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ARTICLE

The impact of botulinum toxin type A in the treatment of drooling in children with cerebral palsy secondary to Congenital Zika Syndrome: an observational study

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ABSTRACT

Objective: The main aim of this study was to determine the impact of botulinum toxin A (BTX-A) on severity and frequency of drooling in children with Cerebral Palsy (CP) secondary to Congenital Zika Syndrome (CZS).

Methods: This is a prospective longitudinal observational study including 23 children who received bilateral injections of BTX in the parotid and submandibular glands. The Thomas-Stonell & Greenberg Drooling Severity and Frequency Scale was applied by a multidisciplinary team including Speech, Language and Hearing professionals. The Global Impression of Improvement (GII) Scale was also applied to assess parents' subjective perceptions of therapeutic response. Swallowing was assessed using Doppler ultrasonography. Univariate logistic regression was used to analyse differences between responders and non-responders.

Results: Participant age varied from 27 to 38 months (mean 31.78, SD = 2.61) all presented with Gross Motor Function Classification System (GMFCS) V. Drooling Severity and Frequency Scale scores ranged from 7 to 9 points (median = 9) prior to BTX administration and from 4 to 6 (median = 6) after. Pre- and post-treatment reduction in drooling severity occurred ($Z = -3.746$; $p < 0.001$). No cases of drooling worsening were reported. Only two subjects presented adverse effects attributed to BTX administration. Correlation was only confirmed with GII.

Discussion: This article presents the safe and positive impact of BTX-A administration guided by anatomical references described in the literature, even on children with microcephaly. Further studies are needed to facilitate the use of Doppler ultrasonography as a tool to characterize changes in sensory processing and motor response following intraoral input in children with CP.

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KEYWORDS
Cerebral palsy; Congenital Zika Syndrome; drooling; botulinum toxin type A; Doppler ultrasonography

Introduction

The Zika Virus (ZIKV) is a single-stranded RNA arbovirus of the genus *Flavivirus* and family *Flaviviridae*. The infection is transmitted by mosquitoes of the genus *Aedes*, the same vector of Chikungunya and Dengue fever [1]. In 2015, a ZIKV epidemic emerged in Brazil, mainly in the Northeast region of the country. In this context, the entity 'Congenital Zika Syndrome' (CZS) emerged, combining a spectrum of abnormalities presented in newborns and children with intrauterine virus infection, characterized by a pattern of structural and functional abnormalities secondary to damage to the central and peripheral nervous system, causing severe forms of Cerebral Palsy (CP).

Oral-motor dysfunction, dysphagia and/or changes in intraoral sensitivity in individuals with CP secondary to CZS can cause drooling which, in addition to the social impact of decreased self-esteem and impeded communication, also involves the risk of aspiration and significant lung damage. The intraglandular BTX injection is widely accepted as an effective treatment for drooling in children with central nervous system disorders [2]. Its anti-secretory mechanism blocks the parasympathetic command of saliva production [3], and inhibits acetylcholine release from nerve terminals [4,5]. However, as CZS is a recently recognized cause of cerebral palsy, a detailed previous description about drooling and its treatment in this specific population has not been done yet.

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The main aim of this study was to determine the impact of botulinum toxin type A (BTX-A), administered in the parotid and submandibular glands, on severity and frequency of drooling in children with CP secondary to CZS, as well as an assessment of the association between a reduction in drooling and children's clinical characteristics and ascertaining the possible predictive factors for therapeutic response.

Methods

Study design and participants

This is a prospective longitudinal observational study, conducted in Neuropediatric Outpatient Clinic at the Federal University of Bahia (Salvador, Brazil), on children aged from 2 years, of both genders, diagnosed with CP secondary to CZS and with a medical recommendation for the administration of BTX to reduce drooling. For the sake of convenience, the sample consisted of 41 children on a waiting list for the administration of BTX-A.

