77	0.38	1.817	0.479	6.901

Discussion

The benefits of using the Polestar low-field iMRI system for achieving maximal resection of brain tumours have been reported by several groups, including ours [1, 2, 12–14].

Senft et al. [14] demonstrated particular benefits of the system for patients with contrast-enhancing tumours. Stereotactic biopsy using the Polestar is an accurate method for obtaining specimens with a high diagnostic yield [15]. An earlier version of the Polestar low-field iMRI system, the Polestar N20, was reported to have high sensitivity and specificity for residual tumour detection [16]. Other groups have also reported a significant benefit of other low-field iMRI systems in the removal of high-grade gliomas [17]. Claus et al. [9] reported a possible association between the extent of the resection of low-grade gliomas using low-field iMRI systems and a lower risk of recurrence or death.

In our study, we present in this cohort the advantages of the third generation low-field iMRI Polestar (N30), allowing for the use of standard surgical equipment, fully controlled and operated by the surgeon to increase the extent of the resection of non-enhancing lesions. The advantages of real-time imaging to localise and define lesion margins in the presence of dynamic changes in fluid and tissue compartments during resection were reported 20 years ago [18–19]. Several other centres have reported the usefulness of iMRI techniques for guidance in neurosurgical procedures [2, 9, 20–25].

Emerging imaging technologies, as well as new intraoperative techniques, have expanded our ability to resect maximal amounts of tumour while preserving essential function. Stimulation mapping of language and motor pathways is known to contribute to the safe resection of intrinsic brain lesions [26, 27]. Additional techniques, including neuro-navigation, fluorescence-guided microsurgery using 5-aminolevulinic acid, iMRI, and ultrasonography, have all been applied to optimise the extent of resection in glioma patients.

Low-field iMRI can be used with other neurosurgical modalities: iMRI with 5-aminolevulinic acid–induced fluorescence provides synergistic effects in glioma resections [28]. Senft et al. [29] reported that the use of iMRI with neurophysiological monitoring in patients with gliomas located in eloquent brain areas increased the extent of the resection, without increasing the rate of neurological deficit.

On the basis of our experience up to 2012 [2], we present our more recent experience with the use of the third generation Polestar, an ultralow-field iMRI system, from February 2012 to the end of August 2018, in 73 craniotomies for intra-axial lesion tumour resection, almost half of which were non-enhancing lesions (35/73). The extent of the resection was expanded mainly for non-enhancing lesions (16/35 [46%]) compared to enhancing lesions (only 8/38 [21%]).

Our experience indicates that iMRI led to an extended resection in 24 of 73 patients with intra-axial brain lesions. Furthermore, iMRI allowed for further resection leading to complete lesion removal in 17 of 59 patients in whom complete lesion removal was intended, leading to a significant increase in complete resections achieved by our group. These findings correlate well with the values reported in previous studies [30]. In addition, we present a cohort of 13 patients in which the initial intent was to perform an incomplete resection and in which iMRI guidance led to additional resection in 6/13 (46%) of the cases.

These findings suggest the usefulness of iMRI guidance for lesions located in eloquent brain regions for which the initial surgical intent was not necessarily to achieve a complete removal, but rather to maximise resection without endangering neurological stability.

In our study, low-grade gliomas were more frequent in cases where additional resection was performed (9/22 compared to high-grade glioma [11/30] and miscellaneous pathologies [4/21] in which extended resection was less frequent). This raises questions about the benefit of iMRI in the resection of various pathologies. Some studies have included mixed pathology cohorts [9], whereas others have demonstrated a benefit in the resection of high-grade gliomas.

Although dividing the patients into three groups is a potential limitation of our study, the purpose of the study was to evaluate the utility of the Polestar N30 to achieve resection control of non-enhancing lesions, regardless of the WHO grading, which means both low-grade and high-grade non-enhancing gliomas.

In our study, multivariate analysis to compare the cases in which iMRI did not lead to further resection to cases in which it enabled maximal extent of resection (without considering the amount of resection) revealed a significant difference in regard to the lesion enhancement properties.

Non-enhancing lesions of all types were three times more likely to require additional resection after iMRI resection control. These findings support our previous experience [2] and point to a possible advantage for all non-enhancing lesions, including non-enhancing high-grade gliomas, which were more common (12/30) in this cohort. No correlation was detected between recurrent tumours in cases in which additional resection was performed.

Imaging duration and extended surgery duration may be a reason for surgeons not to use intraoperative imaging modalities. With the development of user-friendly ultralow-field systems, the increase in surgery duration has become quite reasonable, with a commonly cited mean of 1 h extended overall surgery time [17, 31, 32]. This finding is in accordance with a mean surgical time prolongation of 60 min for all patients in whom more than two sessions were performed in the current cohort.

In our opinion, this is an acceptable delay in surgery completion. Furthermore, in 75% of cases in which iMRI led to complete resection, three scan sessions sufficed, which indicates how infrequently more than three scan sessions were required.

Carabenciov et al. [33] stated that in the context of the new WHO classification system, all low-grade gliomas must have an IDH mutation, with or without a 1p/19q co-deletion. Upon discovery of the tumour, maximal safe surgical resection is the most appropriate first step due to the current inability to differentiate between IDH mutant and IDH wild-type tumours by imaging alone.

Hervey-Jumper et al. [34] reported that low-grade gliomas have 5- and 10-year survival rates of 97% and 91% respectively, when the extent of resection is greater than 90%. Duffau et al. [27] demonstrated the prolonged impact of supratotal resection on malignant transformation of low-grade gliomas. These findings emphasise the importance of maximising the extent of resection of non-enhancing low-grade tumours. Up to 50% of anaplastic gliomas (grade III) are non-enhancing or slurred enhancing lesions, as demonstrated in our cohort as well. Furthermore, Kawaguchi et al. [35] showed in a retrospective study of 124 consecutive patients with newly diagnosed grade III gliomas that strict surgical removal is important to improve the prognosis of patients with grade III gliomas, especially for tumours with the IDH 1/2 mutation without 1p/19q co-deletions.

Leroy et al. [25] reported that iMRI was more useful for non- or minimally-enhancing tumours, as shown in our previous cohort [2]. A retrospective multicentre series of 288 cases of low-grade gliomas indicated an independent association of high-field (1.5-T) iMRI guidance with the rate of gross total resections after surgery, without an accumulated risk of neurological deficits [36]. In a recent analysis, Swinney et al. [37] reviewed 12 studies that included 804 primary operations and 238 extended resections based on iMRI findings. Use of iMRI led to extended tumour resection in 13.3-54.8% of patients (mean 37.3%). Stratification by tumour type showed that additional resection was performed on average in 39.1% of glioma resections (range 13.3–70.0%), 23.5% of pituitary tumour resections (range 13.3–33.7%), and 35.0% of nonspecific tumour resections (range 17.5–40%). These findings are similar to the extent of resections performed in our previous cohort [2] and the current study.

There are very few recent reports on low-field iMRI. Some previous studies demonstrated that low-field iMRI influenced intraoperative decision-making and improved brain tumour resection [9,14,17]. Other intraoperative modalities, such as fluorescence-guided surgery and ultrasound-guided surgery, may be easier to operate and less time-consuming, and may improve the resection of low-grade gliomas [12]. Intraoperative tumour visualisation with 5-aminolevulinic acid (5-ALA) induced protoporphyrin IX (PpIX) fluorescence is widely applied for improved resection of high-grade gliomas: Stummer et al. [6] demonstrated in a series of 139 patients enrolled in a randomised controlled multicentre phase III trial that complete resection of enhancing tumours was increased from 36% (white light) to 65% (5-ALA) and progression-free survival at six months increased from 21% (white light) to 41% (5-ALA). Recently, visible fluorescence of low-grade gliomas was reported as well [38, 39].

Jaber et al. [40] reported that only 15.9% of 82 WHO grade II tumours revealed intraoperative PpIX fluorescence compared to 83.3% of enhancing grade III tumours. Goryaynov et al. [38], however, showed a markedly higher rate of up to 52% visible fluorescence in a series of low-grade gliomas. In addition, they demonstrated that the use of antiepileptic drugs reduces the presence of visible fluorescence in low-grade gliomas. Widhalm et al. [39] showed the benefit of quantitative PpIX analysis in diffusely infiltrating low-grade glioma.

Stepp and Stummer [41] in a recent review summarised the valuable diagnostic options of 5-ALA in the management of malignant gliomas and also explored biological boosters of selective PpIX accumulation for the therapeutic use of 5-ALA. In addition, they looked at surgical guidance tools other than 5-ALA fluorescence-guided surgery.

Sastry et al. [42] reviewed the utility of intraoperative ultrasound since 1982 for brain tumour resection: intraoperative navigation, assessment of extent of resection, and brain shift monitoring and compensation. Selbekk et al. [43] reported techniques to identify and reduce image artefacts in ultrasound images that may occur during brain tumour surgery.

Taking into consideration the advancement of these other modalities raises the question of the need to sustain the low-field iMRI modality. The Polestar N30 is no longer manufactured! Is this the end of the era for low-field iMRI or should we make an effort to preserve this modality, especially for non-enhancing lesions?

The role of iMRI for enhancing and especially for non-enhancing gliomas in the era of fluorescence-guided surgery and advanced ultrasound modalities needs to be better defined.

Our data supports the need to preserve iMRI for extended resection, especially for non-enhancing brain lesions. We believe that it would be wise to preserve this technology for resection control. In contrast to low-field iMRI, however, high-field iMRI has several other benefits, such as the ability to create diffuse tensor images [44], laser-guided surgery [45], and focused ultrasound procedures, including research benefits such as opening of the blood brain barrier [46, 47]. It may be advisable to use high-magnetic power field iMRI for extended resection, taking into consideration its benefits and our findings that support preservation of the modality.

Conclusions

Intraoperative MRI guidance markedly improved the surgeon's ability to maximise the extent of resection in our series of 73 patients with intra-axial lesions.

The iMRI system allowed for additional resection in 32.8% of all cases and for complete resection in 28% of the cases when complete resections was intended. Additionally, iMRI allowed for extended resection in 46.1% of patients for whom

the intent was to perform an incomplete resection. The extent of resection was extended mainly for non-enhancing lesions, 16/35 as opposed to only 8/38 for enhancing lesions.

Non-enhancing lesions were the only independent variable predicting use of iMRI for extended resection. The procedure can be performed under electrophysiological monitoring using magnetic-resonance compatible electrodes, allowing for preserved function with a reasonable mean surgery time elongation of only 60 minutes.

Our results provide additional support for the benefits of this technology for achieving a maximal resection, especially in patients with non-enhancing intra-axial brain tumours.

