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Functional improvement of young children with cerebral palsy treated with integrated/intensive rehabilitation and botulinum toxin injections

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ABSTRACT

Introduction. Patients with cerebral palsy (CP) present mobility limitations altering their activity and participation in social life. The aim of this study was to assess changes in Gross Motor Function Classification System (GMFCS) and Functional Mobility Scale (FMS) in children with CP who received repeated BoNT-A injections within a rehabilitation treatment over a five-year follow-up period.

Material and methods. This retrospective, observational study included 200 consecutive children with bilateral CP (GMFCS I–IV). Annual assessments of the five-year follow-up period were analysed.

Results. The mean age of the patients at the beginning was 32.23 months (± 6.96). The GMFCS level improved in 67 (33.5%) ($p < 0.001$) and worsened in four (2%) children. In children with GMFCS III and IV levels, improvement was observed in 50% and 40%, respectively. FMS 5 and 50 metres improved in 54% and 52.5% of children respectively.

Conclusions. Our study showed a significant, positive effect of integrated treatment on functional mobility in patients with CP.

Key words: cerebral palsy, integrated rehabilitation, botulinum toxin-A, mobility, gross motor function

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Introduction

Cerebral palsy (CP) describes "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]. Cerebral palsy is one of the most common causes of motor disability in children [2].

In children with CP, limited activity directly affects the level of functioning in daily activities and may cause problems that make it difficult to engage in daily life and determine participation restrictions [3].

The Gross Motor Function Classification System (GMFCS) is a five-level classification that describes the gross motor function in children with cerebral palsy. The extended and revised version takes into consideration also children from 12 to 18 years of age and draws attention to personal and environmental factors [4, 5]. The GMFCS is strongly associated with mobility care and domestic life. The fact that also in this study such a strong relationship was found between the GMFCS and mobility, supports the use of the GMFCS to classify a child's mobility performance [6].

GMFCS is known for its stability but it is not an outcome assessment tool. Generally, children stayed at the same GMFCS level from 1–2 years up to 6–12 years of age. Based on Canadian population studies, it has been shown that children with spastic CP on average reach 90% of their motor function at approximately five years of age, then there is a plateau in further motor development at about seven years, and children in GMFCS Groups III, IV, and V suffer a decline through adolescence [7–9].

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The Functional Mobility Scale (FMS) is a reliable scale for classifying functional mobility in children covering three distances, 5, 50 and 500 metres, including assistive devices that the child might use to cover a certain distance [10, 11]. The FMS is sensitive to detect change after intervention e.g. surgery [10].

Opheim et al. [12] showed that adults with bilateral spastic CP and higher levels of GMFCS demonstrate a greater risk of deterioration of their gait function than those with less intensive disorders and better gross motor skills. The authors give the cause of overload resulting from excessive load on the motor system to meet social and environmental requirements.

In light of the above, the process of rehabilitation of children and adolescents with cerebral palsy should be focused on achieving the highest possible functional level allowing for full participation in social and professional life.

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. The biggest breakthrough in the therapy of children with CP was the introduction of multi-level injections of botulinum toxin type A (BoNT-A) as a part of a multimodal rehabilitation process which include physiotherapy and orthoses, among a range of other treatments. Such an integrated approach brings measurable results and changes the natural course of the disease [13, 14]. The answer to the question of the long-term impact of BoNT-A treatment plus physiotherapy on gross motor function in long term is still unclear [15].

The aim of this study was to assess changes in functional mobility for the distances of 5 and 50 metres in patients with cerebral palsy who received repeated botulinum toxin-A (BoNT-A) injections within a rehabilitation treatment over a five-year follow-up period. Moreover, stability of GMFCS in assessed population was observed.

Material and methods

Settings and inclusion criteria

This was a retrospective, single-centre, observational study conducted in the Mazovian Neuropsychiatry Centre in Zagórze, Poland. The retrospective study included 200 consecutive children with CP treated with BoNT-A injections and an integrated rehabilitation programme from February 2004 to August 2019, who met all of the inclusion and none of the exclusion criteria. The inclusion criteria were: (1) children diagnosed with bilateral CP, spastic type; (2) children between the ages of 2 and 4 years at the beginning of the observation; (3) children who had GMFCS level I to IV before first injection; (4) gait assessment and medical records available for 5 years of follow-up; and (5) gait assessment performed before, or at least three months after, each BoNT-A injection. Exclusion criteria included: (1) other forms of CP especially with predominantly dyskinetic type; (2) children who had GMFCS level V; and (3) orthopaedic procedures performed due to CP.