The defining diagnostic criterion was Spastic or Dyskinetic Cerebral Palsy, the presence of motor deficits associated with non-progressive spasticity or involuntary movements affecting functional capacity and arising from pre-, peri- or post-natal brain injury that occurred prior to 2 years of age. The defining diagnostic criterion for CZS took account of the criteria used by França et al. [6] for the selection of highly probable cases: neuroimaging examination (computed tomography and/or MRI of the brain) suggestive of congenital infection (cerebral calcifications, ventricular enlargement or both) and negative tests for other congenital infections (cytomegalovirus, rubella, toxoplasmosis and syphilis). Children who met the following criteria were therefore eligible for selection: (1) born to mothers whose pregnancies occurred at the time of the ZIKV epidemic in Brazil (date of birth after June 2015); (2) manifesting the above-mentioned criteria for probable CZS; and (3) whose mothers had a rash during pregnancy, to reinforce the association with a potential ZIKV infection during pregnancy.

The inclusion criteria were: (1) diagnosis of CP secondary to CZS; (2) presence of drooling; (3) any level of functional impairment; (4) medical recommendation for administration of BTX in the parotid and/or submandibular glands; and (5) parental consent to participate in the study. We did not include individuals with skin lesions at the site of toxin administration, those who had been vaccinated less than a week prior to the study, or who presented with respiratory infections or fever. We excluded participants whose therapeutic scheme (antiepileptic and anticholinergic drugs) changed during the assessment period, since this could interfere with the outcome measurement.

Procedure

Botulinum toxin type-A – 500 U vials of AbobotulinumtoxinA (Dysport®) – was administered as part of the participants' medical treatment by a neuropediatrician, according to the anatomical references described in the literature. All the subjects received topical anaesthetic (EMLA®) 30 minutes prior to administration. Intraglandular injections with a 25 mm needle were made at two administration points in the parotid gland and one in the submandibular, bilaterally at a dose of 25 U per gland, according to the references described in the literature [7,8]. The needle was inserted at a depth of 1 cm into the preauricular region of the parotid gland, behind the angle of the ascending mandibular branch, and then into the inferoposterior region of the gland, located just before the mastoid process. The submandibular administration occurred through percutaneous injection into the submandibular triangle. For participants who received BTX-A in other muscles in order to reduce spasticity, the total administered dose was duly recorded. The applications were performed only once on each child.

Outcome assessment

Participant drooling assessments were performed at two points: (t1) immediately prior to BTX-A administration; and (t2) following administration. The interval between administration and second assessment varied between 42 and 44 days.

The Drooling Severity and Frequency Scale instrument described by Thomas-Stonell & Greenberg in 1988 [9] was applied by a multidisciplinary team including Speech, Language and Hearing professionals. The children were classified according to drooling severity with the following attributions: 1) does not drool; 2) moist lips (mild); 3) wet lips and chin (moderate); 4) damp clothing (severe); and 5) wet clothes, hands and objects (fulsome). For its part, frequency was classified as: 1) never; 2) occasionally; 3) frequently (daily); 4) constantly (the whole time). The scores for the two scales were totalled to generate a combined score, which varied from 2 to 9.

The Global Impression of Improvement (GII) Scale was also applied to ascertain the parents' subjective perception of the therapeutic response, based on seven possible responses: 1) very much improved; 2) much improved; 3) minimally improved; 4) no change; 5) minimally worse; 6) much worse; and 7) very much worse.

Responders were considered to be those participants who presented a reduction in at least one point on the Drooling Severity and Frequency Scale. All the children's clinical characteristics were assessed by a multidisciplinary team including a physiotherapist;

a Speech, Language and Hearing professional; and a neuropediatrician, at t1.

Swallowing assessment with Doppler ultrasonography

Swallowing was one of the clinical characteristics assessed at t1, before BTX-A administration, through cervical auscultation with Doppler ultrasonography. We used a portable ultrasonic detector (model DF-4001, Martec®) with a single crystal flat disk transduce to measure five variables: initial sound wave frequency (IF), peak frequency (PF), initial intensity (II), peak intensity (PI), and swallowing duration (T) – the elapsed time from the beginning to the end of the acoustic signal. During assessment, the children remained in breastfeed position on their mothers' laps, with necks free. The transducer beam angle was positioned between 30 and 60º in the right lateral region of the trachea, immediately below the cricoid cartilage, and gel was used to optimize skin contact. All subjects received the same food consistency during the procedure, assessing swallowing of pasty food (Danoninho®, petit suisse yogurt), offered with a spoon, and liquid (water), offered with a glass or bottle. Feeding, which was carried out by the parents, was provided spontaneously – volume could not therefore be determined.