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- *RH and NK collected and interpreted the data.*
- *MH, MA, ZF, JZ, AW, and RS performed the surgical procedures or were part of the decision-making process.*
- *All authors read and approved the final manuscript.*

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Clinical course and outcome of SARS-CoV-2 infection in multiple sclerosis patients treated with disease-modifying therapies — the Polish experience

Agata Czarnowska[1], Waldemar Brola[2], Olga Zajkowska[3], Stanisław Rusek[4], Monika Adamczyk-Sowa[5], Katarzyna Kubicka-Bączyk[5], Alicja Kalinowska-Łyszczarz[6], Karolina Kania[7], Agnieszka Słowik[8], Marcin Wnuk[8], Monika Marona[8], Aleksandra Podlecka-Piętowska[9], Monika Nojszewska[9], Beata Zakrzewska-Pniewska[9], Elżbieta Jasińska[2,10], Katarzyna Gołuch[10], Beata Lech[11], Magdalena Noga[11], Adam Perenc[11], Małgorzata Popiel[11], Anetta Lasek-Bal[12], Przemysław Puz[12], Katarzyna Maciejowska[12], Marta Kucharska-Lipowska[13], Michał Lipowski[14], Katarzyna Kapica-Topczewska[1], Monika Chorąży[1], Joanna Tarasiuk[1], Jan Kochanowicz[1], Joanna Kulikowska[1], Sławomir Wawrzyniak[15], Anna Niezgodzińska-Maciejek[15], Anna Pokryszko-Dragan[16], Ewa Gruszka[16], Sławomir Budrewicz[16], Marta Białek[17], Iwona Kurkowska-Jastrzębska[18], Katarzyna Kurowska[18], Adam Stępień[19], Agata Włodek[20], Violetta Ptasznik[21], Małgorzata Pawełczyk[22], Piotr Sobolewski[23], Henryka Lejmel[24], Katarzyna Strzalińska[25], Maciej Maciejowski[26], Andrzej Tutaj[27], Jacek Zwiernik[27, 28], Anna Litwin[27], Bożena Lewańczyk[29], Izabela Paprocka[29], Beata Zwiernik[28], Aleksandra Pawlos[30], Andrzej Borysowicz[31], Anna Narożnik[31], Anna Michałowska[27], Krzysztof Nosek[30], Małgorzata Fudala[32], Marta Milewska-Jędrzejczak[23], Alina Kułakowska[1]*, Halina Bartosik-Psujek[33]*

*Senior authors

[1]Department of Neurology, Medical University of Bialystok, Poland
[2]Collegium Medicum, Jan Kochanowski University, Kielce, Poland
[3]Faculty of Economic Sciences, University of Warsaw, Poland
[4]Department of Neurology, Specialist Hospital Ludwika Rydygiera in Krakow, Poland
[5]Department of Neurology, Faculty of Medical Sciences in Zabrze, Medical University of Silesia in Katowice, Poland
[6]Department of Neurology, Division of Neurochemistry and Neuropathology, Poznan University of Medical Sciences, Poland
[7]Department of Neurology, Poznan University of Medical Sciences, Poland
[8]Department of Neurology, Jagiellonian University Medical College, Krakow, Poland
[9]Department of Neurology, Medical University of Warsaw, Poland
[10]Clinical Centre, Resmedica, Kielce, Poland
[11]Neurology Clinic with Brain Stroke Sub-Unit, Clinical Hospital No. 2 in Rzeszow, Poland
[12]Department of Neurology, School of Health Sciences, Medical University of Silesia in Katowice, Poland
[13]Department of Neurology, Specialist Hospital in Konskie, Poland
[14]Department of Urology, Specialist Hospital in Konskie, Poland
[15]Department of Neurology, 10th Military Research Hospital and Polyclinic, Independent Public Healthcare Centre, Bydgoszcz, Poland
[16]Department of Neurology, Wroclaw Medical University, Wroclaw, Poland
[17]Department of Neurology, Regional Specialised Hospital No. 4 in Bytom, Poland
[18]2nd Department of Neurology, Institute of Psychiatry and Neurology, Warsaw, Poland
[19]Department of Neurology, Military Institute of Medicine, Warsaw, Poland
[20]Department of Neurology, Masovian Voivodeship Hospital in Siedlce, Poland

Address for correspondence: Agata Czarnowska, Department of Neurology, Medical University of Bialystok M. Skłodowskiej-Curie 24A Str., 15-276 Bialystok, Poland; e-mail: agata.czarnowska@umb.edu.pl

[21]Department of Neurology, Specialist Hospital in Pila, Poland
[22]Department of Neurology and Stroke, Medical University of Lodz, Poland
[23]Department of Neurology and Stroke Unit in Sandomierz, Collegium Medicum, Jan Kochanowski University in Kielce, Poland
[24]Department of Neurology, The Regional Hospital in Suwalki, Poland
[25]Department of Neurology, The Regional Hospital in Lomza, Poland
[26]KMK Clinical, MS Centre, Katowice, Poland
[27]Neurology Ward, Provincial Specialist Hospital, Olsztyn, Poland
[28]Department of Neurology, University of Warmia and Mazury, Olsztyn, Poland
[29]Neurology Ward, Provincial Integrated Hospital, Elblag, Poland
[30]Department of Pharmacology and Toxicology, Faculty of Medicine, University of Warmia and Mazury, Olsztyn, Poland
[31]Department of Neurology, Specialist Hospital Dr Tytus Chałubinski, Radom, Poland
[32]Department of Neurology, Regional Hospital in Skarzysko-Kamienna, Poland
[33]Department of Neurology, Institute of Medical Sciences, Medical College of Rzeszow University, Poland

ABSTRACT

Background. The aim of this study was to report the course and outcome of SARS-CoV-2 infection in multiple sclerosis (MS) patients treated with disease-modifying therapies (DMTs) in Poland.

A major concern for neurologists worldwide is the course and outcome of SARS-CoV-2 infection in patients with MS treated with different DMTs. Although initial studies do not suggest an unfavourable course of infection in this group of patients, the data is limited.

Materials and methods. This study included 396 MS patients treated with DMTs and confirmed SARS-CoV-2 infection from 28 Polish MS centres. Information concerning patient demographics, comorbidities, clinical course of MS, current DMT use, as well as symptoms of SARS-CoV-2 infection, need for pharmacotherapy, oxygen therapy, and/or hospitalisation, and short-term outcomes was collected up to 30 January 2021. Additional data about COVID-19 cases in the general population in Poland was obtained from official reports of the Polish Ministry of Health.

Results. There were 114 males (28.8%) and 282 females (71.2%). The median age was 39 years (IQR 13). The great majority of patients with MS exhibited relapsing-remitting course (372 patients; 93.9%). The median EDSS was 2 (SD 1.38), and the mean disease duration was 8.95 (IQR 8) years. Most of the MS patients were treated with dimethyl fumarate (164; 41.41%). Other DMTs were less frequently used: interferon beta (82; 20.70%), glatiramer acetate (42; 10.60%), natalizumab (35;8.84%), teriflunomide (25; 6.31%), ocrelizumab (20; 5.05%), fingolimod (16; 4.04), cladribine (5; 1.26%), mitoxantrone (3; 0.76%), ozanimod (3; 0.76%), and alemtuzumab (1; 0.25%). The overall hospitalisation rate due to COVID-19 in the cohort was 6.81% (27 patients). Only one patient (0.3%) died due to SARS-CoV-2 infection, and three (0.76%) patients were treated with mechanical ventilation; 106 (26.8%) patients had at least one comorbid condition. There were no significant differences in the severity of SARS-CoV-2 infection regarding patient age, duration of the disease, degree of disability (EDSS), lymphocyte count, or type of DMT used.

Conclusions and clinical implications. Most MS patients included in this study had a favourable course of SARS-CoV-2 infection. The hospitalisation rate and the mortality rate were not higher in the MS cohort compared to the general Polish population. Continued multicentre data collection is needed to increase the understanding of SARS-CoV-2 infection impact on the course of MS in patients treated with DMTs.

Key words: multiple sclerosis, COVID-19, SARS-CoV-2, disease-modifying therapies

(*Neurol Neurochir Pol 2021; 55 (2): 212–222*)

Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is an enveloped, single-stranded, RNA virus, and a member of the family Coronaviridae. It was isolated for the first time on 7 January 2020 in China. Since the first unexplained pneumonia cases reported from Wuhan, China in early December 2019, the global spread of the novel coronavirus had resulted in over 100,000,000 confirmed cases and over 2,000,000 deaths by the end of January 2021 [1, 2]. The World

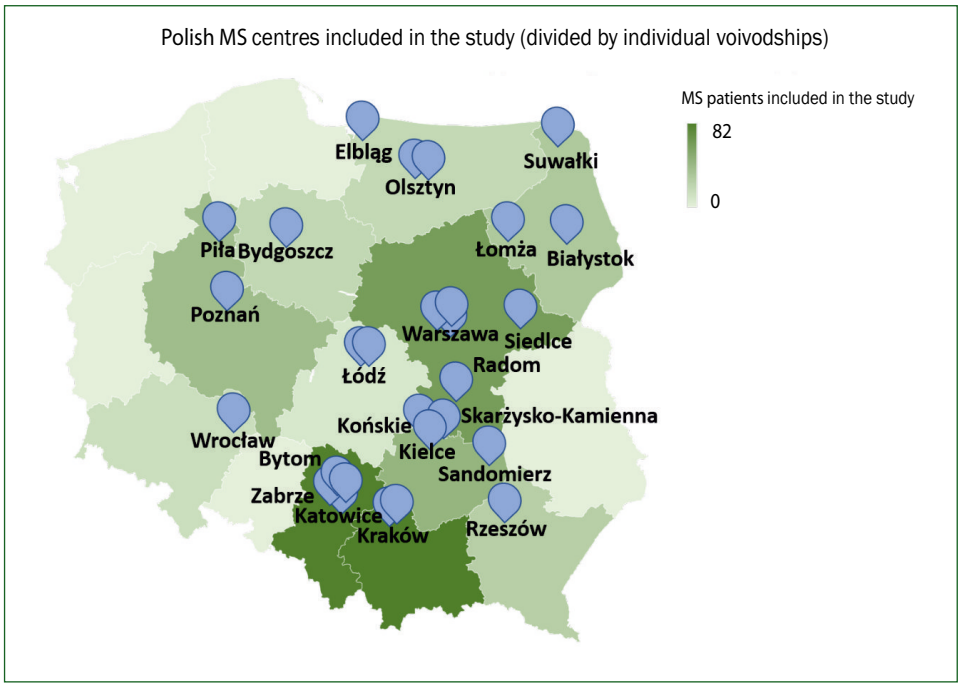

Figure 1. Locations of MS centres participating in study

Health Organisation (WHO) declared a pandemic in March 2020. The current coronavirus outbreak led to a much larger global threat compared to previous outbreaks caused by severe acute respiratory syndrome (SARS-CoV) in late 2002 or the Middle East respiratory syndrome (MERS-CoV) in 2012 [3].

The majority of SARS-CoV-2 infections are asymptomatic. The most common clinical presentation in symptomatic individuals is pneumonia, now termed Coronavirus Disease 2019 (COVID-19). However, the clinical spectrum of SARS-CoV-2 infection is broad, and is a particular threat to those over 60 years of age and those with comorbidities [4]. The virus primarily targets the respiratory tract; however, there is clinical evidence of neuro-invasive properties. According to scientific reports published so far, 18–80% of patients can develop neurological symptoms such as headache, olfactory and gustatory dysfunctions, encephalopathy, encephalitis and cerebrovascular pathologies, acute myelitis, and Guillain-Barré syndrome [5, 6]. The exact mechanism by which SARS-CoV-2 infects the central nervous system (CNS) is still under investigation. The entrance points to the CNS for SARS-CoV-2 include retrograde transfer from the olfactory nerve, increased permeability of the blood-brain barrier during the viremia phase, and a synapse-connected route from the peripheral nerve terminal [7].

Neurologists are interested in understanding whether patients with multiple sclerosis (MS) undergoing disease-modifying therapies (DMTs) are more susceptible to developing COVID-19 or worse clinical outcomes. The initial studies do not suggest an unfavourable course of the infection due to the use of most DMTs, although the data is limited [8–10]. Some immunosuppressive therapies may even play a protective role because overactive immune response can lead to clinical deterioration during the course of COVID-19 [11].

To better understand the impact of SARS-CoV-2 infection on the MS population, we collected data from 28 Polish MS centres. The aim of our study was to report symptoms, the course and short-term outcomes of SARS-CoV-2 infection in MS patients treated with different DMTs.

