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# Use of botulinum toxin A in children with cerebral palsy

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ORIGINAL ARTICLE

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## **BACKGROUND**

For more than 20 years, intramuscular injections of botulinum toxin A have been an established treatment for spasticity in children with cerebral palsy. We investigated the proportion of children with cerebral palsy who receive such treatment in Norway and the guidelines that apply to the treatment.

## **MATERIAL AND METHOD**

Data from the five-year registration in the Cerebral Palsy Registry of Norway were used to investigate the proportion of children with cerebral palsy born in the period 1999–2010 treated with botulinum toxin A, and whether there were any variations in the proportion of children treated between the habilitation centres. We conducted an online survey to identify the treatment guidelines that were applied in all of the 21 habilitation centres.

## **RESULTS**

A total of 1 414 children (average age 6.3 years) were included, of whom 775 (55 %) had been treated with botulinum toxin A. The proportion of children who received treatment varied considerably between the habilitation centres (38–80 %;  $p < 0.001$ ). The maximum dose of botulinum toxin A per treatment per patient was 200–600 units of Botox. Five centres reported to have written guidelines for the treatment indication.

## **INTERPRETATION**

The proportion of children with cerebral palsy who are treated with botulinum toxin A varies considerably between Norwegian habilitation centres.

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## Main message

More than 50 % of all children with cerebral palsy in Norway have been treated with botulinum toxin A before the age of six

The dosage of botulinum toxin A and the proportion of children who receive it vary considerably between hospitals

Large variations in treatment practices underscore the need for more evidence-based knowledge

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Cerebral palsy is a collective designation for a group of conditions caused by a brain injury that occurs during pregnancy or in the course of the two first years of life (1). Each year, 2–3 children per 1 000 live births are given this diagnosis (2). Based on the dominant symptoms, cerebral palsy is classified into the subtypes of spastic, dyskinetic and ataxic cerebral palsy (3). The spastic subtypes (unilateral and bilateral spastic cerebral palsy) account for nearly 90 % (4). Reducing spasticity is therefore an important treatment objective in clinical practice (4–6).

Over the last 20–30 years, intramuscular injections of botulinum toxin A have become the standard treatment for reducing spasticity in children and adolescents with cerebral palsy (6). The treatment blocks nerve impulses to the muscle fibres and causes temporarily reduced muscle activation (7). Reduction of focal spasticity in the calf muscle of ambulatory patients is the only approved indication for botulinum toxin A in treatment of children with cerebral palsy in Norway. In clinical practice, however, there are far more indications, and the drug is widely used outside its approved description (6). The treatment indications are largely based on clinical experience, and there is a dearth of established guidelines for the treatment procedure (6). International guidelines are consensus-based, non-specific and underscore the need for further research (4, 5).

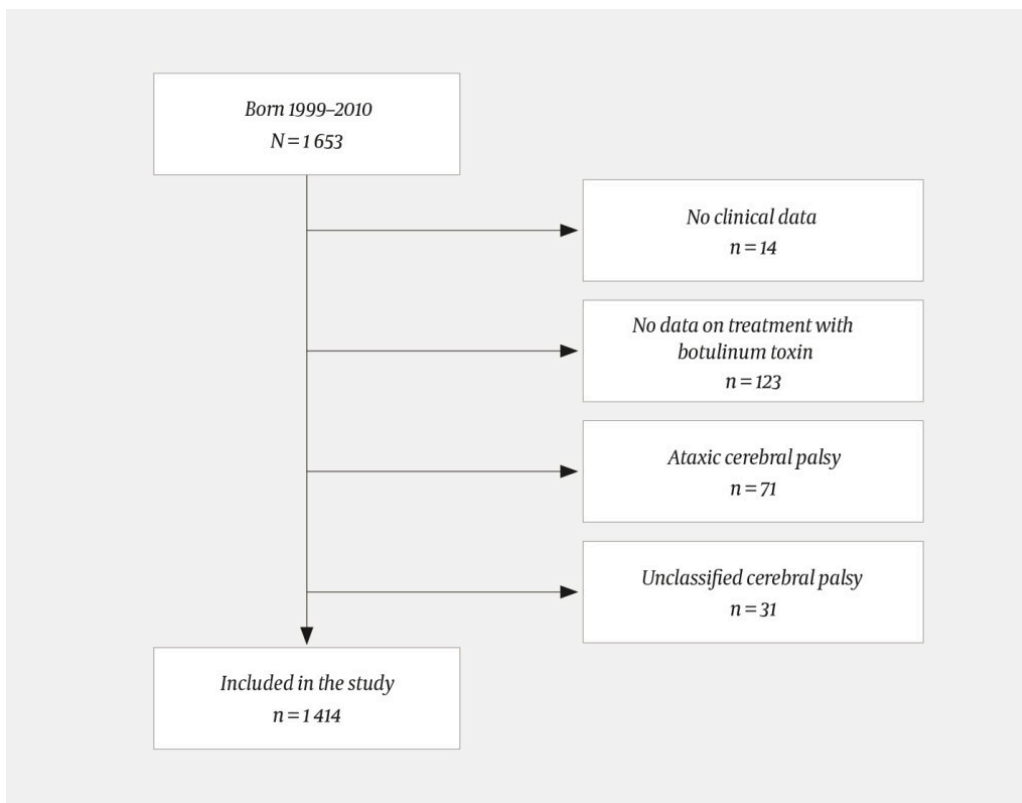
In a Norwegian study that included 411 children born in the years 1999–2003 and registered in the Cerebral Palsy Registry, approximately 60 % of the children with cerebral palsy had been treated with botulinum toxin A by the age of six (8). The Cerebral Palsy Registry has registered more than 1 600 children born before the end of 2010 (9), and we wished to produce updated information on the proportion of children with cerebral palsy who receive botulinum toxin A injections and other interventions to reduce spasticity. We have also investigated variations that may occur in treatment practice depending on the degree of functional impairment, associated impairments and place of treatment, and mapped Norwegian practices regarding this treatment.