Ethical aspects and statistical analysis

The study was approved by the FIOCRUZ Research Ethics Committee (IRB number 3.184.683) and is included in the research line under cooperation from this agency with the Medical School of Bahia at the Federal University of Bahia (Salvador, Brazil). Participating children were part of the BTX-A drooling treatment programme and were only included in the study following written and verbal informed consent from their parents.

To characterize the sample and report adverse effects, a descriptive statistical analysis was performed on the data. Evaluation measures' adherence to the normality curve was determined by the Shapiro-Wilk test. Median, minimum and maximum values were calculated for continuous variables with non-normal distribution and mean and standard deviations for those with normal distribution. The Wilcoxon test for nonparametric variables and related samples was applied to compare the ordinal drooling scale scores before and after treatment. Spearman's correlation test was used to analyse the difference between scores and clinical characteristics. Univariate logistic regression was also applied to analyse the differences between responders and non-responders. The SPSS V22 for Windows statistical programme was used, and $p < 0.05$ values were considered statistically significant.

Results

Participant characteristics

Of the 41 children aged between 2 and 3 years selected through the defining diagnostic criteria, 10 did not present drooling with a recommendation for BTX-A treatment and the parents of one did not consent to their participation in the study. Thirty children therefore fulfilled all the inclusion criteria and were subject to BTX administration. Of these, 23 completed the two assessments and constitute the final sample with 15 (65.2%) female and 8 (34.8%) male. All received 25 U of BTX-A bilaterally in the submandibular and parotid glands. Participant age varied from 27 to 30 months (mean = 31.78, SD = 2.61). The children were orally fed, none had undergone gastrostomy and drooling was predominantly anterior. All the children presented spasticity in both upper and lower limbs and Gross Motor Function Classification System (GMFCS) V. In terms of skill acquisition, 17 children (73.9%) had cervical balance, 6 (26.1%) partially rolled, 2 (8.7%) rolled completely, while only one (4.3%) was able to sit without support, crawl and stand with support, and no child could walk either with or without support. Table 1 contains the population's clinical characteristics.

All the children were enrolled in physiotherapy rehabilitation programmes. Approximately 19 (82.6%) and 17 (73.9%) also participated in speech,

Table 1. Clinical characteristics at t1 (n = 23) of children with cerebral palsy secondary to CZS.

Characteristics	n (%)
Head circumference at birth (cm)*	29.50 (±1.87)
Mean	
Current head circumference (cm)*	40.38 (±2.97)
Mean	
Head circumference difference (cm)*	10.78 (±2.61)
Mean	
Weight (kg)*	11.37 (±2.19)
Mean	
Visual impairment	11 (47.8)
Yes	12 (52.2)
No	
Hearing impairment	1 (4.3)
Yes	22 (95.7)
No	
Arthrogryposis	1 (4.3)
Yes	22 (95.7)
No	
Epilepsy	17 (73.9)
Yes	6 (26.1)
No	
Orofacial dyskinesia	8 (34.8)
Yes	15 (65.2)
No	
Dystonia	3 (13)
Yes	20 (87)
No	
Number of PRs **	1 (0–3)
Median	
Total weight-based dose (U/kg)*	33.56 (±4.59)
Mean	

* Head circumference at birth, current head circumference, head circumference difference, weight and total weight-based dose are given as means (standard deviation). **Number of PRs (primitive reflexes) is given as the median (minimum/maximum).

language and hearing therapy, as well as occupational therapy. Three children (13%) participated in music therapy programmes and one (4.3%) in hippotherapy. Two children (8.7%) were on a ketogenic diet for the treatment of refractory epilepsy.

Four children had been hospitalized for bronchopneumonia treatment, with the hospitalization periods varying from three to ten days. No child had been hospitalized more than once.

Assessment of drooling

Participant scores on the Drooling Severity and Frequency Scale varied from 7 to 9 points (median = 9) prior to BTX administration (t1), and from 4 to 6 (median = 6) following treatment (t2) (Figure 1). The Wilcoxon test for nonparametric variables and related samples revealed a pre- and post-treatment reduction in drooling severity ($Z = -3.746$; $p < 0.001$). On the severity scale alone, scores varied from 4 to 5 (median = 5), at t1, and from 2 to 5 (median = 4) at t2 ($Z = -3.461$; $p < 0.001$). For the frequency scale alone, the variation ranged from 3 to 4 points (median = 4) at t1, and 2 to 4 (median = 3) at t2 ($Z = -3.879$; $p < 0.001$).

