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The tonic response to the infant knee jerk as an early sign of cerebral palsy

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ABSTRACT

Background: Early identification of infants at risk of cerebral palsy (CP) is desirable in order to provide early intervention. We previously demonstrated differences in knee jerk responses between 3-month-old high risk and typically developing infants.
Aims: To improve early identification by investigating whether the presence of tonic responses (continuous muscle activity occurring after the typical phasic response), clonus or contralateral responses to the knee jerk during infancy is associated with CP.
Study design: Longitudinal EMG-study.
Subjects: We included 34 high-risk infants (median gestational age 31.9 weeks) who participated in the LEARN2MOVE 0–2 years trial.
Outcome measures: Video-recorded knee jerk EMG-assessments were performed during infancy (1–4 times). Developmental outcome was assessed at 21 months corrected age (CA). Binomial generalized estimating equations models with repeated measurements were fitted using predictor variables.
Results: Infants who later were diagnosed with CP (n = 18) showed more often than infants who were not diagnosed with CP i) tonic responses – from 4 months CA onwards, ii) clonus - from 13 months CA onwards, and iii) contralateral responses - from 15 months CA onwards.
Limitations: The main limitation is the relatively small sample size.
Conclusions: The assessment of tonic responses to the knee jerk using EMG may be a valuable add-on tool to appraise a high risk of CP.

1. Introduction

Cerebral Palsy (CP) is the most common cause of physical disability in childhood. The diagnosis of CP indicates a permanent disorder of the development of movement and posture, attributed to disturbances in the fetal or infant brain [1]. The majority of children with CP are diagnosed with a spastic form [2]; they often exhibit pathological reflexes, including exaggerated patellar tendon reflexes [3].

Early identification of infants at risk of CP is desirable in order to provide early intervention, in a phase when the brain is most plastic [4]. However, the characteristics of the young nervous system hamper prediction. For instance, hyperexcitability of spinal circuitries, e.g., expressed by low thresholds for eliciting tendon reflexes and the occurrence of reflex irradiation, is a physiological phenomenon in early infancy [5,6]. In addition, spasticity is rarely present at early age in infants who develop CP [7]. Recently, we noticed that some high-risk infants showed a tonic reaction in response to the knee jerk. We therefore studied knee jerk responses with the help of surface electromyography (EMG) in infants aged three months corrected age (CA). We were able to demonstrate that EMG responses in infants at very high risk of CP differ from those in typically developing infants [8]. For example, the three-month-old high-risk infants more often showed tonic responses (TRs), i.e. continuous muscle activity occurring after the typical phasic response, and more often clonus and contralateral phasic responses than typically developing peers.

The aim of the present, longitudinal study was to evaluate the

Abbreviations: CA, corrected age; CP, cerebral palsy; CPG, central pattern generator; EMG, electromyography; GMs, general movements; L2M, Learn2Move; TINE, Touwen Infant Neurological Examination; TR, tonic response

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Table 1
Child characteristics.

Baseline characteristics	*n* = 34
Gestational age, weeks (median + range)	31.9 (25.9–41.3)
Birth weight, grams (median + range)	1794 (720–5400)
Sex, n (boys/girls)	19/15
Type of brain lesion, n	
Basal ganglia and/or thalamus lesion	5
Cortical infarction	2
Cystic periventricular leukomalacia	10
Periventricular leukomalacia (without cysts)	2
Posthemorrhagic porencephaly	8
Non-specific or no significant lesions	7
Corrected age at 21 months assessment, months (median + range)	21.3 (19.1–22.5)
Outcome at 21 months	
No cerebral palsy	16
GMFCS level I	3
GMFCS level II	5
GMFCS level III	4
GMFCS level VI	3
GMFCS level V	3