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## Material and method

This study consists of two sub-studies. Sub-study 1 is a cross-sectional study of children with cerebral palsy born in the period 1999–2010 who are registered in the Cerebral Palsy Registry of Norway. The registry is a consent-based national medical quality registry containing demographic and clinical information on children and

adolescents with cerebral palsy born after 1 January 1996. A comparison with the Norwegian Patient Registry and a review of patient records showed that for the years 1999–2010, altogether 88 % of the children were included in the registry (9). There was no bias between different subtypes of cerebral palsy registered in the Norwegian Patient Registry and the Cerebral Palsy Registry respectively (2). In Norway, the hospitals' habilitation centres are responsible for follow-up and treatment of children and adolescents with cerebral palsy, and in each of the 21 habilitation centres there is a consultant who is responsible for the information reported to the Cerebral Palsy Registry. In this study, we have used the information on subtypes, fine and gross motor function, associated impairments, anti-spasticity treatment and county of residence as registered when the patient was around five years old. Children with ataxic cerebral palsy, unclassified cerebral palsy or with no clinical data in the registry (only the diagnosis and the consent form registered) were excluded (Figure 1).



**Figure 1** Flowchart of the study population. Children with cerebral palsy born in the years 1999–2010 and registered in the Cerebral Palsy Registry of Norway. Children for whom there was no information on their subtype of cerebral palsy or treatment with botulinum toxin A, and children with ataxic or unclassified cerebral palsy were excluded.

Cerebral palsy is diagnosed and classified into the subtypes of spastic unilateral, spastic bilateral, dyskinetic and ataxic, in accordance with the recommendations from the Surveillance of Cerebral Palsy in Europe network (SCPE) (2, 3).

Gross motor function is classified into five levels with the Gross Motor Function Classification System (GMFCS). Level I denotes the lowest degree of motor impairment (children who can walk without any limitations), while Level V describes children who have the most pronounced motor impairment (and are moved in a manual wheelchair) (10). Fine motor function levels are classified with the aid of the Manual Ability Classification System (MACS). This system classifies the children's ability to

handle objects in daily activities and provides a total assessment of both hands on a scale from I (handles objects easily and successfully) to V (does not handle objects and has severely limited ability to perform even simple actions) (11).

The Cerebral Palsy Registry records whether the child has received spasticity treatment (botulinum toxin A, peroral baclofen, intrathecal baclofen) or undergone orthopaedic surgery (soft-tissue surgery, bone surgery). For children who have received botulinum toxin A injections and/or orthopaedic treatment, the records show whether this applies to the upper extremities, the lower extremities or both.

The registry contains information on the children's cognitive functioning. On this basis, the children were separated into two groups: those who had normal cognitive abilities and those who were cognitively impaired. We registered whether the children had epilepsy, defined as current use of anti-epileptic treatment, as well as if they had eating difficulties that necessitated use of a gastrostomy.