Responses to the Global Impression of Improvement (GII) Scale varied from very much improved (1) to no change (4) (median = 3). Six children's (26.1%) parents perceived their therapeutic response to be very much improved (1), 5 (21.7%) much improved (2), 6 (26.1%) minimally improved (3), while no change was perceived in 6 (26.1%) (4). No cases of worsening of drooling were reported.

Only two subjects presented adverse effects attributed to BTX-A administration. In one, a thickening of saliva and dysphagia occurred 2 weeks following administration and lasted for 7 days, while in another, a two-day dry cough was observed, starting 2 days following the procedure.

Predictive factors

The difference between Severity and Frequency Scale scores varied from 0 to 5 (median = 2). There was a negative and moderate correlation between score differences and GII perceptions ($\rho = -0.653$; $p < 0.001$), indicating that the greater the reduction in drooling, the lower the GII, representing a more significant improvement according to parent perception. There was no correlation between the difference in scores and head circumference growth since birth ($\rho = -0.188$; $p = 0.414$), total weight-based dose ($\rho = -0.148$; $p = 0.502$), or number of primitive reflexes ($\rho = -0.386$; $p = 0.069$). There was also no correlation between GII and head circumference growth since birth ($\rho = 0.085$; $p = 0.713$), total weight-based dose ($\rho = 0.021$; $p = 0.925$), or number of primitive reflexes ($\rho = 0.238$; $p = 0.274$).

Eighteen children (78.3%) obtained a reduction equal to or above one point on the Severity and Frequency Scale and were thus considered responders. Table 2 includes the OR values for the potentially plausible predictive factors for therapeutic response. None of the variables presented statistical significance.

Assessment of swallowing

Swallowing was assessed in ten children using Doppler ultrasonography in t1, prior to toxin administration. Table 3 presents this data. A negative and moderate correlation was found between peak frequency for liquids and score on the Drooling Frequency Scale prior to BTX administration ($\rho = -0.698$; $p = 0.025$). We also found a positive and strong correlation between perceived GII and initial frequency for liquids ($\rho = 0.780$; $p = 0.013$). No other parameter demonstrated a correlation with frequency and severity of drooling at t1, score differences following toxin administration, or GII scale. It was not possible to

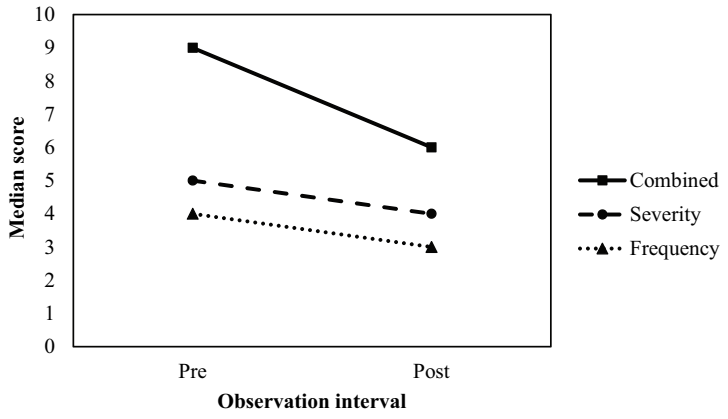

Figure 1. Chart comparing pre- and post-treatment drooling measures. The continuous line illustrates the median values variation of the combined Drooling Severity and Frequency Scale described by Thomas-Stonnel & Greenberg, which is composed by the total score of the two subscales – Severity (dashed line) and Frequency (dotted line). The chart shows a decrease in median values of all scales after BTX-A administration ($p < 0.001$).

Table 2. Number of responders (R) and non-responders (NR) and ORs with 95% confidence interval based on univariate logistic regression.