Materials and methods

Participants were recruited from 28 MS centres from across the country (Fig. 1). The Multiple Sclerosis and Neuroimmunology Section of the Polish Neurological Society published an announcement about the study at www.ptneuro.pl and every MS centre in Poland was invited to participate. The data was obtained by neurologists using a pre-prepared questionnaire (the same for all MS centres). We included patients with a confirmed diagnosis of MS according to the 2010 and 2017 McDonald criteria who were being treated with DMTs. [12, 13]. Only patients with confirmed SARS-CoV-2 infection were included in the study. The infection was detected by positive polymerase chain reaction (Seegene Allplex 2019 nCoV assay, PCR, SARS-CoV-2 Real Time PCR LAB-KIT™ by BIOMAXIMA S.A., GeneProof SARS-CoV-2 PCR Kit), positive antigen test against SARS-CoV-2 (Panbio™ COVID-19 Ag Rapid Test, Abbott), or the presence of antibodies against SARS-CoV-2 (EUROIMMUN Anty-SARS-CoV-2 ELISA IgA, IgG). Disability was assessed by the Expanded Disability Status Scale (EDSS) [14]. We collected patient demographics,

Table 1. Demographics and clinical characteristics of MS cohort

Demographics	No.	(%)	Range	Mean	MEDIAN	IQR	SD
Number of patients	396	100					
Age			18–68	40.05	39	13	9.97
Male	114	28.8					
Female	282	71.2					
Smokers	46	11.6					
Clinical characteristics due to MS	**No.**	**(%)**	**Range**	**Mean**	**MEDIAN**	**IQR**	**SD**
Disease course							
RRMS	372	93.9					
PPMS	22	5.6					
SPMS	2	0.5					
EDSS			0–6.5	2.37	2	2.5	1.38
Disease duration (years)			0–33	8.95	8	8	5.91
Duration of DMTs use (years)			0–19	5.79	5	2	4.07
DMTs:							
Interferon beta	82	20.70					
Glatiramer acetate	42	10.60					
Dimethyl fumarate	164	41.41					
Teriflunomide	25	6.31					
Fingolimod	16	4.04					
Natalizumab	35	8.84					
Ocrelizumab	20	5.05					
Cladribine	5	1.26					
Alemtuzumab	1	0.25					
Mitoxantrone	3	0.76					
Ozanimod	3	0.76					

MS — multiple sclerosis; SD — standard deviation; RRMS — relapsing remitting multiple sclerosis; PPMS — primary progressive multiple sclerosis; SPMS — secondary progressive multiple sclerosis; EDSS — Expanded Disability Status Scale; DMTs — disease-modifying therapies

current DMT use, and information about the course of SARS-CoV-2 infection (symptoms, need for hospitalisation, oxygen therapy, pharmacotherapy and short-term outcome). Data was collected up to 30 January 2021. Additional data about COVID-19 cases in the general Polish population was obtained from official reports of the Polish Ministry of Health [15].

Demographics, MS duration, level of disability, DMT use, method of SARS-CoV-2 infection confirmation, symptoms, number of hospitalisations, treatment during SARS-CoV-2 infection, and key comorbidities were reported with descriptive statistics, using range, mean and standard deviation or median and interquartile range depending on the data type. For between-group comparisons, a parametric two-sided t-test, Fisher's exact p-test, and a nonparametric Mann-Whitney test were used. We compared age, duration of the disease, EDSS, DMT use, and the presence of comorbid diseases between patients who required oxygen therapy/hospitalisation and the rest of the cohort. Multivariate analysis and univariate analysis were used to evaluate the odds ratio for hospitalisation according to treatment with different DMTs. All calculations were performed with STATA 15 software (StataCorp 2017) [16].

The study was approved (approval No. 6/2021) by the Bioethics Committee at Collegium Medicum, Jan Kochanowski University in Kielce, Poland.

Results

The study finally included information about 396 MS patients with confirmed SARS-CoV-2 infection and treated with different DMTs. Demographics and clinical characteristics of the study group are set out in Table 1.

There were 106 (26.8%) patients with at least one comorbid condition: 10 had two, and two subjects had three comorbid diseases. The most common comorbidities were: hypertension (44 patients; 11.1% of the cohort), diabetes in 12 (3%) patients, coronary artery disease in six (1.5%), asthma in nine (2.3%), and chronic liver disease in four (1%); 55 (13.9%) patients had one other comorbidity (chronic obstructive pulmonary

Table 2. Number of SARS-CoV-2 infection diagnoses confirmed by different diagnostic tests

	No. of patients	Percentage of cohort
Positive PCR	333	84
Positive antigen test confirmed by PCR	23	5.8
Positive PCR/antigen test and presence of antibodies against SARS-CoV-2	20	5
Positive antigen test against SARS-CoV-2	39	9.9
Presence of antibodies against SARS-CoV-2	36	9.1

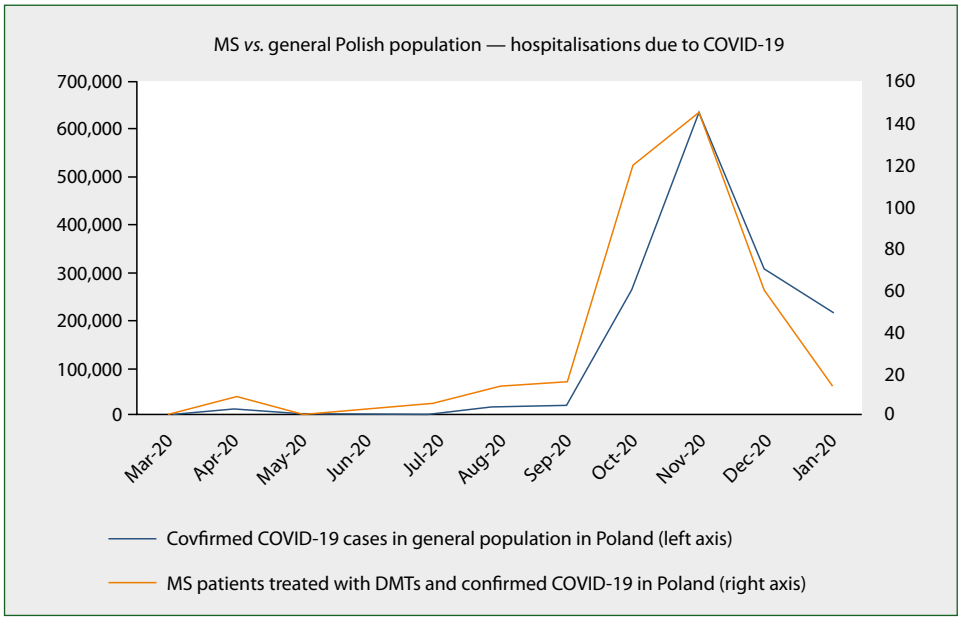

Figure 2. Confirmed cases of COVID-19: MS *vs.* general Polish population

disease, neoplastic disease, depression, autoimmune diseases of the thyroid gland, etc.). There was no statistically significant difference in the percentage of hospitalised patients between groups with and without comorbidities (Fisher's exact = 0.555).

In 332 cases (84%), the infection was confirmed by PCR tested on a nasopharyngeal swab, in 39 (9.9%) cases the antigen test was positive, and 36 (9.1%) patients had antibodies against SARS-CoV-2. A combination of different tests was used in some subjects (Tab. 2).

The vast majority of the MS cohort was diagnosed with SARS-CoV-2 infection between October and December 2020. The peak incidence of COVID-19 in the MS cohort generally overlapped with a trend in the general population in Poland (Fig. 2). A similar trend was observed with regard to hospitalisation (Fig. 3). We found that 264 (66.7%) patients reported contact with someone infected with SARS-CoV-2, 82 (20.7%) patients denied contact with an infected person, and 50 (12.6%) cases had no information about any possible contact.

The overall hospitalisation rate due to COVID-19 in the cohort was 6.81% (27 patients). Only one patient (0.3%) died due to COVID-19 infection, and three patients were treated with mechanical ventilation. The hospitalisation rate due to COVID-19 in the general Polish population was 7.98%, and the mortality rate was 2.46% [15]. The characteristics of hospitalised individuals in the MS cohort are set out in Table 3. The distribution of DMTs in the group of hospitalised patients and those who were not hospitalised is set out in Figure 4 and Table 4.

In our observation, patients treated with ocrelizumab were the most likely to be hospitalised while being infected with SARS-CoV-2 ($p = 0.004$). We did not consider interferon beta, glatiramer acetate, or dimethyl fumarate as increasing hospitalisation probability because univariate analysis did not confirm the significance of the result; 48 (12.1%) patients interrupted DMTs therapy during SARS-CoV-2 infection, and of these nine were hospitalised. A Mann-Whitney test showed no significant difference in disability (EDSS) between hospitalised and non-hospitalised patients in the cohort ($p = 0.08211$) (Fig. 5).

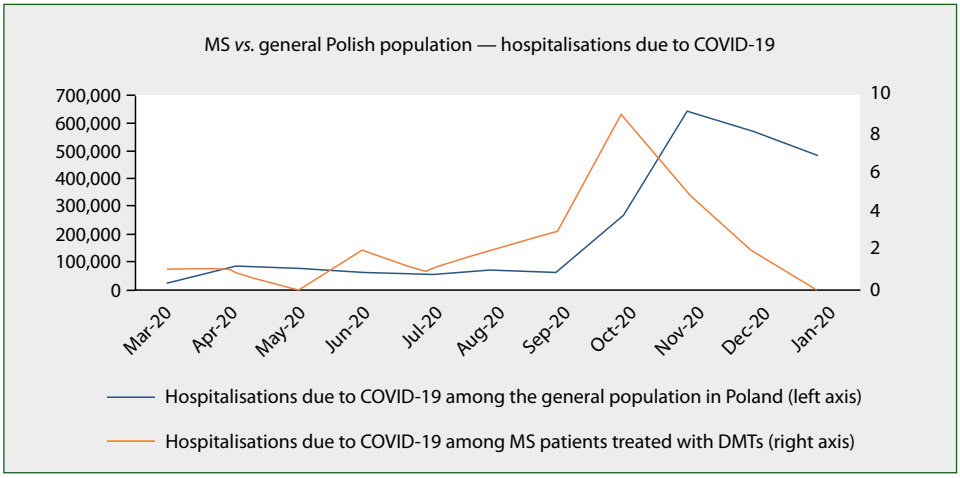

Figure 3. Hospitalisations due to COVID-19: MS *vs.* general Polish population

Table 3. Characteristics of hospitalised MS patients

Characteristics of hospitalised patients	No. (%)
Number	27 (100)
Hospitalisation > 10 days	12 (44.4)
Hospitalisation < 10 days	15 (55.5)
Passive oxygen therapy	12 (44.4)
Mechanical ventilation	3 (11.1)
Deaths	1 (3.7)
Treatment	
Remdesivir	3 (11.1)
Glucocorticosteroids	6 (22.2)
Convalescent plasma therapy	8 (29.6)
Antibiotics	23 (85.2)

The mean age of hospitalised patients was 42.42 years, and the mean age of non-hospitalised patients was 39.88. A two-sided t-test suggested that this difference was not statistically significant (p = 0.209) (Fig. 6). The patients who were in need of oxygen therapy during COVID-19 were on average 6.17 years older than those who did not require oxygen support (p = 0.0227).

Laboratory findings in the MS cohort are set out in Table 5. There was no significant difference in the rate of hospitalisation between patients with and without lymphopenia (Fisher's exact = 0.400). Patients with lymphopenia also did not require oxygen therapy (passive and active oxygen therapy) more often than did patients without lymphopenia (Fisher's exact = 1.000). Symptoms presented during COVID-19 infection are set out in Table 6.