Sub-study 2 is an online survey conducted in the autumn of 2016. The questionnaire, which was sent to the responsible senior consultants in the 21 habilitation centres for children, dealt with treatment routines in the hospitals: who provides the treatment, indications, drugs, dosages, methods for muscle identification, analgesia, sedation procedures and guidelines for treatment with botulinum toxin A, if available.

Both studies were approved by the Regional Committee for Medical and Health Research Ethics (REK no. 046–02).

## Statistics

Pearson's chi-square test was used to compare categorical variables. Differences in proportions between the centres were also analysed using standardised Pearson's residuals (12), as well as a mixed-effect logistic regression model with botulinum toxin A as dependent variable and centre as a random effect, unadjusted and adjusted for each of the following clinical variables, one at a time: gross motor function level, fine motor function level, gender, age at registration, subtype, gastrostomy, epilepsy and cognition. The statistical significance level was set to 5 %. SPSS 23 and Stata 15 were used for the data analysis.

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## Results

### Sub-study 1

Of a total of 1 653 children with cerebral palsy born 1999–2010, 1 414 (86 %) children were included (Figure 1). The average age of the children upon registration in the Cerebral Palsy Registry was 6.3 years (SD 1.8), and 59 % of the children were boys. In terms of associated impairments, 326 children (26 %) had epilepsy, 165 (13 %) a gastrostomy and 286 children (28 %) were cognitively impaired (out of 1 277, 1 299 and 1 017 children with complete registrations respectively).

A total of 775 (55 %) children had received intramuscular injections of botulinum toxin A. Of these, 461 (59 %) were boys and 314 (41 %) girls ( $p = 0.548$ ). The injections had been given only in the lower extremities in 531 children (70 %) and only in the upper extremities in 52 children (7 %), while 173 (23 %) children had received treatment in

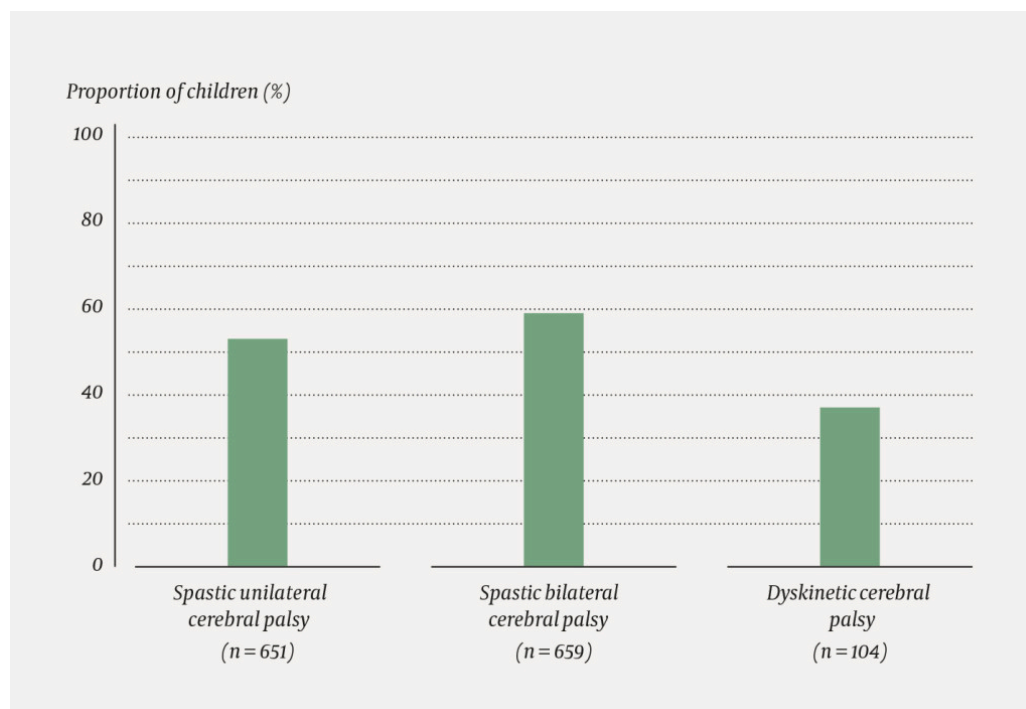
both the upper and lower extremities. Table 1 shows different treatments for spasticity. Baclofen, peroral and intrathecal, were administered to only 5 % and 3 % respectively (Table 1). Approximately three-quarters of those who received this treatment were at gross motor function level V (data not shown).