BoNT-A treatment and rehabilitation programme

During the follow-up period, all children underwent BoNT-A injections, an individual physiotherapy programme and used ankle foot orthosis (AFO). BoNT-A most often was administered once or twice a year; patients received from 5 to 10 injections during the observation period. Total doses per session varied from 20 μ/kg to 30 μ/kg for ABOBoNT-A or from 10 μ/kg to 20 μ/kg for OnaBoNT-A. During the five-year treatment period, children could receive both toxins, and in the majority multilevel injections were performed. The treatment scheme was developed by the authors based on our experience and available recommendations [13, 14]. Hip flexors and adductors, knee flexors, and foot plantar flexor muscles were usually selected for the treatment based on detailed assessment including: muscle tone, range of motion, strength, and gait analysis. Injections were administered under mild sedation, and ultrasound as a guidance method was used. The physiotherapy programme was planned individually for each child and was intended to achieve their specific functional goals, which were set across all components of the International Classification of Functioning, Disability and Health for Children and Youth (ICF-CY) [16]. Therapists during the intensive physiotherapy period used this model to select the measurement tools, goal setting and evaluation of the outcomes. Functional goals were defined to structure the therapy process. Goals focused on functional mobility, comprising the activities of daily living which were established with children and parents. Goals were set on the five SMART principles: specific, measurable, achievable, realistic, and time-bound [17, 18]. The long-term goals of physical therapy aimed to improve the child's mobility and independence during daily living activities and related participation in social life. The short-term goals were focused on body structure level and included improving passive and active range of motion, muscle strength and selective motor control [19, 20]. The inpatient rehabilitation ranged from one to four three-week stays per year, and usually took place 2–4 weeks after BoNT-A injection. Physiotherapy included individual and group training, lasting an average of 120 minutes per day. Physiotherapists used analytical therapy techniques as well as functional and task-oriented training approaches. Additionally, during each intensive physiotherapy period, the children had aquatic therapy, occupational therapy, speech therapy, and therapeutic horse-riding [21]. After evaluating the outcomes, the children and caregivers were given guidance on which exercises and activities they should focus on during community-based rehabilitation between intensive physiotherapy periods. Community rehabilitation ranged from two to five times per week and was conducted in kindergarten, school, or at home for all assessed children. All patients used rigid or semirigid ankle foot orthoses (AFO) along with proper footwear. AFO were tuned individually based on ground reaction vector visualisation. The purpose of orthotic management was to improve

gait parameters and movement patterns. 169 (84.5 %) children wore AFO 5-8 hours per day, while 31 (15.5%) wore them for less than five hours daily.

Outcome measures

The objective of the analysis was to document the long-term changes in FMS in the presented group; additionally, changes in GMFCS were analysed. GMFCS describes a child's or youth's abilities and limitations in gross motor function based on self-initiated movement with particular emphasis on sitting, transfers, and mobility. According to the general guidelines, children classified at level I walk fully independently, while those whose gross motor function is assessed at level V are dependent on assistive technology and the assistance of a caregiver. Accurate determination of the current level of gross motor function was possible due to detailed descriptions of five functional levels referring to specific age groups, which were divided as follows: up to 2 years of age, 2 to 4 years of age, 4 to 6 years of age, 6 to 12 years of age and 12 to 18 years of age [5]. The FMS (Functional Mobility Scale) classifies functional mobility in children over distances of 5, 50 and 500 metres and includes assistive devices requisite to cover a certain distance. The indicated distances play a largely informative role, because the most important element is the environmental factor. The functional mobility over distances of 5, 50 and 500 metres represents mobility at home, in the school environment including the playground, and outdoors e.g. in a shopping centre or high street. A mobility rating of 6 describes complete independence when a child walks on various surfaces and has the ability to overcome obstacles. If a child uses sticks, crutches or a walking frame, the FMS scores would be 4, 3 and 2, respectively. A score of 1 describes a child who uses a wheelchair and can make some steps supported by a caregiver [10, 22].