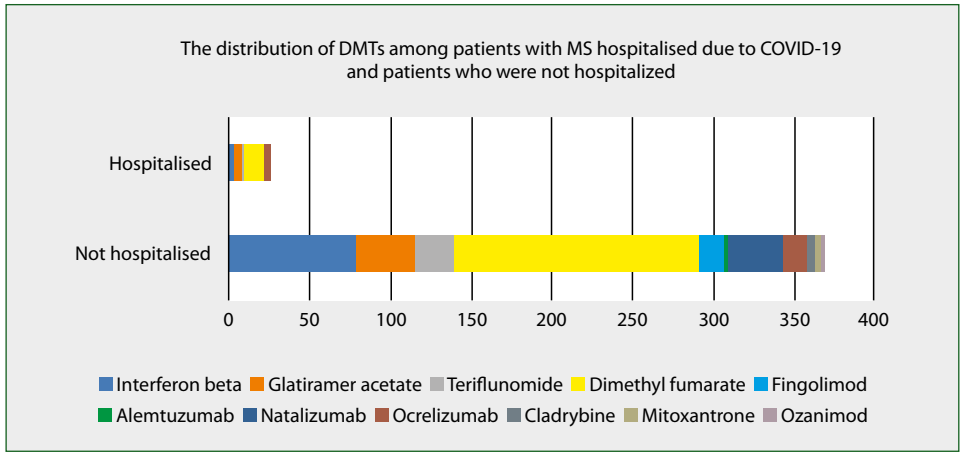

Figure 4. Distribution of DMTs among hospitalised and non-hospitalised MS patients

Table 4. Distribution of DMTs among hospitalised and non-hospitalised MS patients

DMT	Non-hospitalised patients no.	Hospitalised patients no.	Percentage of patients hospitalised on particular DMT in relation to all patients treated with particular DMT
Interferon beta	79	3	3.66 (3 out of 82)
Glatiramer acetate	37	5	11.90 (5 out of 42)
Dimethyl fumarate	151	13	7.93 (13 out of 164)
Teriflunomide	24	1	0.04 (1 out of 25)
Fingolimod	16	0	0
Natalizumab	35	0	0
Ocrelizumab	15	5	25 (5 out of 20)
Cladribine	5	0	0
Alemtuzumab	1	0	0
Mitoxantrone	3	0	0
Ozanimod	3	0	0

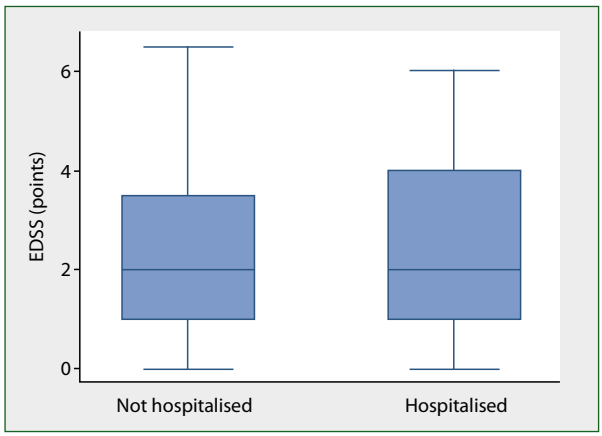

Figure 5. Distribution of EDSS among hospitalised and non-hospitalised patients in MS cohort

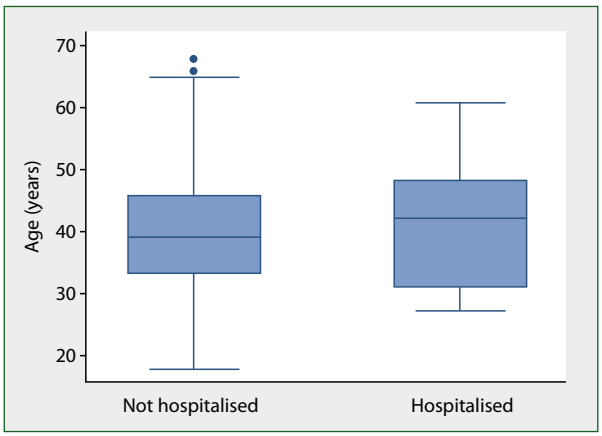

Figure 6. Distribution of age among hospitalised and non-hospitalised patients in MS cohort

Table 5. Laboratory findings among MS cohort during SARS-CoV-2 infection

Laboratory findings during COVID-19	No. of patients	Percentage of cohort
Lymphopenia (< 1 x 10^3/μL)	69	17.4
No lymphopenia	283	71.5
Lymphocytes result unknown	44	11.1
Leukopenia (< 3 x 10^3/μL)	13	3.3
No leukopenia	338	85.4
WBC result unknown	45	11.4

COVID-19 — coronavirus disease 2019; WBC — white blood cells

Discussion

To the best of our knowledge, this is the largest cohort of Polish MS patients with concomitant SARS-Cov-2 infection.

Our study showed that the outcome of COVID-19 in the group of MS patients treated with DMTs compared to the general population was favourable. The SARS-CoV-2 infection among MS patients treated with DMTs is a concern for neurologists. The disease itself, and the use of immunomodulatory and immunosuppressive therapies, raise questions regarding the safety of MS patients during the pandemic. The cause and effect relationship between MS or accelerated neurodegeneration and viral infections has been under discussion for a long time [17, 18]. Recently, a nationwide study from Sweden showed that patients with MS are generally at a greater risk of infections [19]. Safety concerns among Polish MS patients is underlined by the fact that the prevalence of MS in Poland is tending to increase [20, 21].

Our findings suggest favourable infection outcomes in multiple sclerosis patients treated with different DMTs. Most patients had mild symptoms and did not require hospitalisation. Only 27 (6.81%) patients required hospitalisation, and only one patient (0.3%) died due to COVID-19 infection; three (0.76%) patients were treated with mechanical ventilation.

The second wave of COVID-19 in Poland emerged in early November 2020, and most cases of SARS-CoV-2 infection in

Table 6. Symptoms presented among patients with MS treated with DMTs during SARS-CoV-2 infection

Symptoms during SARS-CoV-2 infection	Percentage of cohort	Risk of hospitalisation (odds ratio)
Fever	56.2	1.921
Fatigue	40.5	1.004
Loss of smell	36.5	0.593
Muscle pain	35.7	1.471
Cough	34.9	1.791
Headache	28.1	0.709
Bone and joint pain	23.8	0.715
Chills	12.4	1.252
Loss of taste	12.2	1.723
Sore throat	11.6	0.923
Swelling of nasal mucosa	10.6	1.000
Shortness of breath	7.1	7.347
Asymptomatic	5.6	0.637
Rash	1.8	2.327
Diarrhoea	1.5	1.000
Pneumonia	0.3	1.000
Vomiting	0.3	1.000
Abdominal pain	0.3	1.000

the MS cohort occurred during that time. The peak of MS patient hospitalisations was in October 2020, a month earlier than the peak of all hospitalisations due to COVID-19 in Poland (Fig. 3). It seems that at the beginning of the second wave of COVID-19 in Poland, doctors' decisions to hospitalise MS patients with SARS-CoV-2 infection might have been determined largely due to the MS coexistence, rather than by the patient's actual clinical condition. Initial observations on the favourable course of SARS-CoV-2 infection in MS patients meant that patients with MS were hospitalised less frequently than the general population at later periods. Finally, the hospitalisation rate and the mortality rate were slightly lower in our MS cohort compared to the general Polish population (6.81% *vs.* 7.98% and 0.3% *vs.* 2.46%, respectively).

The initial observational studies also suggest that patients with MS treated with DMTs are generally not at greater risk of severe COVID-19 infection [22–25]. However, in an Iranian MS cohort, the incidence of COVID-19 was comparable to the general population, but the hospitalisation rate was significantly higher [26]. On the other hand, preliminary reports on Italian MS patients, as well as Brazilian and Chilean observations, showed that most patients with MS exhibit a mild course of SARS-CoV-2 infection despite the maintenance of DMTs [9, 27, 28]. The vast majority of our patients (87.9%) also continued treatment during their SARS-CoV-2 infection. Similar observations indicating no association between immunotherapy and the risk of COVID-19 were found in a group of more than 2,000 patients with NMOSD under appropriate immunotherapy in China. In this group, only two patients developed COVID-19 [29].

The favourable course of SARS-CoV-2 infection in MS patients could be due to the fact that most of them are younger and have fewer comorbidities than do patients from the general population. People aged over 60 and with multiple comorbidities often have severe disease [30, 31]. The median age in our cohort was 39. Age did not significantly differ between hospitalised and non-hospitalised patients with MS. However, the mean age of patients who required oxygen therapy was higher than those who did not require oxygen support. In a French multicentre study of 347 patients with MS who developed COVID-19, age, obesity, and MS-related disability were independent risk factors for more severe COVID-19, but DMT exposure was not associated with COVID-19 severity [22]. In our study, the degree of disability as assessed by EDSS was similar in hospitalised and non-hospitalised patients, but patients included in our study were in the early stage of the disease, with a median EDSS of 2.0.

We found no association between comorbid diseases and the severity of SARS-CoV-2 infection. Most of our MS patients (more than 70%) had no comorbidities. Only one patient who required hospitalisation and oxygen therapy had more than one comorbid disease: hypertension and chronic obstructive pulmonary disease. Chronic pulmonary diseases are known to be a strong risk factor for serious COVID-19 [32]. Another risk factor for a severe clinical course of SARS-CoV-2 infection is diabetes mellitus [33] Among 12 (3%) patients with diabetes in our cohort, one required hospitalisation due to low saturation and unilateral pneumonia. Two patients in our cohort had three comorbid diseases although none of them required hospitalisation during SARS-CoV-2 infection. We emphasise that comorbid diseases, known to be a worse prognostic factor for COVID-19, were only present in a minority of our patients, probably due to the young age of our cohort which consisted mainly of RRMS patients treated with DMTs.

In Poland, from the beginning of the pandemic, only symptomatic patients were tested for SARS-CoV-2. Therefore, the MS cohort in our study consisted mostly of those who had symptoms of COVID-19. In a few asymptomatic patients, the infection was detected for professional reasons or before a planned hospitalisation.

The most common symptoms of SARS-CoV-2 infection presented in the Polish MS cohort were fever, fatigue, cough and hyposmia. These symptoms were similar to those reported from multicentre studies of general populations worldwide [35]. The course of the disease did not differ greatly between patients with MS and the general population. About 20% of our subjects denied contact with an infected individual. This shows that asymptomatic carriers can be a major threat [34].

Among the MS cohort, we registered one death during the course of COVID-19. The patient with a fatal outcome was

a 51-year-old female non-smoker with comorbid hypertension. She had been diagnosed with relapsing-remitting multiple sclerosis 19 years prior to infection. Her EDSS was 6.0, and she has been treated with ocrelizumab for six years (no other immunomodulatory treatment was used before). The last dose of ocrelizumab was given in February 2020, and she was diagnosed with COVID-19 in August 2020 (at the moment of COVID-19 diagnosis there was no lymphopenia).

In the study group, three patients required mechanical ventilation (one male, two female). Interestingly, they were younger (31, 38, and 39 years) and did not suffer from any comorbid diseases. Maximal EDSS in this group was 4.0, and the longest duration of the disease was eight years. They were treated with glatiramer acetate, interferon beta, and dimethyl fumarate, respectively.

One major concern for neurologists treating MS patients with SARS-CoV-2 infection is the safety of B-cell depleting therapies. B-cells are responsible for generating neutralising antibodies. Therefore, there is uncertainty regarding the clinical course of the infection and the effectiveness of the reaction to future vaccination. Most data does not support higher susceptibility toward more severe SARS-CoV-2 infection among patients treated with B-cell depleting therapies [22, 23, 36, 37]. However, Sormani et al. showed an increased risk of severe COVID-19 disease in patients treated with an anti-CD20 agent [38]. Sharifian-Dorche et al. recently reviewed almost 2,500 MS patients with COVID-19 from different studies. They found that patients treated with anti-CD20 agents (ocrelizumab, rituximab) had the highest mortality rate during the infection [39]. In our cohort, patients treated with ocrelizumab had a higher risk of hospitalization due to SARS-CoV-2 infection. However, three out of five patients hospitalized theated with these therapy suffered form PPMS. Our observation of patients with COVID-19 while being on ocrelizumab treatment is limited to 20 individuals, and thus we are not drawing any definite conclusions. Nonetheless, we draw attention to the need to closely monitor patients treated with anti-CD20 agents during SARS-CoV-2 infection.