**Table 1**

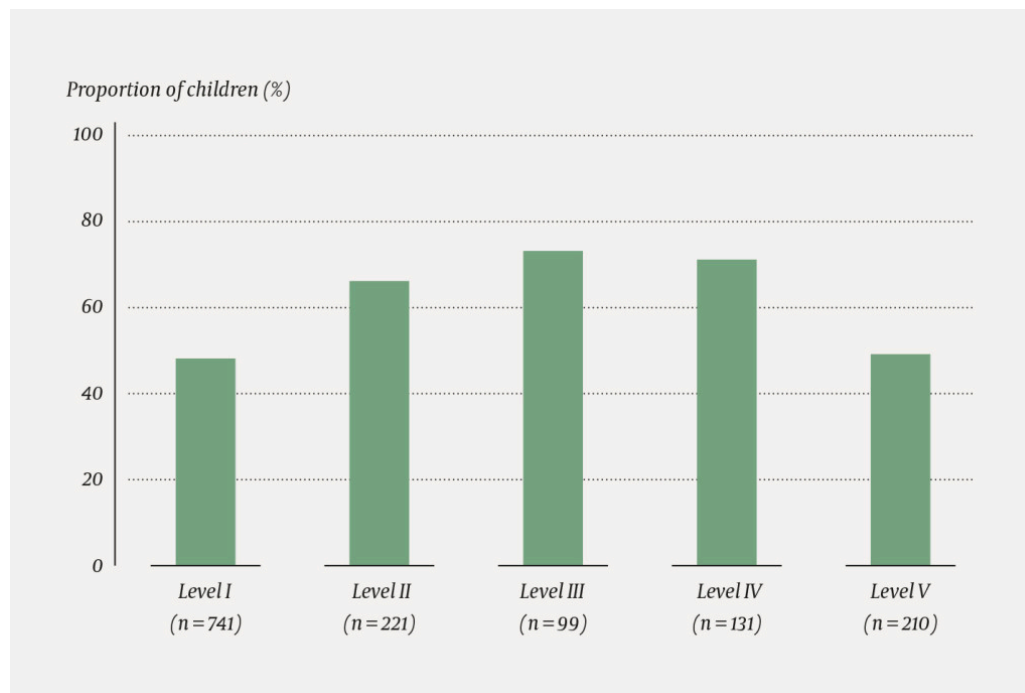
Children with cerebral palsy born in the period 1999–2010 who had been given drug-based treatment for spasticity or had undergone orthopaedic surgery

Type of treatment	Treatment received, n (%)	Children with complete information, n
Botulinum toxin A	775 (55)	1 414
Baclofen, peroral	72 (5)	1 357
Baclofen, intrathecal	44 (3)	1 406
Orthopaedic surgery	253 (18)	1 405

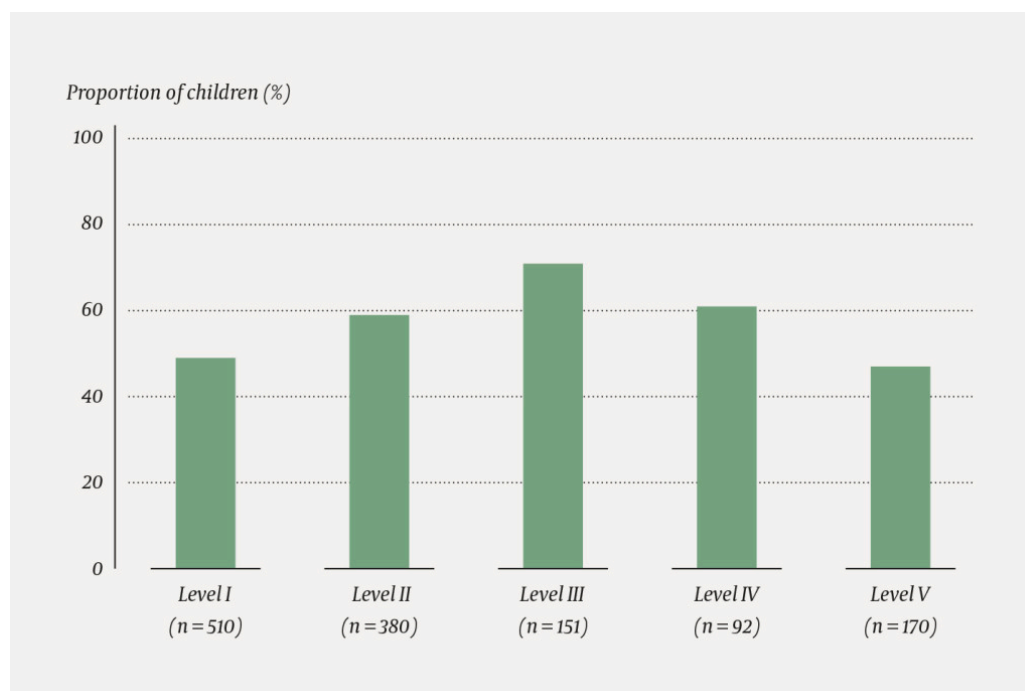
The proportion that received botulinum toxin A was lower among children with the dyskinetic subtype when compared to children with the spastic subtype ( $p \leq 0.001$ ), and the proportion of children with the spastic unilateral subtype that received botulinum toxin A was lower than the proportion among children with spastic bilateral cerebral palsy ( $p = 0.032$ ) (Figure 2). There were differences in the proportions of children who received botulinum toxin A treatment between the various levels of gross and fine motor function ( $p < 0.001$  for both). The treatment was most frequently administered to children with gross motor function level III (Figur 3) and to children with fine motor function level III (Figure 4). Cognitive ability, the use of anti-epileptic treatment and eating difficulties had no significant bearing on whether the children had been treated with botulinum toxin A or not (data not shown).