Data collection procedure

A treatment, casting, physiotherapy, orthoses, GMFCS level and FMS score for 5 and 50 metres was collected from medical records, structured interviews, corridor tests and goal assessment charts based on GAS methodology, conducted on the first and last days of each intensive physiotherapy period by therapists working in the Neurorehabilitation Department. From the available measurements, those that were made at about annual intervals were selected to show the dynamics of changes. Additionally, GMFCS level and FMS score was reassessed based on two-plane clinical video recordings performed in all children. For the purposes of this study, data from assessments prior to, or at least three months after, injection of BoNT-A were analysed for a 5-year period. All assessors involved in the study were well trained and had many years of experience. Due to the retrospective nature of this study, including the analysis of medical records, no application was submitted to the Bioethics Committee for research and scientific use of the obtained results. The authors (MB, WP) are employees of the Neurorehabilitation Department and took part in the treatment of the assessed group in the past.

Statistical analysis

All calculations were performed using the R statistical package, version 3.6.0. The level of significance was $\alpha = 0.05$. The statistical significance of differences in the assessment of patients over the five-year follow-up period was assessed using the Friedman test. In the case of a significant Friedman test result, a post hoc analysis of these results was performed using the Wilcoxon test with the Bonferoni correction when multiple assessments were presented for the follow-up period.

Results

The study group consisted of 120 males and 80 females aged from 24 to 46 months. The mean age was 32.23 months (± 6.96). Before the treatment, six (3%) children were rated at GMFCS level I, 96 (48%) at GMFCS II, and 72 (36 %) and 26 (13%) at GMFCS levels III and IV respectively (Tab. 1).

During a five-year follow-up period, 71 (35.5%) children changed the level of their GMFCS, of which the majority, 67, improved, and four deteriorated (Tab. 2). The results were statistically significant ($p < 0.001$). The highest numbers of improvements were observed in children with GMFCS III and IV levels, with an improvement in 32 (50%) and nine (40%) respectively. Post hoc analysis revealed significant differences in the GMFCS between all assessments except 2–3, 3–4, 3–6 and 5–6. 54% of patients improved mobility measured with FMS at the 5 m distance (Tab. 3). The number of children rated 6 increased from three (1.5%) to 29 (14.5%), whereas the number of patients rated 1 decreased from 77 (38.5%) to seven (3.5%) (Tab. 1). In 48 of the patients (24%), the rating increased by 1, while in 22 (11%) and 32 (16%) patients the ratings increased by 3 and 4, respectively. Similar results were obtained for the 50 m distance (Tab. 3). Also, at this distance, there was a decrease in the number of children rated 1 from 79 (39.5%) to seven (3.5%) and an increase in those rated 6 from three (1.5%) to 27 (13.5%). 45 patients (22.5%) improved by one point, 24 (12%) by three points, and 32 (16%) by four points according to the FMS scale (Tab. 1). All changes on functional mobility between the first and last assessments were statistically significant ($p < 0.001$). For both distances, post hoc analysis showed significant differences in the assessment of the patient's functional mobility between all assessments except 3–4, 4–5, 4–6 and 5–6.

Discussion

Our long-term, retrospective study showed a positive effect of the applied treatment on the motor development of children with cerebral palsy. Gross motor skills and mobility have changed significantly over the course of five years of observation. The majority of children showed either stability

Table 1. Percentages (numbers) of patients reaching specified FMS score and GMFCS level before treatment and during annual follow-up assessments. P-values indicating a statistically significant result are in bold