Patients with progressive forms of MS are more disabled and tend to have a more severe clinical course of SARS-CoV-2 infection [22, 40]. Here, 24 (6%) patients were diagnosed with progressive MS: 22 patients with PPMS and two with SPMS. Among patients with progressive MS subtypes, four required hospitalisation and passive oxygen therapy. The statistical difference in the course of SARS-CoV-2 infection between RRMS and progressive phenotypes of the disease was not significant in our study. The numbers of patients with PPMS and SPMS were limited, and final conclusions should only be drawn from a larger observation.

Importantly, MS patients with lymphopenia were not hospitalised more often than patients without lymphopenia. This information is an additional indication for how to consider DMT continuation in real-world practice. Our findings are consistent with the initial Dutch experience, but far more data is needed to be certain that lymphopenia is not associated with a more severe course of the disease [41].

In our MS cohort, any obvious advantage of one drug over another was not found in hospitalised patients or in those who needed oxygen therapy. Some studies have shown a trend for an increased risk of infection with immune-resetting drugs versus injectables, but no final conclusions were drawn because of the small number of observations [42]. In our study, none of the 35 MS patients treated with natalizumab required hospitalisation or oxygen therapy. Only one of the 25 patients treated with teriflunomide and only three of the 82 patients treated with interferon beta were hospitalised.

Some studies have shown a potential protective role of interferons in COVID-19, as these are natural antiviral and anti-inflammatory proteins [43, 44]. There are also studies pointing to some antiviral activity of teriflunomide [45]. In our MS cohort, the percentage of patients treated with interferons beta (20.70% of all patients) in relation to those treated with dimethyl fumarate (41.41% of all patients) is much lower than in the entire Polish MS population. In Poland, dimethyl fumarate and interferons beta are used by similar numbers of MS patients (5,939 and 6,095 patients in 2019 respectively). In our MS cohort, patients were most frequently treated with dimethyl fumarate, and 13 of them (7.93% of the dimethyl group) needed hospitalisation. However, our cohort is not large enough to draw conclusions about the use of DMT and any protective or non-protective role during SARS-CoV-2 infection.

A potential source of bias in our study is that we included only patients who were treated in specialised MS centres. Also, immobile patients with a high degree of motor and/or cognitive disability were not included in our study, and in that group the outcomes could potentially be worse. Finally, we could not assess differences between treated versus non-treated MS patients, since our study group only included subjects on DMTs.

Conclusions

Our study did not provide evidence of a more severe course of COVID-19 in a group of Polish patients treated with several DMTs. Most patients did not require hospitalisation or oxygen therapy. Only one patient died. We did not observe a significant difference in the severity of SARS-CoV-2 infection regarding age, MS duration, the degree of disability as measured by EDSS, presence of comorbidities, lymphocyte count, or the use of different DMTs. There is an urgent need to continue multicentre data collection to increase the understanding of SARS-CoV-2 infection impact on MS course in patients treated with DMTs, especially concerning the long-term complications after SARS-CoV-2 infection.

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SHORT COMMUNICATION

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Effect of COVID-19 pandemic on stroke admissions and quality of stroke interventional treatment in Masovian Voivodeship

Aleksander Dębiec[1], Marta Bilik[2], Piotr Piasecki[3], Adam Stępień[1], Jacek Staszewski[1]

[1]Clinic of Neurology, Military Institute of Medicine, Warsaw, Poland
[2]Department of Neurology with Stroke Unit, John Paul II Western Hospital, Grodzisk Mazowiecki, Poland
[3]Department of Interventional Radiology, Military Institute of Medicine, Warsaw, Poland

ABSTRACT

Aim of study. To assess the impact of the coronavirus disease 2019 (COVID-19) pandemic on the pathway of stroke interventional services and major quality indicators of stroke reperfusion therapies in Masovian Voivodeship.

Materials and methods. An exploratory retrospective analysis was performed at two comprehensive stroke centres to assess changes in stroke care between the early phase of the COVID-19 pandemic (weeks 10–18 of 2020) and the same period in 2019.

Results. Of the 419 included stroke patients, 186 (44.4%) presented during the COVID-19 period. There was an increase in in-hospital delays for reperfusion therapies, and a significant decrease in the number of acute cerebrovascular accident admissions, predominantly related to a low number of transient ischaemic attack (TIA) admissions to hospital (-20.17%). The delays were shorter in the mothership paradigm than in the drip-and-ship paradigm of acute stroke care (onset-to-groin 293 *vs.* 232 min, p = 0.03). No differences in stroke aetiology, large-vessel occlusion frequency, or severe stroke admissions in the COVID-19 period were observed.

Conclusions and clinical implications. COVID-19's emergence was correlated with a significant reduction in admissions to stroke departments, particularly for TIAs, and a prolonged delay in reperfusion stroke treatment, especially in the drip-and-ship paradigm. An educational campaign to raise public awareness of TIA and/or stroke symptoms and immediate reorganisation of stroke care during the COVID-19 era are necessary.

Key words: stroke, COVID-19, healthcare system, mechanical thrombectomy, stroke quality measures

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Introduction

The World Stroke Organisation has identified a marked fall in stroke presentations and a widespread impact of the coronavirus 2019 (COVID-19) pandemic on stroke services, with reduced evaluations and admissions for stroke during the first half of 2020 [1].

Despite the potential consequences of untreated or undiagnosed strokes, patients are less willing to seek medical care. This is related to the call for social distancing and increased use of remote teleconsultations recommended by the Polish Ministry of Health instead of face-to-face meetings [2, 3]. The pandemic has required drastic changes in resource allocation, which can affect stroke care delivery. Knowledge of the gaps in the stroke interventional service pathway is important because of the great impact of delays on stroke outcome. Reports of the effect of COVID-19 on Polish health services in acute cerebrovascular accidents are lacking.

Methods

The aim of this study was to assess the impact of the COVID-19 pandemic on the stroke interventional service pathway and care quality indicators for stroke management. In this exploratory retrospective analysis, we collected data

Address for correspondence: Aleksander Dębiec, Clinic of Neurology, Military Institute of Medicine, Szaserow 128 Str., 04-141 Warsaw, Poland, e-mail: adebiec@wim.mil.pl

on the number of consecutive hospital admissions of adults aged 18-plus admitted due to a final diagnosis of acute cerebrovascular accident (ischaemic stroke, haemorrhagic stroke, subarachnoid haemorrhage (SAH) and transient ischaemic attack [TIAs]), stroke subtypes (using the TOAST classification), reperfusion therapies and stroke quality measures (door-to-needle [DTN], door-to-computed tomography [DTCT], door-to-groin [DTG], onset-to-groin [OTG], effective recanalisation [TICI 2b or 3], and 30-day mortality rate).

Data was collected from two comprehensive stroke centres (CSCs) covering majority of interventional stroke services for Masovian Voivodeship that serve as referral bases for 15 primary stroke centres in this region, which has a population of 800,000, and included all patients hospitalised in weeks 10 to 18 of 2020 (the initial COVID-19 period) and the same period in 2019 (the pre-COVID-19 period). 1 March 2020 (week 10) was selected as the start date of the COVID-19 period, as this was the date when the first patient developed COVID-19 symptoms with serological confirmation of SARS-CoV-2 infection. On 20 March 2020, Poland was placed into lockdown by government, but social distancing and the cancellation of scheduled hospital admissions had been encouraged since the beginning of March. The number of stroke/TIA cases is presented as cases/100,000 inhabitants, and the population was assumed to remain stable from 2019 to 2020 because the change in population in recent years has been small, and no mass migration from cities was observed. Data was compared by univariate analysis using the Wilcoxon-Mann-Whitney test and 2-tailed Fisher's exact test using PQStat software. Differences with p values < 0.05 were considered statistically significant.

Results

Of the 419 included patients, 186 (44.4%) presented in the COVID-19 period (Tab. 1). There was a significant decrease in the number of acute cerebrovascular accident admissions (-20.17%) between the pre-COVID-19 and COVID-19 periods, which was related to the low number of TIA admissions, especially in weeks 12, 13 and 17 (Fig. 1). There were no differences in stroke aetiology, the frequency of large-vessel occlusions, severe stroke admissions, or reperfusion procedures between 2020 and 2019. However, major delays (DTCT, DTN, DTG, and OTG) in patients receiving reperfusion treatment significantly increased during the COVID-19 period. There was also a significant increase in OTG time for patients treated in a drip-and-ship model compared to that for patients treated with the mothership paradigm (293 *vs.* 232 min, p = 0.03). The 30-day mortality rates and functional outcomes were similar in the COVID-19 and pre-COVID-19 periods.

Discussion

We conducted an exploratory analysis to estimate the change in the number of new stroke diagnoses in our region, and to evaluate the impact of the COVID-19 pandemic on major stroke quality measures.

Our study showed that the stroke care system in the Masovian Voivodeship was significantly affected by COVID-19, with a 20% decrease in acute cerebrovascular accident admissions. The World Stroke Organisation reported a global reduction of 42% in acute cerebrovascular accident admissions [4]. A recent paper revealed a decrease in general stroke admissions of 19.4% and a reduction in stroke unit admissions of 24.6% from January to May 2020 compared to the same months in 2019 in Malopolska Voivodeship. Moreover, the number of patients treated with interventional services declined during the COVID-19 pandemic [-32% for intravenous recombinant tissue plasminogen activator (rtPA) and -25% for mechanical thrombectomy] compared to the previous year. The exact figures, including stroke quality measures, were not provided [5].

Decreases in the number of acute stroke admissions could be caused by fear of COVID-19. Strict social distancing rules persuaded patients to avoid face-to-face medical consultation. Additionally, isolation could also have an impact through reducing the chance of another individual noticing stroke symptoms [2]. The decrease in the number of admissions to stroke departments during the COVID-19 pandemic observed in our study was mainly related to fewer admissions due to TIAs. TIA patients have a high short-term risk of developing ischaemic stroke, especially within the first 48 hours, so a public education campaign raising awareness of stroke as well as TIA signs, the need for timely diagnosis, and urgent preventive treatment, are all essential to reduce this risk.

The major problems revealed in our study involved pre- and in-hospital delays. Factors causing delays were the COVID-19 screening process and the reallocation of medical staff and protective equipment to COVID-19 care, which led to a shortage of resources at non-COVID hospitals and an inability to create or maintain fast-track stroke-care channels [2]. Moreover, healthcare professionals faced physical and mental pressure due to the continuously high risk of SARS-CoV-2 infection and were overworked because of quarantined or relocated colleagues [6, 7].

COVID-19 testing should not cause any impact on or delay to stroke diagnostics or treatment. Therefore, some authors have suggested the addition of chest CT to standard stroke protocols, which could identify pulmonary COVID-19 complications, and/or the implementation of fast screening, for example rapid antigen testing for SARS-CoV-2, the results of which may be later confirmed with RT-PCR testing. Furthermore, every patient must be treated as potentially infected and wear a mask throughout the whole diagnostic pathway, with the exception of a facial nerve palsy examination to facilitate appropriate NIHSS evaluation [2]. The introduction of masks and antigen testing in our stroke centres improved the in-hospital flow of patients and boosted the sense of safety among staff. However, exact data on how these measures affected quality metrics in stroke care is lacking.