**Figure 2** Proportion of children (%) born in the period 1999–2010 who were treated with botulinum toxin A, by cerebral palsy subtype (N = 1 414).



**Figure 3** Proportion of children (%) with cerebral palsy born in the period 1999–2010 who were treated with botulinum toxin A, by gross motor function level (GMFCS). N = 1 402 (no information on gross motor function level in 12 of 1 414 children).



**Figure 4** Proportion of children (%) with cerebral palsy born in the period 1999–2010 who were treated with botulinum toxin A, by fine motor function level (MACS). N = 1 303 (no information on fine motor function level for 111 of 1 414 children).

We found considerable differences in the proportions of children who were given botulinum toxin A treatment between the various habilitation centres (Pearson's chi-square test with 20 degrees of freedom,  $p < 0.001$ ) (Table 2). The proportions varied from 38 % in Førde Hospital Trust to 80 % in Stavanger Hospital Trust. The variation between the centres remained unchanged after adjustment for the clinical variables described in the methodology chapter (data not shown).

**Table 2**

Number (N) and proportion (%) of children with cerebral palsy born in the period 1999–2010 who had been given injections of botulinum toxin A in all 21 Norwegian habilitation centres for children

Habilitation centre	Given botulinum toxin, N, (%)	Total number of children
Stavanger Hospital Trust	93 (80)	116
Telemark Hospital Trust	27 (71)	38
Hospital of Southern Norway, Arendal	23 (68)	34
Innlandet Hospital Trust, Oppland	32 (64)	50
Nordland Hospital Trust, Bodø	30 (61)	49
St. Olavs University Hospital, Trondheim	65 (59)	110
Møre og Romsdal Hospital Trust, Kristiansund Hospital	13 (59)	22
Vestfold Hospital Trust	51 (59)	87
Østfold Hospital Trust	42 (58)	72
Hospital of Southern Norway, Kristiansand	32 (56)	57
Nord-Trøndelag Hospital Trust	13 (54)	24
Fonna <sup>1</sup> Hospital Trust	11 (52)	21
Bergen Hospital Trust	58 (52)	111
Akershus University Hospital	88 (52)	169
Oslo University Hospital	60 (50)	120
University Hospital of North Norway	26 (50)	52
Møre og Romsdal Hospital Trust, Ålesund Hospital	17 (45)	38
Finnmark Hospital Trust	6 (43)	14
Vestre Viken Hospital Trust	50 (38)	130
Innlandet Hospital Trust, Hedmark	27 (38)	71
Førde <sup>1</sup> Hospital Trust	11 (38)	29
<b>Total</b>	<b>775 (55)</b>	<b>1414</b>

<sup>1</sup>Referred patients to another hospital for the treatment.

### Sub-study 2

The results are based on 19 out of 21 habilitation centres that provided botulinum toxin A treatment on-site at the hospital.

Only five habilitation centres had guidelines that specified the indications, while 13 had guidelines for dosage. Of the 13 habilitation centres that had guidelines for dosage, seven used recommendations that had originally been published on a website that no longer exists ([www.wemove.org](http://www.wemove.org)). However, printed versions of these experience-based recommendations are available. All hospitals used the Botox drug, but the maximum dose per treatment varied from 200 to 600 units, and the maximum dose per kilo varied from 10 to 25 units. This applied to children with gross motor function level I–III and children with gross motor function level IV–V.