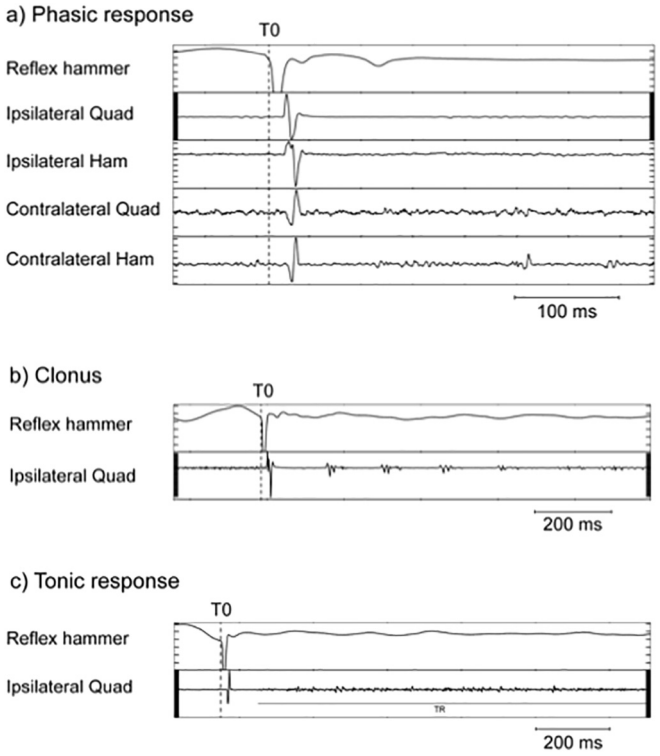

Fig. 1. EMG responses to the knee jerk
Responses were considered a phasic response if they a) occurred within 40 ms after T0, b) lasted maximally 15 ms, c) were bi- or triphasic, and d) significantly differed from background activity and muscle activity prior to tap application (Fig. 1A). The presence and the number of repeats of repetitive phasic responses (clonus) were recorded (Fig. 1B). Reponses were considered as tonic response if they a) started within 150 ms after a phasic response, b) lasted at least 500 ms, and c) visual inspection indicated continued activity of a similar intensity (Fig. 1C). Adapted from Hamer et al. [8].

development of knee jerk responses in high-risk infants during the first two years of life. We investigated whether the presence of TRs, clonus or contralateral responses during infancy is related to the diagnosis of CP.

We hypothesized that in particular the persistence of tonic responses is associated with CP, as the occurrence of tonic responses in early infancy is related to an abnormal quality of the infant's general movements (GMs) [8], and abnormal GMs are associated with CP [9,10]. In addition, we hypothesized that contralateral reflex irradiation of phasic responses may be a typically transient phenomenon of early ontogeny that persists in children with CP [11,12].

2. Materials and methods

2.1. Participants

Out of the 43 infants who had participated in the LEARN2MOVE (L2M) 0–2 years project, 34 infants had underwent at least one proper knee jerk EMG assessment and had participated in the assessment around 21 months CA and were therefore included in this study (Table 1). The L2M 0–2 years project was primarily designed as a randomized controlled trial to study the effect of early intervention [13]. Inclusion criteria of the L2M 0–2 years project were maximally nine months CA at enrolment and the presence of at least one of the following conditions: (1) cystic periventricular leukomalacia, (2) parenchymal lesion of the brain, (3) severe neonatal hypoxic-ischaemic encephalopathy with brain lesions on MRI and (4) neurological dysfunctions suggestive of the development of CP [13]. Children with severe congenital disorders or with caregivers having insufficient understanding of the Dutch language were excluded. The project was approved by the Ethics Committee of the University Medical Centre Groningen and registered under trial number NTR1428. Parents gave informed consent.

2.2. Knee jerk assessment

We aimed to perform a videotaped knee jerk EMG assessment at baseline, i.e., between 0 and 9 months of age, at 6 and 12 months after baseline, and around 21 months CA, as part of the L2M research protocol. Bipolar surface electrodes (inter-electrode distance 14 mm) were placed over the bellies of the right and left quadriceps and right and left hamstrings. Surface EMG signals were continuously recorded by means of an electro-physiological front-end amplifier (Twente Medical Systems International, Enschede, The Netherlands) at a sampling rate of 2000 Hz. The EMG amplifier simultaneously recorded accelerations of the connected reflex hammer to allow for precise determination of tap application. In each infant, the knee jerk was elicited approximately ten times on each side.

2.3. Video and EMG analysis

The PedEMG software (Developmental Neurology, University Medical Center Groningen, The Netherlands [14]) allows for analyses of synchronized signals, such as surface EMGs, reflex hammer and video recordings. The videos were analysed to include only trials in which a clear kick of the leg was observed in response to the tendon tap. The EMGs were subsequently analysed in random order and without video to allow for blinded analysis. First, the tap-signal from the reflex hammer was used to define T0 of the knee jerk latency (Fig. 1). Next, onset times of phasic and tonic responses (PRs and TRs, respectively) were determined with the use of the model-based algorithm of Staude and Wolf, which detects significant changes in muscle activity [8,14].

For each child at each assessment, the percentages of occurrence of ipsilateral and contralateral PRs as well as TRs and clonus were calculated. Parameters were only computed if at least five suitable trials were available for analysis.

2.4. Developmental assessments

At the last assessment, i.e., around 21 months CA, we performed the Touwen Infant Neurological Examination (TINE) [15] to specify whether or not the child had CP, in accordance with the criteria of the Surveillance of Cerebral Palsy in Europe [3]. The diagnosis of CP implies the presence of abnormalities in movement and posture,