Table 1. Clinical characteristics of studied cohort

	Pre-COVID-19	COVID-19	P
n (%)	233 (55.6)	186 (44.4)	
Sex (F) n (%)*	124 (53.2)	88 (47.3)	0.2
Age mean (± SD)*	71.9 (13.6)	69.8 (13)	0.1
Acute cerebrovascular incident admissions/100,000 inhabitants in study period	29.125	23.25	0.04
Reason for acute cerebrovascular hospital admission			
TIA	45 (19.3)	20 (10.7)	0.01
non-TIA	188 (80.7)	166 (89.2)	-
Ischaemic stroke	170 (72.9)	153 (82.2)	0.2
Intracerebral haemorrhage	18 (7.7)	11 (5.9)	0.2
SAH	0	2 (1)	-
Ischaemic stroke aetiology			
LAD	50 (23.2)	46 (26.13)	0.2
CS	68 (31.6)	42 (23.8)	-
SVD	48 (22.3)	47 (26.7)	-
LVO**	77 (33)	56 (30)	0.7
Intravenous rtPA	68 (29.2)	54 (29)	0.9
DTN	29.7 (21)	48 (23.5)	< 0.01
DTCT	25.9 (10)	37.7 (25)	< 0.01
rtPA+ mechanical thrombectomy	27 (11.6)	30 (16)	0.1
Mechanical thrombectomy	39 (16.7)	34 (18.3)	0.6
NIHSS>8 p	77 (45)	71 (47)	0.9
NIHSS admission	11.9 (8)	10.2 (7)	0.05
NIHSS discharge	6.3 (7)	4.9 (5)	0.06
mRS discharge	3.3 (2)	3.1 (2)	0.2
mRS admission	4.2 (3)	4.4 (2)	0.6
mRS 30 day	4.3 (2)	4.6 (2)	0.4
30-day mortality	35 (15)	21 (11.5)	0.7
DTCT	27.1 (10)	41.2 (27)	0.04
DTG (drip-and-ship)	35 (41)	73 (76)	0.04
DTG (mothership)	75.9 (56)	123.7 (75)	0.03
OTG (all patients)	223 (71)	259 (80)	< 0.01
OTG (drip-and-ship)	240 (69)	293 (51)	0.01
OTG (mothership)	203 (74)	232 (104)	0.04
Effective recanalisation (2b, 3) n (%)	27 (73)	24 (88.8)	0.11
30-day mortality n (%)	9 (24)	9 (28)	0.7
30-day mRS mean (±SD)	3.8 (2.1)	2.9 (2.4)	0.14
NIHSS admission	17 (6)	15.5 (5)	0.1
NIHSS discharge mean (±SD)	11 (10)	6.3 (4.1)	0.02

*Data expressed as means (± SD) or numbers (%); **vs. no LVO; TIA — transient ischaemic attack; SAH — subarachnoid haemorrhage; LAD — large artery atherothrombotic disease; CS — cryptogenic stroke; SVD — cerebral small vessel disease; LVO — large vessel occlusion; rtPA — recombinant tissue plasminogen activator; DTN — door-to-needle; DTCT — door-to-computed tomography; NIHSS — National Institutes of Health Stroke Scale; mRS — modified Rankin scale; DTG — door-to-groin; OTG — onset-to-groin

Mechanical thrombectomy is provided in Poland via two main organisational paradigms: the mothership, in which the patient is directly brought to a CSC, and the drip-and-ship model, in which initial assessment and eventual thrombolytic treatment at the primary stroke centres are followed by 'shipping' out to a CSC. The choice of one model over the other implies clinical consequences for treated patients as well as for local health policies, including the distribution of hospital facilities over the region of interest.

Our data shows that the mothership model provided significantly shorter OTG delays, of more than one hour. This may indicate that it might be considered the model of choice during the pandemic. Avoidance of additional triage in overcrowded emergency

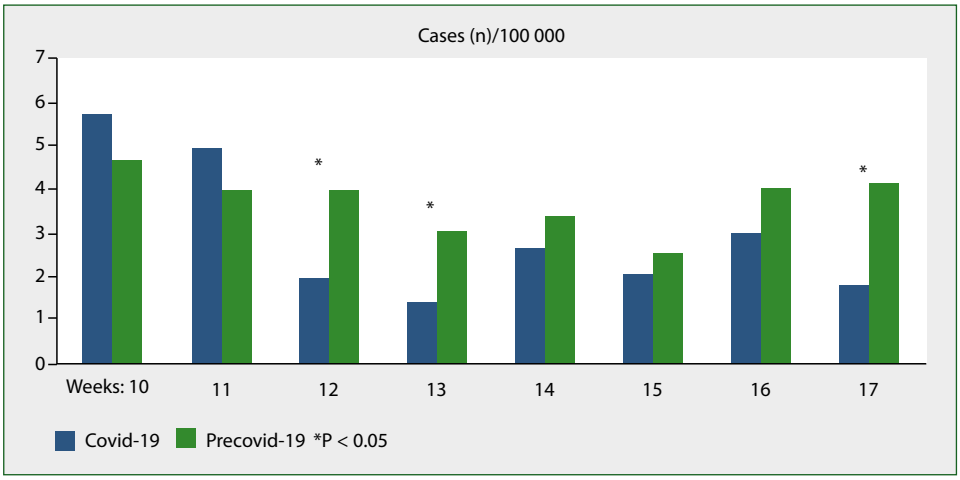

Figure 1. Acute cerebrovascular incident admissions during COVID-19 pandemic compared to those during same period in 2019

departments, and arranging transport, both of which are necessary in the drip-and-ship model, could prevent delays caused by a lack of resources that are otherwise engaged in COVID-19 care.

In November and December 2020, Poland's healthcare system struggled with the second wave of the coronavirus pandemic, with the number of new daily cases reaching over 27,000, and a national quarantine was expected. The limitation of the presented study is that the results might not be representative of other regions of Poland. Although we did not find a significant difference in stroke outcomes between patients treated during the COVID-19 and pre-COVID-19 periods, this might have been related to limited sample size. The reason for the difference in the number of stroke admissions between the weeks of the COVID-19 pandemic and the frequency of recent TIA in patients hospitalised due to stroke have not been analysed in our study, so a follow-up study looking at these metrics in the second wave would be important.

However, due to the limited number of other studies, our data might be important in terms of optimising acute stroke care before a third wave and until a COVID-19 vaccine becomes widely available.

Future directions

Our study shows that even countries less affected by the COVID-19 pandemic during the first wave, such as Poland, experienced collateral adverse effects on stroke-care quality metrics. The onset of the COVID-19 pandemic was correlated with a reduction in the number of admissions to stroke departments, and resulted in a significant increase in stroke interventional treatment delays. To combat this trend, optimising healthcare resources before subsequent pandemic waves is necessary. These actions should include reorganisation of the stroke-care network, with promotion of the mothership paradigm; the development of new in-hospital care pathways based on continuous analysis of local data; and nationwide education campaigns about the importance of immediate response to stroke and TIA symptoms. Moreover, a campaign is required to reassure patients that hospitals provide safe in-person medical care in cases of alarming symptoms.

As these findings are preliminary conclusions from our data, the full impact of the COVID-19 pandemic on stroke management in Poland still needs to be evaluated. Furthermore, studies evaluating the impact of peri-stroke COVID-19 on the risk and aetiology of stroke are needed.

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TECHNICAL NOTE

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Anterior odontoid screw fixation extrusion as reason for oesophagus perforation

Paula Piątek[1]*, Andrzej Maciejczak[1,2]*

[1]Department of Neurosurgery, St Lukas Hospital, Tarnow, Poland
[2]Medical Faculty, University of Rzeszow, Poland

ABSTRACT

Background. Type II odontoid fractures are mostly encountered in the elderly. Due to a high risk of non-union fractures in the case of conservative treatment, surgical fixation is widely recommended. Anterior odontoid screw fixation (AOSF) is a method that allows for a wide range of cervical mobility, and it is a relatively safe procedure that is recommended as the method of choice, although rare complications can be fatal when it leads to life-threatening oesophageal perforation.

Purpose. The aim of this study is to present potential risk factors which lead to these rare complications, and possible methods of treatment.

Methods. This article presents the case of a patient hospitalised in the Neurosurgery Department of St Lukas Hosital in Tarnów in 2016. A literature review was performed using PubMed; search criteria included the phrases 'odontoid fracture perforation' and 'anterior cervical spine perforation'. The search returned 235 articles, of which 55 publications were in line with the subject of this paper, with only 12 deemed appropriate for consideration.

Result. The authors present the case of an elderly patient with a history of odontoid fracture. Ten weeks after primary AOSF, the patient came to the Neurosurgery Department due to expectorating screws. This implied the need for further examination and even oesophageal reconstructive surgery or another spinal surgery. In laryngological examination and in gastroscopy there were no signs of fistula. In this case conservative treatment was proceeded. Due to odontoid fracture, non-union cervical posterior stabilisation was necessary.

Conclusion. Patients with oesophageal perforation should be treated with special care.

Key words: anterior odontoid screw fixation, oesophagus perforation, odontoid fracture

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Background and importance

Elderly patients who undergo surgical treatment are at higher risk. This is connected with the lower resistance and lower regenerative potential of their tissue. It manifests in the higher risk of non-union fractures, and intra- or postoperative perforation [1, 2]. Decisions about surgical treatment must be well thought through, especially in elderly patients. Due to a relatively low risk and high chance of union, anterior stabilisation is recommended in type II odontoid fractures [1, 3]. A rare but serious and life-threatening complication is oesophageal perforation [1, 2, 4, 5]. The strategy for treatment mainly depends on the size and location of the fistula. If the fistula is relatively small, conservative treatment is adequate. In extensive perforations, oesophageal reconstruction is required. In simpler cases, suture may be sufficient. Nevertheless, in more extensive cases vasculised flap implantation is necessary. The screws and implant should be removed [5–8]. Additional neurosurgical treatment depends on the state of healing of the fracture.

Address for correspondence: Paula Piątek, Department of Neurosurgery, St Lukas Hospital, Wałowa 33/5 Str., 33-100 Tarnów, Poland, e-mail: paulapiatek89@gmail.com

*Both authors contributed equally to this work.

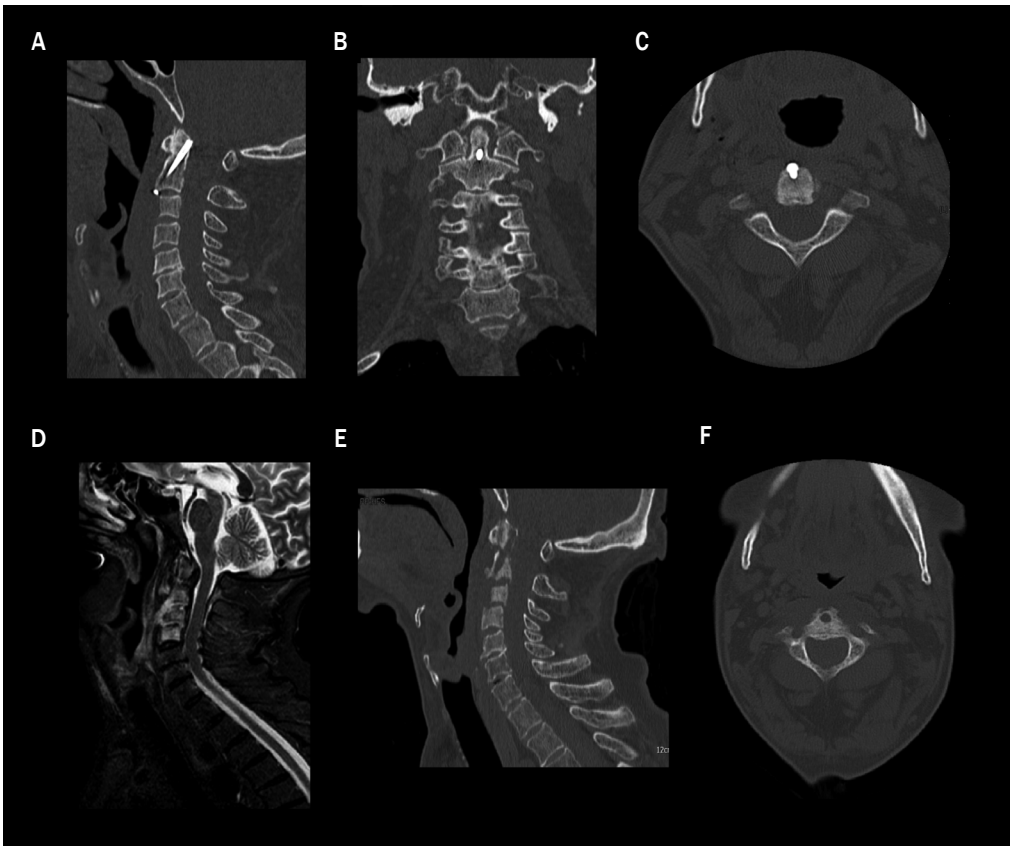

Figure 1. **A.** Postoperative sagittal CT — proper position of screw fixation; **B.** Postoperative coronal CT; **C.** Postoperative transversal CT; **D.** Postoperative saggital MRI — fistula canal in posterior pharynx extends into the larynx. Diffuse inflammatory of C2-C4 infiltrates into intervertebral discs; **E.** Postoperative sagittal CT — after screw extrusion. Fracture fissure with signs of osteolysis; **F.** Postoperative transversal CT