Number of subjects				
Characteristics	R (%) (n = 18)	NR (%) (n = 5)	OR (IC 95%)	p-Value
Sex	7 (38.9)	1 (20)	1.00 (reference)	0.444
Male	11 (61.1)	4 (80)	0.39 (0.03–4.27)	
Female				
Weight*	11.68 (±2.28)	10.24 (±1.45)	1.54 (0.79–3.02)	0.201
Mean				
Age*	32.00 (±2.27)	31.00 (±3.80)	1.18 (0.76–1.84)	0.446
Mean				
Head circumference difference*	10.80 (±3.24)	10.72 (±1.63)	1.01 (0.71–1.43)	0.956
Mean				
Total weight-based dose*	35.17 (±4.60)	36.96 (±4.76)	0.91 (0.73–1.14)	0.438
Mean				
Orofacial dyskinesia	6 (33.3)	2 (40)	1.00 (reference)	0.782
Yes	12 (66.7)	3 (60)	1.33 (0.17–10.25)	
No				
Cervical balance	13 (72.2)	4 (80)	1.00 (reference)	0.727
Yes	5 (27.8)	1 (20)	1.53 (0.13–17.33)	
No				
Number of PRs **	0.5 (0–3)	2 (1–3)	0.62 (0.28–1.39)	0.255
Median				

*Weight, age, head circumference difference and total weight-based dose are given as means (standard deviation). **Number of PRs is given as the median (minimum/maximum). R, responders; NR, non-responders; OR, odds Ratio; PR, primitive reflexes.

assess the role of the Doppler ultrasonography as a predictor of therapeutic response, since only two subjects were considered non-responders.

Discussion

Drooling is considered a significant problem for approximately one third of children with CP, affecting the quality of life and determining increased morbidity. The main mechanism in its most severe forms is considered brainstem dysfunction, rather than increased saliva production [10]. The repercussions of drooling go beyond psychosocial impact and carer overload which recent findings suggest that leads to several mental health concerns [11]. Saliva contact with skin increases the risk of abrasions and fungal infections, and dehydration may occur when the escape is intense. Furthermore, in children with brainstem dysfunction and pseudobulbar paralysis with immature defence mechanisms, saliva aspiration, asphyxia, and increased risk of severe and recurrent lung infections may occur [12]. Reducing saliva is therefore a priority for the care of children with CP, not only in order to reduce morbidities but also to prevent potentially high-cost hospitalizations.

In a prospective cohort of children with neurological dysfunction and GMFCS V, BTX was found to be effective in reducing severity and frequency of drooling. They also observed a reduction in the number of respiratory infections in children without underlying lung disease, compared to those observed prior to the start of the intervention. Follow-up occurred between 3 and 42 months post intervention and, despite the small sample (15 subjects), the effect was maintained over successive applications. The majority of children in their study presented with predominantly posterior drooling and were orally fed [13].

The data demonstrates a positive effect for the treatment of drooling in children with cerebral palsy secondary to CZS. Child studies provide evidence of the existence of significant variability in administration techniques in relation to the number of points, dose and toxin dilution. Furthermore, some variables cannot be directly measured, such as intra and extraglandular diffusion of the toxin [14]. In children with microcephaly, these injections should be guided by ultrasonography. The non-availability of this resource was mitigated through anatomical references of the parotid and submandibular glands, obtained from examinations of four children with microcephaly arising from CZS and not included in this sample. Here, it was observed that, despite the presence of

Table 3. Median swallowing parameters obtained through Doppler ultrasonography.

Median (minimum/maximum)					
Consistency	IF (Hz)	PF (Hz)	II (dB)	PI (dB)	T (s)
Liquid	684.78 (647.20–724.84)	1055.59 (890.68–1100.62)	54.02 (50.25–64.22)	87.42 (79.88–91.06)	0.66 (0.38–1.55)
Pasty	667.39 (647.20–790.06)	1050.93 (998.14–1100.62)	52.06 (50.25–63.11)	86.58 (81.83–91.06)	1.01 (0.46–1.32)

IF, initial frequency; PF, peak frequency; II, initial intensity; PI, peak intensity; T, total time.

microcephaly, these anatomical references were no different from those described in the literature. Furthermore, other studies in which injections were not guided by ultrasonography have yielded positive results [15,16].

One study that compared the impact of administering the toxin in the parotid gland to combined administration in the parotid and submandibular glands in children with dyskinetic and spastic CP, did not observe any advantage between the two [17]. At rest, approximately 70% of saliva is secreted in the submandibular and sublingual glands. During stimulation (feeding, chewing movements), the parotids produce most of the saliva. However, in our study, the assistant medical team considered the possibility of exclusively blocking the parotid to determine the increase in saliva thickness and consequent dysphagia, particularly in treating children with severe brain impairment and without compensatory resources to deal with changes in saliva consistency.