	Score/ /level	Baseline	After one year	After two years	After three years	After four years	After five years	
FMS 5 metres	1	38.5% (N = 77)	19% (N = 38)	9% (N = 18)	4.5% (N = 9)	3.5% (N = 7)	3.5% (N = 7)	**(p < 0.001)**
	2	8.5% (N = 17)	18% (N = 36)	17.5% (N = 35)	15% (N = 30)	14.5% (N = 29)	13.5% (N = 27)	
	3	0% (N = 0)	0% (N = 0)	0% (N = 0)	0% (N = 0)	0% (N = 0)	0% (N = 0)	
	4	2.5% (N = 5)	4% (N = 8)	9% (N = 18)	13.5% (N = 27)	13% (N = 26)	13.5% (N = 27)	
	5	49% (N = 98)	57% (N = 114)	57.5% (N = 115)	55.5% (N = 111)	54% (N = 108)	55% (N = 110)	
	6	1.5% (N = 3)	2% (N = 4)	7% (N = 14)	11.5% (N = 23)	15% (N = 30)	14.5% (N = 29)	
FMS 50 metres	1	39.5% (N = 79)	19.5% (N = 39)	10% (N = 20)	5% (N = 10)	3.5% (N = 7)	3.5% (N = 7)	**(p < 0.001)**
	2	7.5% (N = 15)	17.5% (N = 35)	16.5% (N = 33)	14.5% (N = 29)	14.5% (N = 29)	13.5% (N = 27)	
	3	0% (N = 0)	0% (N = 0)	0% (N = 0)	0% (N = 0)	0% (N = 0)	0% (N = 0)	
	4	2.5% (N = 5)	4.5% (N = 9)	9% (N = 18)	13.5% (N = 27)	13.5% (N = 27)	13.5% (N = 27)	
	5	49% (N = 98)	56.5% (N = 113)	58% (N = 116)	56.5% (N = 113)	55% (N = 110)	56.5% (N = 113)	
	6	1.5% (N = 3)	2% (N = 4)	6.5% (N = 13)	10.5% (N = 21)	13.5% (N = 27)	13% (N = 26)	
GMFCS	I	3% (N = 6)	3% (N = 6)	7.5% (N = 15)	11.5% (N = 23)	14.5% (N = 29)	14% (N = 28)	**(p < 0.001)**
	II	48% (N = 96)	56% (N = 112)	56.5% (N = 113)	54.5% (N = 109)	54.5% (N = 109)	55% (N = 110)	
	III	36% (N = 72)	28% (N = 56)	24.5% (N = 49)	22.5% (N = 45)	20.5% (N = 41)	20.5% (N = 41)	
	IV	13% (N = 26)	13% (N = 26)	11.5% (N = 23)	11.5% (N = 23)	10.5% (N = 21)	10.5% (N = 21)	

FMS — Functional Mobility Scale; GMFCS — Gross Motor Function Classification System

Table 2. Change in GMFCS level over 5-years follow up period

GMFCS	Change	Percentage (number) of patients
	Improvement by one level	33.5% (N = 67)
	No change	64.5% (N = 129)
	Deterioration by one level	2% (N = 4)

GMFCS — Gross Motor Function Classification System

Table 3. Change in FMS 5 and FMS 50 score over 5-years follow up period

Distance	Change	Percentage (number) of patients
FMS 5 metres	Increase	54% (N = 108)
	No change	46% (N = 92)
FMS 50 metres	Increase	52.5% (N = 105)
	No change	47.5% (N = 95)

FMS — Functional Mobility Scale

of mobility or a change to less assistance required. The GMFCS classification level changed for 71 (35.5%) patients, of whom 67 (33.5%) improved by one degree, and four (2%) deteriorated, also by one degree. Children with GMFCS level III who had been able to walk on flat surfaces with the help of a hand-held device before starting the treatment were the largest group in which an improvement in motor skills was observed: 36 of them (50%) achieved the ability to walk without assistance. The second largest group in which a change in GMFCS level was observed were patients classified at level II. After five years, almost 25% of these patients were able to walk independently without any limitations. In the smallest group of 26 patients classified as level IV before the treatment, a change was observed in nine (41%).

Improvement from level IV to III means that a patient can walk independently using a hand-held support device. This significantly changes the quality of life because children and adolescents from level IV require physical assistance or a powered device support. They function for most of the day in a sitting position, exercising the ability to walk only for short distances with a walking frame and under supervision [5, 7].

The results for the rest of the patients reflected the motor development curves, remaining unchanged. Population-based studies indicate that GMFCS level may change over time for a certain percentage of children with cerebral palsy [23]. Palisano et al. [24] assessed the stability of levels in a group of 610 Canadian children and found that 73% of children remained at the same GMFCS level throughout the observation period. Similarly, Alriksson-Schmidt et al. [25] examined the stability of GMFCS levels in 736 children from Sweden and showed that 74% of the participants received the same GMFCS level at their first and their last registered follow-up. However, it is worth emphasising that these studies concerned the entire population of children with cerebral palsy. If we narrow the criteria, in the entire population studied by Alriksson-Schmidt et al. [25] there were 297 children with diplegia, of whom only 11% improved their motor skills (level change to a lower level) and 15% worsened (level change to a higher level). Another register-based study from the Stockholm region of Sweden on 768 children with at least two GMFCS ratings, showed that as many as 616 children (80%) were rated at the same