Clinical presentation

A patient was admitted to the neurosurgery department due to a type II odontoid fracture. This injury was the result of a fall down stairs five days earlier. On admission, the patient complained of neck and arm pain. A neurological examination revealed no abnormalities. The patient underwent ASOF. Control CT presented an acceptable screw position. Ten weeks after primary surgery, the patient returned to hospital for expectorating screw fixations (Fig. 1 A–C). The patient did not report any complaints. In laryngological examination, there were no signs of a fistula. Also gastroscopy was normal, with no signs of a fistula, bleeding, or wounds. While in MRI (Fig. 1 D), features of diffuse inflammation and signs of fistula were described. As a conservative treatment, a stiff cervical collar was used. Parenteral nutrition and antibiotic therapy were introduced. There was no pathology in thorax and cervical CT (Fig. 1 E–F). The patient was admitted to the thoracic surgery department to complete the examination. After three months, the patient was admitted to the neurosurgery department due to a primary non-union fracture. Posterior stabilisation of the C1 pedicle and C2-side mass were completed with a C1–C2 spondylodesis. In a postoperative exam, the CT implant position was correct. The patient did not report any complaints. A neurological examination revealed no abnormalities.

Discussion

A type II odontoid fracture in the Anderson and D'Alonso classification is the most frequent type of fracture in elderly patients, and is estimated at 10–15% of all cervical fractures [1, 6, 9]. In cases of non-union following conservative treatment, which is estimated to comprise from 20-56%, surgical treatment is widely recommended as the treatment of choice [1, 3]. The fusion rate in cases of anterior odontoid screw fixation is estimated to be more than 90% [1, 3, 6]. There is no conclusive evidence that patient age increases the risk of non-union fractures. Tian et al. estimated that the risk of non-union fractures is about 6% in younger patients and 25% in patients who are over 50. This is a result of osteoporosis and diminished bone quality. According to the authors, patients who are aged over 70 have the highest risk of non-union fractures [1]. The treatment method of choice is AOSF. This method provides

immediate stabilisation. Additionally, it does not limit the mobility of the spine in the C0–C2 segment and eliminates the high risk of vertebral artery damage. This technique results in high fusion rates that range from 89% to 100% [6]. The general risk of non-union fractures is estimated at 10% [1].

Surgical treatment of type II odontoid fractures is mainly performed via an anterolateral approach. The most common complications are associated with this approach. Specific complications related to anatomic areas are postoperative dysphagia (10%) or hoarseness (1.2%), wound haematomas (0.2%), and spinal cord injury (up to 0.2%). The overall rate of infection is 0.2%. About 5% of patients need revision surgery [1].

One possible complication is oesophageal perforation. The overall risk is estimated at less than 1% [1, 2]. Acute perforation is the result of an intraoperative oesophagus injury which may be the result of sharp-edged surgical instruments, implants or bones, or aggressive surgery exposure. Delayed perforation may be a consequence of local tissue necrosis, erosion or an inflammatory process in this area [2, 8]. Bones or screws, especially malpositioned or extruded, cause chronic compression or repetitive friction that can lead to local ischaemia and necrosis which result in delayed mucosal perforation of the oesophagus [5, 6, 8]. Oesophagus or pharynx perforation can lead to life-threatening complications such as aspiration pneumonia, mediastinitis, pleuritis, pericarditis, systemic sepsis or airway obstruction [2, 4, 5, 7]. The average mortality rate is estimated at 20–50% [4, 5].

Symptoms that may suggest oesophageal perforation are fever, difficulty in swallowing (dysphagia or odynophagia), weight loss, painful neck swelling or subcutaneous emphysema of the neck [7, 8]. Additionally, patients may experience foreign body sensation or a persistent cough [6]. Notwithstanding this, perforation may be asymptomatic. Only individual cases of oral screw extrusion have been described [8].

Suspected possible factors of screw extrusion are screw malposition and local infection [5, 6, 10]. Statistically, authors have reported that AOSF failure is a result of osteoporosis or poor bone quality, nonoptimal fracture compression or reduction, and non-union fractures [5, 7, 10]. Cho et al. and Koivikko et al. reported a strong influence of treatment delay and fracture gap width on surgery failure [11, 12].

In small perforations of less than 1cm, conservative treatment is preferred [8]. Treatment includes solely extraoral nutrition and antibiotic therapy [7, 8]. Cases of spontaneous healing and recovery have been reported [5]. Larger defects require surgical revision. Surgical methods of treatment include primary suture, microlaryngological transpharyngeal endoscopic techniques, and vasculised flap implantation connected with implant removal [6–8].

Conclusion

It is good practice to closely observe patients after cervical spine. Nonspecific symptoms such as fever, foreign body sensation, persistent cough or difficulty in swallowing can be the first symptoms of oesophagus perforation. Patients with a suspected oesophageal perforation should be diagnosed and treated with particular care.

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LEADING TOPIC

Constipation due to a stroke complicated with pseudo-obstruction (Ogilvie's Syndrome)

Mariusz Madalinski

Royal Stoke University Hospital, Stoke-on-Trent, United Kingdom,
Northern Care Alliance NHS Group, Royal Oldham Hospital, United Kingdom

Key words: botulinum toxin, bowel pseudo-obstruction, stroke, anal sphincter

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To the Editors:

Constipation often occurs after a stroke, with an incidence of 29-79% [1]. Although dysfunction of the brain-gut axis in stroke is recognised as the main cause of changes in bowel movement, several other factors can also contribute to constipation. Examples include reduced physical mobility and reduced fluid and/or fibre intake, especially in patients with associated dysphagia. Medication can affect bowel movement function, and there are also psychological aspects: depending on others to be able to use a toilet can lead to constipation too [1].

Constipation is probably also an independent risk of ischaemic stroke and coronary heart disease events (CHDE). This was demonstrated in a retrospective cohort study of over 3 million US veterans with a glomerular filtration rate (eGFR) ≥ 60 mL/min/1.73 m^2. The study found that constipation was linked to a higher risk of the incidence of ischaemic stroke (19%) and of CHDE (11%) [2]. A prospective study of 45,112 Japanese men and women with a 13.3-year follow-up showed that a lower defecation frequency is associated with a higher risk of overall cardiovascular disease mortality and all forms of stroke mortality [3].

Constipation is accompanied by intestinal dysbiosis; chronic inflammation partly due to bacterial endotoxins or altered gut metabolites may serve as a potential explanation for the observed associations [4]. It remains unclear whether the microbiota have an impact on the outcome of acute brain injury, but some studies have shown that alterations in the intestinal flora can reduce ischaemic brain injury in a rat model — an effect which can be transmissible by faecal transplants [5].

Nowak et al. [6] reported constipation due to a stroke complicated with pseudo-obstruction. This condition can be categorised as either acute or chronic in nature [7]. Chronic idiopathic intestinal pseudo-obstruction is clinically divided into two types: small intestinal and colonic. This causes severe, long-term constipation or abdominal pain, and can develop secondary to systemic diseases such as Parkinson's Disease or hypothyroidism, although most cases are idiopathic.

Acute colonic pseudo-obstruction (ACPO) described by the authors — also known as Ogilvie's Syndrome [8] — is a clinical entity characterised by severe colonic dilatation with no evidence of underlying mechanical or anatomical cause. The usual symptoms are acute massive abdominal distension with or without associated abdominal pain, nausea or vomiting, and constipation which is not consistently present [7].

Plain abdominal radiographs will reveal a diffusely dilated colon (≥ 6 cm), but CT is the imaging modality of choice in order to rule out mechanical obstruction. This also allows the confirmation of potential metastasis and differentiation from toxic megacolon (a complication of a variety of infectious, ischaemic or inflammatory diseases of the colon), which is characterised by its hallmark feature of marked bowel wall thickening, loss of haustration, segmental wall thinning, and the appearance of multilayers due to alternating densities of oedematous submucosa and hyperaemic mucosa (target sign) [9, 10].

Increased colonic dilatation up to 130 mm concerned the authors greatly due to a risk of perforation [7, 9]. The degree and duration of colonic distension determine the pace and sequence of management options. The authors faced the clinical dilemma of whether to treat the patient with conservative measures or to proceed with medical or endoscopic

Address for correspondence: Mariusz Madalinski, Royal Stoke University Hospital, Newcastle Road, Stoke-on-Trent, ST4 6QG. Stoke-on-Trent, United Kingdom, e-mail: mariusz.madalinski@googlemail.com

decompression of the dilated colon. The conservative measures should be directed towards eliminating or reducing factors known to contribute to the problem, and usually involve correcting electrolyte abnormalities or fluid resuscitation, ceasing opiates or any antimotility agents, and discontinuing oral intake with or without nasogastric tube decompression [7, 9].

Medical decompression with neostigmine is regarded as the initial therapy of choice for patients not responding to conservative therapy, provided if there are no contraindications to its use. This acetylcholinesterase inhibitor causes a large high amplitude of colonic peristalsis and subsequent flatus with bowel movement. It should be noted that the parasympathetic stimulation can cause not only subsequent abdominal discomfort, emesis, and excessive salivation, but also a profound bradycardia, meaning that a monitored cardiac setting is required [7]. In general, if a patient fails to respond after two doses of neostigmine, colonoscopic decompression is advised [7, 11].

Successful colonoscopic decompression has been reported in many retrospective series, but its efficacy has not been established in randomised clinical trials. It is usually performed without a preceding oral bowel preparation or enema. Colonoscopy without gas insufflation can be a technically challenging procedure and carries unknown risks [11].

Percutaneous decompression (cecostomy) is invasive and can be complicated by local infection or bleeding [11]. Percutaneous endoscopic colostomy (PEC) provides an alternative management option with the placement of PEC tubes in the caecum by a combined radiological or colonoscopic approach. The major advantage of PEC is the avoidance of general anaesthesia, but the method has not been compared to other methods of decompression [7, 11].

The exact pathophysiology of ACPO remains a topic of investigation, and no effective prevention strategy is known [7, 11]. In 1948, Ogilvie [8] first described ACPO in two patients with retroperitoneal malignancy and hypothesised that the carcinoma was responsible for disrupting the balance between the parasympathetic and sympathetic nervous system, but the specific mechanism of action has not yet been revealed. It is probably impaired a spinal reflex of defecation which is triggered by distention of the rectal wall. The defecation reflex involves the evacuation of faeces from the rectum in response to stimulation of afferent nerves in the distal bowel. The myenteric defecation reflex is responsible for eliciting a contraction of the smooth muscle of the colon and rectum, and propelling the stool toward the rectum. Simultaneous inhibition of somatic efferent pathways to the external anal sphincter permit concurrent opening of the anal canal [7].