Currently, there is no recommended protocol for the administration of BTX to reduce drooling in children with CP. This is due to the broad heterogeneity of studies in which total administered dose varies widely. A systematic review including 16 child studies found that the median dose was 70 units (10–100 U) when using the OnabotulinumtoxinA (Botox®) formulation with a median of 25 U per gland (5–35 U). In the only study that used AbobotulinumtoxinA (Dysport®), the total administered dose was 140 U [18]. In our study, the children received 25 U of AbobotulinumtoxinA per gland, this is available free-of-charge through the Brazilian Unified Health System [19], with total dose equal to 100 U. The assistant medical team opted to conduct the first application with a lower dose of BTX-A than is commonly used, and the therapeutic response was surprisingly positive. All the parents, even those who did not perceive a change in drooling frequency or intensity, confirmed that they would repeat the dose in a few months' time.

In a recent study, one third of children subject to BTX administration experienced adverse effects, principally in problems related to swallowing, but the majority were considered mild and self-limiting and did not require specific management [2]. In our study, the effects were transitory and infrequent – only two cases – despite involving children who were exclusively orally fed and who could have presented worsening dysphagia following treatment.

Several ways to measure drooling have been put forward, to assess both need for intervention and outcome. Among the objective methods, saliva flow (mL/min), number of bibs used per day, saliva weight and drooling quotient are all quantitative parameters reported in research, although complicated by their use in daily clinical practice [4]. For their part, subjective scales, such as the Drooling Impact Scale and the Drooling Severity and Frequency Scale, provide an assessment of the impact on family members, carers and the individuals themselves. The ideal method to assess the effectiveness of any drooling treatment is one that measures improvements in the child's quality of life and facilitation of the carer's life. Our study used the Drooling Severity and Frequency Scale, the outcome measure most frequently used in studies [17], and we also applied the GII.

Cervical auscultation using Doppler ultrasonography is a non-invasive, low-cost technique, which is used for the clinical assessment of swallowing [20]. One cohort study assessed swallowing sounds using Doppler ultrasonography with food of liquid and pasty consistency in children from different age groups, including between 2 and 5 years old, and without oropharyngeal dysfunction [21]. There was no statistically significant difference between genders in any of the parameters in this age group for foods of liquid and pasty consistency. In our study, the median values found for initial frequency (IF), peak frequency (PF), initial intensity (II) and peak intensity (PI) were significantly lower than those reported. Further, the children in our study presented median total time greater than that reported for the swallowing of liquid foods and less for pasty foods. Assuming that greater frequency and intensity are related to improved swallowing performance, the results found are in line with the children's neurological immaturity. Furthermore, evidence of a negative correlation between PF and Drooling Frequency Scale score is consonant with the hypothesis that improved swallowing is associated with less severe drooling. At the same time, it is possible that the positive correlation between the GII and IF reflects less perceived improvement, due to lower prior severity of this problem. However, the Doppler typology in these studies requires further examination, with a larger sample and with records obtained prospectively for a number of age groups. Also, we did not perform swallowing evaluation after the administration of BTX-A.

To the best of our knowledge, this is the first study to assess the impact of BTX-A on the specific treatment of drooling in children with CP associated with microcephaly secondary to CZS. This article presents the safe and positive impact of the administration of BTX-A guided by anatomical references described in the literature, even on children with microcephaly. It also considers the possibility of therapeutic response using a lower dose of BTX. Finally, it sets out the need for other studies to facilitate the use of the Doppler ultrasonography as a tool to assess drooling and characterize changes in sensory processing and motor response following intraoral input in children with CP.

Bilateral intraglandular administration of AbobotulinumtoxinA in the parotid and submandibular glands, guided by anatomical references, had a positive impact, as perceived by parents, in reducing the frequency and severity of drooling in children with CP associated with microcephaly secondary to CZS. For the dose applied, adverse effects were infrequent, short term and self-limiting. No clinical variables associated with therapeutic response were identified.

Disclosure of interest

The authors report no conflicts of interest.

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Disclosure statement

No potential conflict of interest was reported by the authors.

References

[1] Lyra PPR, Campos GS, Bandeira ID, et al. Congenital chikungunya virus infection after an outbreak in Salvador, Bahia, Brazil. Am J Perinatol Rep. 2016;6:299–300.