level in the first and the last assessments [26]. In studies of specific interventions, authors have demonstrated the stability of GMFCS after a single-event multilevel surgery [9], and hip reconstructive surgery [27]. Ailon et al. [28] assessed the long-term effects of selective dorsal rhizotomy. Ten of 44 (23%) assessed children improved by one level. These children were evenly distributed between GMFCS II, III, and IV. Dursun et al. [29] showed that at least 40% of patients with CP with a diverse clinical picture have the potential to improve GMFCS levels after using botulinum toxin in combination with an intensive rehabilitation programme. These results are the closest to those observed in our study. Longitudinal changes in the functional mobility of patients over a distance of 5 and 50 metres correspond to mobility at home and in a school environment. Based on the conducted analyses, a statistically significant ($p < 0.001$) difference of the results obtained for both distances, between the subsequent tests and the first and the last test were demonstrated. 54% of patients improved over the 5m distance, of whom 16% improved by as much as four levels. The group of children with the highest rating (6 — functioning completely independently on all surfaces without the use of any supporting device or assistance) increased from three (1.5%) during the first assessment to 29 (14.5%) during the last. The number of patients rated at 1, i.e. who were able to make only a few steps with the help of another person or using a walking frame, systematically decreased: from 77 (38.5%) during the first assessment to seven (3.5%) during the last. For the 50m distance, 52.5% of children improved, including 16% of patients who improved by four levels. Also, for this distance, a decrease in the number of patients graded 1 from 79 (39.5%) to seven (3.5%) was observed. 40 children changed level after the first year of treatment, regardless of age. This may suggest the role of applied therapy. For five years, an increase in the number of patients with the highest FMS score (6) from three (1.5%) up to 26 (13%) was observed. For functional reasons, an increase in mobility measured at 50 m is particularly important because it allows patients to move around in their environment, e.g. at school. Very few publications presenting a similar follow-up period can be found in the available literature. In a retrospective study by Harvey et al. [11], the authors observed changes in FMS in some patients over a five-year follow-up period after multilevel surgery and intensive postoperative rehabilitation. In 156 patients (GMFCS I–III), with an average age of 11 years and one month (6–19), the changes were most common in the group of patients classified at GMFCS level III. There was an increase in FMS 5m and FMS 50m in 51% and 34%, respectively, and a decrease in 16% and 15% of children. In the group of children with GMFCS I, II, an improvement in FMS 5m and FMS 50m was observed in 18% and 20%, and deterioration in 6% and 14% of children respectively.

Our study showed a significant, positive, effect of integrated treatment on gross motor function and mobility in patients with CP. Moreover, the study showed that children with CP can change GMFCS level over the course of treatment. Improvement was especially observed in patients with higher mobility impairment. An important factor responsible for the significant improvement in the parameters described in our study may be physiotherapy combined with BoNT injections and appropriately prescribed and tuned orthotics [30–32]. An individually planned therapy programme based on tasks aimed at achieving clearly set goals also seems to be crucial [33].

The main strength of this study is the homogenous group of young children with bilateral spastic cerebral palsy treated in one centre with a standardised intensive therapy programme. Other strengths include the experienced therapists who had extensive training in the application of the assessments used in the study, and detailed reassessment based on video recordings. Limitations of the study include the retrospective design and the lack of a control group, which could potentially introduce bias. Another limitation is the absence of a standard of home therapy.

Clinical implications/future directions

The results of this study encourage the use of integrated rehabilitation and BoNT-A injections to improve gross motor skills and mobility in children with spastic bilateral cerebral palsy. Future studies would benefit from incorporating validated, patient-centred outcome measures focused on life satisfaction and quality of life. It will also be important to assess whether improvements in mobility are sustained and persist over longer periods of time, i.e. until adolescence or adulthood.

Conflicts of interest/funding: *Marcin Bonikowski was an investigator in Allergan, Ipsen studies, and received research support from Ipsen, Allergan, and personal fees for consultancy and speaking from Ipsen and Allergan. Weronika Pyrzanowska was a sub-investigator in Ipsen studies, and received personal fees for speaking from Ipsen and Allergan.*

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