The patient described by Nowak et al. [6] had trans-anal decompression. Potential surgery (subtotal resection with primary anastomosis) in the near future had to be taken into account to prevent a colonic perforation. However, the authors' published result of therapy with botulinum neurotoxin (BoNT) raises the question as to whether failure of the anal sphincter to relax plays a crucial role in the physiology of Ogilvie's Syndrome? Should we in fact regard the syndrome as an escalation of an outlet obstruction type of constipation, and consider whether BoNT should be applied earlier, given that the problem with constipation started after the stroke? About 20 years ago, observational studies suggested that the application of BoNT releases the blockage in glyceryl trinitrate bioactivation in smooth muscle cells and suppresses basal continuous sympathetic activity, causing modulation of anal sphincters [12]. That explanation is consistent with the current theory that favours a relative excess of sympathetic over parasympathetic tone of anal sphincters [13, 14].

It is impossible to say whether the patient had impaired rectal propulsion with paradoxical contraction of anal sphincters (type II of pelvic dyssynergia) or with incomplete relaxation of anal sphincters (type IV of pelvic dyssynergia) [15]. Contradicting Albanese and Cadeddu (pioneers of BoNT injections for anal dyssynergia), a Polish team applied 125 units of abobotulinumtoxin A for spastic pelvic floor syndrome without transrectal ultrasonography or electromyographic control [15, 16]. That was a novel approach for BoTN injections over 15 years ago [15]. I am pleased to read that the algorithm for inappropriate anal sphincter contraction found epigones without seeking a diagnostic method for locating the place for injection.

In conclusion, Nowak et al. [6] present a very interesting case of stroke complicated with Ogilvie's Syndrome where for the first time BoNT has been applied as a successful remedy. This may work over 8–12 weeks, which is an advantage over the therapy with neostigmine due to the half-life of neostigmine being only one to two hours [7]. Although the BoNT requires 24–72 hours to take effect, peaking at about 10 days, its long-lasting effect and good safety profile may challenge other therapies which are not entirely effective approaches in preventing the recurrence of Ogilvie's Syndrome.

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Myasthenia gravis and premature ovarian failure — a causal link

Noorasyikin Mohamed Arifin*, Ching Soong Khoo*, Dalleen Leong, Tze Yuan Tee, Hui Jan Tan

Department of Medicine, Universiti Kebangsaan Malaysia Medical Centre, Kuala Lumpur, Malaysia

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To the Editors:

Myasthenia gravis (MG) is a well-recognised autoimmune disease of the postsynaptic neuromuscular junction resulting in fluctuating weakness and fatigue of the skeletal muscles. Autoantibodies against the acetylcholine receptor (AChR) are most commonly found in MG. Like other autoimmune conditions, MG has been reported in association with thyroiditis, pernicious anaemia and systemic lupus erythematosus [1]. Premature ovarian failure (POF) is defined as anovulation with amenorrhoea in females younger than 40 years with evidence of hypo-oestrogenic and hypergonadotropic serum levels [2]. Recognised as being of autoimmune aetiology, there have been, however, very few reports on POF in conjunction with MG. We herein describe two cases of MG with coexisting POF, and perform a brief literature review.

Case 1

A 24-year-old nulliparous woman presented with bilateral thigh weakness, ptosis and diplopia for the past two years. She had also been afflicted with amenorrhoea two years preceding the limb weakness. Attaining menarche at the age of 14, her menses had always been regular. On examination, she had normal secondary sexual characteristics and there were no features of hypothyroidism, hyperpigmentation or vitiligo. She had bilateral incomplete ptosis with a normal visual field. The muscle power of both hips was 3/5. Antibodies to the AChR were detected. Computed tomography (CT) of the chest revealed no thymic enlargement. Her single-fibre electromyography (SFEMG) showed prolonged jitter and repetitive nerve stimulation (RNS) revealed a significant decremental response. She had hypo-oestrogenemia with a post-menopausal range of follicle-stimulating hormone (FSH) and luteinising hormone (LH) levels. She was treated with pyridostigmine 60 mg four times a day and azathioprine 75 mg daily. She was referred to a gynaecologist, and after much deliberation oral contraceptives (OCPs) were prescribed as treatment. After six months of treatment, she remained asymptomatic of MG and her menses resumed. Her condition has been stable with pyridostigmine 60 mg once daily and azathioprine 75 mg daily since then. Her periods have been regular without OCPs in the last six months of follow up.

Case 2

A 35-year-old para 1 woman presented with bilateral ptosis at the end of each day of three months' duration. Cessation of menses had occurred seven months preceding the ptosis. Upon review, there was bilateral ptosis with fatigability. Antibodies to the AChR were positive. Her SFEMG showed prolonged jitter with positive RNS study. Her blood tests revealed hypo-oestrogenemia with a post-menopausal range of both FSH and LH levels. Her chest CT revealed a thymic mass, for which thymectomy was performed. The histology concluded that the resected tissue was follicular thymic hyperplasia. She regained menses 20 months after thymectomy, and her symptoms of MG were controlled with a low dose of pyridostigmine.

Human ovaries have long been recognised as a target for autoimmune attacks leading to ovarian dysfunction, especially premature ovarian failure (POF). POF is heterogeneous and

Address for correspondence: Ching Soong Khoo, Neurology Unit, Department of Medicine, Universiti Kebangsaan Malaysia Medical Centre, Jalan Yaacob Latif, Bandar Tun Razak, Cheras, 56000 Kuala Lumpur, Malaysia, e-mail: chingsoongkhoo@gmail.com

*Both authors have contributed equally to this work.

Table 1. Summary of our case series and previously reported cases

	Case 1	Case 2	Williams on, 1980 (1) [6]	Williams on, 1980 (2) [6]	Kuki, 1981 [8]	Bateman, 1983 [5]	Chung, 1993 [11]	Ryan, 2004 [1]	Li, 2010 [7]	Çakir, 2011 [9]
Age at onset (MG)	24	35	19	17	23	21	27	41	19	15
Age at onset (POF)	22	35 (7 months preceding MG symptoms)	18	29	19	21	27	27	19	18
MG symptoms	Ptosis, diplopia, proximal lower limb weakness	Ptosis, fatigability	Muscle weakness	Muscle weakness	Diplopia, bulbar muscle weakness	Muscle weakness	Ptosis, fatigability, proximal muscle weakness	Diplopia, fatigability, difficulty with fine motor manipulations	Ptosis, fatigability, proximal muscle weakness, respiratory muscle weakness	Ptosis, muscle weakness
Anti-AChR Ab	+	+	N/A	N/A	N/A	N/A	N/A	+	+	+
Ab related to POF	N/A	N/A	AOA +	AOA +	Anti-LH Ab +	N/A	N/A	Anti-FSH Ab +	AOA +	AOA -
Ovarian biopsy	N/A	N/A	+	+	N/A	+	N/A	+	N/A	N/A
Treatment	Pyridostigmine, azathioprine	Thymectomy, pyridostigmine	Ambenonium, OCP	Thymectomy, pyridostigmine, prednisolone	Thymectomy, pyridostigmine, hormone	Thymectomy, PE	Thymectomy, pyridostigmine, HRT	Thymectomy, pyridostigmine, HRT	PE, pyridostigmine, prednisolone	Pyridostigmine, prednisolone, thymectomy
MG outcome	Good	Good	Partial response	Partial response	Partial response	Good	Good	Worse during menstruation Improved with thymectomy	Worse with HRT	Partial response
Resumption of menses	Yes	Yes	No	No	No	Yes	Spontaneous pregnancy	No	No	Yes

	Liu, 2018 [12]	Cao, 2019 (1) [13]	Cao, 2019 (2) [13]	AlAsiri, 2020 [14]
Age at onset (MG)	23	20	21	37
Age at onset (POF)	22	20	21	17
MG symptoms	Ptosis, fatigability, dysarthria, dysphagia	Unexplained exhaustion on walking short distances	Right eyelid ptosis, diplopia	Right eyelid ptosis, diplopia, easy fatigability, weakness in upper limbs
Anti-AChR Ab	+	+	+	+
Ab related to POF	N/A	N/A	N/A	-
Ovarian biopsy	N/A	N/A	N/A	N/A
Treatment	Pyridostigmine, thymectomy, methylprednisolone and IVIg	Pyridostigmine, methylprednisolone, mycophenolate mofetil	Pyridostigmine, thymectomy	Pyridostigmine, HRT
MG outcome	Worse with HRT Remitted after immunosuppressants	Good	Good	N/A
Resumption of menses	Yes	Yes	No	No

Ab — antibody; MG — myasthenia gravis; POF — premature ovarian failure; AChR — acetylcholine receptor; N/A — not available; AOA — anti-ovarian antibody; PE — plasma exchange; OCP — oral contraceptive pill; HRT — hormone replacement therapy; LH — luteinising hormone; FSH — follicle-stimulating hormone; IVIg — intravenous immunoglobulin

can be due to other causes such as environmental factors, genetic aberrations, and metabolic conditions. Up to 20% of patients with POF are reported to have concomitant autoimmune conditions such as adrenal insufficiency, thyroiditis, and/or diabetes mellitus [3].

POF is also well known as a part of autoimmune polyglandular syndrome. Myasthenia gravis (MG) is an autoimmune disorder with autoantibodies against the acetylcholine receptor (AChR) most commonly found. These autoantibodies are detected in up to 90% of MG patients. Other antibodies found in MG are directed to muscle-specific receptor tyrosine kinase (MuSK), which is a transmembrane component of the postsynaptic neuromuscular junction, and to lipoprotein-related protein 4 (LRP4), which is an agrin receptor needed for agrin-induced activation of MuSK and AChR clustering and neuromuscular junction formation. Only a minority of MG patients are seronegative. It has been reported that MG patients might have an increased number of oestrogen receptors α in thymocytes and peripheral T lymphocytes [4]. This finding could propagate the development of POF. It has been hypothesised that AChR could exist in the ovaries, and that cross-reactivity with antibodies to the muscles and AChR could explain POF associated with MG [5]. Autoimmunity is further strengthened by the presence of anti-ovarian antibodies (AOA) found in three patients with MG and POF [6, 7].

Interestingly, in our literature review, one patient was found to have autoantibodies directed to the follicle-stimulating hormone, and another patient had autoantibodies against the luteinising hormone [1, 8]. AOA were not tested in our two cases as the test is not available in our country, which is a limitation of our study. However, the significance of the presence of circulating AOA and their predictive value in diagnosing POF are matters for discussion.

Both our cases presented with secondary amenorrhoea preceding MG, with no other associated autoimmune condition. One of our patients resumed her menses after thymectomy, which accords with the cases published by Bateman and Çakir [5, 9]. This indicates that the thymus might play a role in the pathogenesis of both conditions, which are already known to be a source of driving autoimmunity. AChR autoantibodies are thought to originate from the hyperplastic germinal centres in the thymus. This could well explain why most of the reported cases, including our two, are AChR positive where a causal link is observed. Genetic factors may contribute to the pathophysiology of immune-mediated diseases, namely the human leukocyte antigen (HLA) types. For instance, HLA-DR3 is significantly associated with POF as well as with MG [10]. A summary of our patients and other published cases is appended to this article (Tab. 1).

In conclusion, there is a causal link between MG and POF, the occurrence of which is not purely coincidental. This is based upon the presence of autoantibodies, and the resolution of amenorrhoea after thymectomy or immunotherapy in some cases. Further large-scale studies are required in order to provide better insights into the pathogenesis of both these diseases.

Conflict of interest: *The authors declare that they have no conflict of interest.*

Ethical approval: *This study was conducted in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments.*

Informed consent: *Informed consent was obtained from both patients in this study.*

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