[2] van Hulst K, Kouwenberg CV, Jongerius PH, et al. Negative effects of submandibular botulinum neurotoxin A injections on oral motor function in children with drooling due to central nervous system disorders. Dev Med Child Neurol. 2017. DOI:10.1111/dmcn.13333.

[3] Porte M, Chaléat-Valayer E, Patte K, et al. Relevance of intraglandular injections of botulinum toxin for the treatment of sialorrhea in children with cerebral palsy: a review. Eur J Paediatr Neurol. 2014. DOI:10.1016/j.ejpn.2014.05.007

[4] Scofano Dias BL, Fernandes AR, Maia FH. Sialorrhea in children with cerebral palsy. J Pediatr (Rio J). 2016. DOI:10.1016/j.jpedp.2016.06.002

[5] Bandeira ID, Jagersbacher JG, Barretto TL, et al. Botulinum toxin type A in the treatment of facial myotonia in Schwartz-Jampel syndrome. Muscle Nerve. 2017;56:2.

[6] Franca GVA, Schuler-Faccini L, Oliveira WK, et al. Congenital Zika virus syndrome in Brazil: a case series of the first 1501 livebirths with complete investigation. Lancet. 2016;388(10047):891–897.

[7] Ondo WG, Hunter C, Moore W. A double-blind placebo-controlled trial of botulinum toxin B for sialorrhea in Parkinson's disease. Neurology. 2004;62(1):37–40.

[8] Jackson CE, Gronseth G, Rosenfeld J, et al. Randomized double-blind study of botulinum toxin type B for sialorrhea in ALS patients. Muscle Nerve. 2009;39(2):137–143.

[9] Thomas-Stonell N, Greenberg J. Three treatment approaches and clinical factors in the reduction of drooling. Dysphagia. 1988;3(2):73–78.

[10] Senner JE, Logemann J, Zecker S, et al. Drooling, saliva production, and swallowing in cerebral palsy. Dev Med Child Neurol. 2004;46(12):801–806.

[11] Barreto TM, Bento MN, Barreto TM, et al. Prevalence of depression, anxiety, and substance-related disorders in parents of children with cerebral palsy: a systematic review. Dev Med Child Neurol. 2020;62(2):163–168.

[12] Dohar JE. Sialorrhea & aspiration control – a minimally invasive strategy uncomplicated by anticholinergic drug tolerance or tachyphylaxis. Int J Pediatr Otorhinolaryngol. 2019;116:97–101.

[13] Gubbay A, Marie Blackmore A. Effects of salivary gland botulinum toxin-A on drooling and respiratory morbidity in children with neurological dysfunction. Int J Pediatr Otorhinolaryngol. 2019;124:124–128.

[14] Lim ECH, Seet RCS. Use of botulinum toxin in the neurology clinic. Nat Rev Neurol. 2010;6(11):624–636.

[15] Alrefai AH, Aburahma SK, Khader YS. Treatment of sialorrhea in children with cerebral palsy: a double-blind placebo controlled trial. Clin Neurol Neurosurg. 2009;111(1):79–82.

[16] Bothwell JE, Clarke K, Dooley JM, et al. Botulinum toxin A as a treatment for excessive drooling in children. Pediatr Neurol. 2002;27(1):18–22.

[17] Gonzalez-Luís MD, Martinez C, Fortuny IB, et al. Factors in the efficacy, safety, and impact on quality of life for treatment of drooling with botulinum toxin type A in patients with cerebral palsy. Am J Phys Med Rehabil. 2017;96(2):68–76.

[18] Rodwell K, Edwards P, Ware RS, et al. Salivary gland botulinum toxin injections for drooling in children with cerebral palsy and neurodevelopmental disability: a systematic review. Dev Med Child Neurol. 2012;54(11):977–987.

[19] Bandeira ID, Mendoza J. Medical education and leadership: a call to action for Brazil's mental health system. Int J Med Educ. 2018;9:170–172.

[20] Lagos HNC, Santos RS, Abdulmassih EM, et al. Characterization of swallowing sounds with the use of sonar Doppler in full-term and preterm newborns. Int Arch Otorhinolaryngol. 2013;17(4):383–386.

[21] Cagliari CF, Jurkiewicz AL, Santos RS, et al. Doppler sonar analysis of swallowing sounds in normal pediatric individuals. Braz J Otorhinolaryngol. 2009;75(5):706–715.