All hospitals provided botulinum toxin A treatment in the lower extremities, whereof 12, 6 and 1 hospitals most often used ultrasound, palpation and electrostimulation respectively for muscle identification. A total of 14 hospitals provided botulinum toxin A treatment in the upper extremities, whereof 8, 1 and 5 hospitals most often used ultrasound, palpation and electrostimulation respectively for muscle identification.

The various types of sedation and analgesia used during botulinum toxin A injections were distributed as follows: eight hospitals most often used general anaesthesia ( $\geq 50\%$  of all treatments), 17 hospitals used benzodiazepines (alone or in addition to other sedation), three hospitals used nitrous oxide, one hospital used only analgesics (paracetamol and local anaesthesia) and 18 hospitals used both analgesics and sedation.

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## Discussion

The study shows that more than one-half of all children with cerebral palsy in Norway have been treated with botulinum toxin A injections by the age of six. The proportion that received such treatment was highest among children with the spastic bilateral subtype and increased with higher degrees of functional impairment up to gross and fine motor function level III, while the proportion was markedly lower in children with the most pronounced degree of functional impairment (Level V). We found considerable variations in the proportion of children who received treatment as well as in dosages, muscle identification methods and use of sedation in the different habilitation centres in Norway.

One possible explanation for the large differences between the habilitation centres in terms of the proportion of children treated with botulinum toxin A might be that levels of functioning and other patient characteristics vary from one centre to another. However, the variation between the centres remained unchanged even when these factors were adjusted for.

The strength of the study lies in its use of data from the Cerebral Palsy Registry, which registers patients prospectively. Altogether 88 % of all children with cerebral palsy in Norway are included in the registry, and the population is thereby representative of all children with cerebral palsy in Norway (2). It is a weakness, however, that the registry does not specify which muscles have been treated with botulinum toxin A, treatment intervals, dosages and clinical effects of the treatment, nor any additional treatment such as the use of orthoses and physiotherapy/occupational therapy.

We found that the proportion of children who received injections of botulinum toxin A was comparable to what was found by a previous Norwegian study (8). The proportion of children treated with botulinum toxin A is high when compared to a recent Swedish

study, which found that no more than approximately one-third of the children in a national follow-up programme had been treated at the age of 4–6 (13). We are not aware of any other studies that have investigated the frequency of botulinum toxin A treatment in a total population of children with cerebral palsy. We found, however, that a smaller proportion of the children with gross motor function level V had been treated in our study (49 %) when compared to what is suggested in the consensus report from 2009 (75–100 %) (5).

A total of 50–70 % of all children with cerebral palsy have hand impairments (14), but only 30 % of the children in our study had been injected with botulinum toxin in the upper extremities. This is disconcerting, since a systematic review from 2013 showed that such treatment in the upper extremities in combination with occupational therapy has the best documented effect (15).

Comorbidity and a higher total dose of botulinum toxin A may increase the risk of complications and adverse effects of the treatment, and children with severe functional impairment (gross motor function levels IV and V) and comorbidity appear to be at an increased risk of serious adverse effects (1, 6, 9). The explanation for why children with the poorest motor function levels were more rarely treated with botulinum toxin A could be a greater concern for serious adverse effects in this group (4, 5). The indication for treating children with the most serious impairments is normally to reduce pain and ease provision of care, and we may speculate as to whether children with the most severe forms of functional motor impairment are undertreated. Baclofen was most frequently administered to children with gross motor function level V, although relatively few had received such treatment.

Many treatment institutions used only palpation to identify muscles, even though the palpation method has been shown to have reduced accuracy. It is therefore recommended to use ultrasound as guidance during injections of botulinum toxin A in children (4, 5).

Our study cannot provide a definitive answer to the question of what constitutes the correct treatment level, and the consensus-based guidelines for treatment that have been published are largely experience-based and non-specific (4–6). A lack of evidence-based guidelines for botulinum toxin A treatment is the most likely explanation for the large variations in treatment practices that this study reveals.

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## Conclusion

Our study shows that the use of botulinum toxin A for treatment of spasticity in children with cerebral palsy is widespread in Norway, but that there are large variations in treatment practices. The results indicate a need for more research-based knowledge, as well as for national guidelines that will ensure more equality in treatment.

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