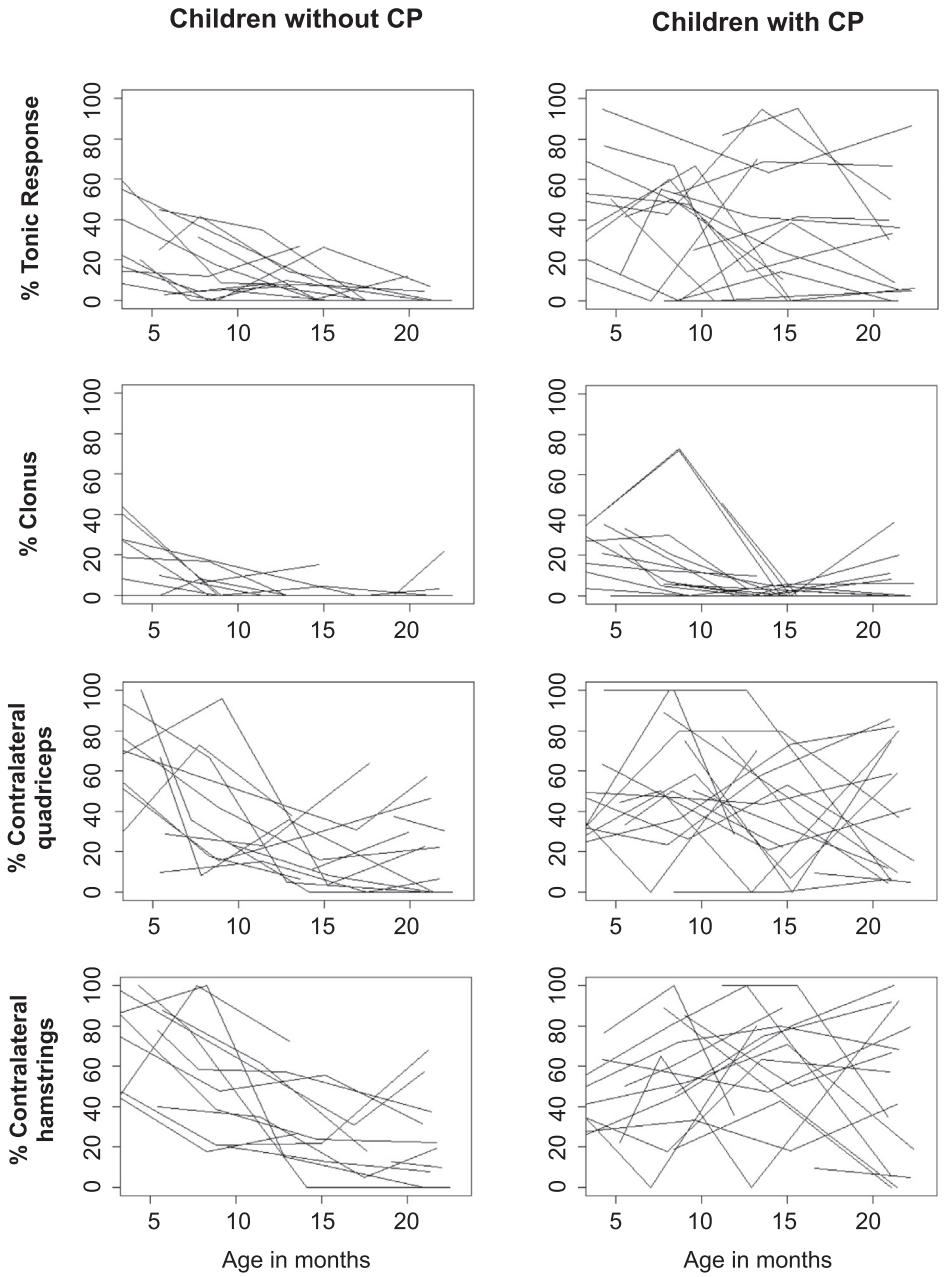

Fig. 2. Development of tonic responses, clonus, and contralateral responses in very high-risk infants without and with cerebral palsy
The horizontal axes indicate the infant's age in months; the vertical axes the percentage of occurrence of a specific response. Individual lines represent developmental changes in individual infants; the left graphs represent infants who did not have cerebral palsy (CP), the right graphs represent infants with CP.

dysfunctional muscle tone regulation, and pathological reflexes. Note that when we write on the following pages "infants diagnosed with CP" we imply 'infants diagnosed with CP at 21 months CA'. The TINE is a reliable instrument [16].

2.5. Data analysis

For the descriptive statistics, SPSS package for Windows, version 20.0 was used. Next, generalized linear mixed models with binomial link-function were fitted in R [17] using linear predictor variables age and CP, which take into account all repeated measurements over time per child. The results of these models were used to create time-profiles describing the average development of the outcome parameter per group (CP/non-CP). Using these profiles, the earliest age was calculated at which the difference between groups became statistically significant ($p < 0.05$). For the parameter of primary interest (i.e., the TR) as indicator of CP, we generated a ROC curve between 4 and 12 months CA.

3. Results

At 21 months CA, 18 children (53%) had CP. A total of 112 EMG assessments were included in the analysis. Most children underwent three ($n = 13$) or four ($n = 16$) suitable EMG assessments. Of the other five children one (n = 1) or two ($n = 4$) EMG assessments could be included for analysis. There was no difference in the number of EMG assessments between children with or without a diagnosis of CP (data not shown). Also developmental outcome of the 34 L2M-infants who were included in this knee jerk project and that of the other 9 L2M-

Table 2
Occurrence of tonic responses, clonus and contralateral responses.

Age	Parameter	No cerebral palsy		Cerebral palsy	
			N		N
< 4 months corrected age	% tonic responses	24 (9–62)	7	34 (18–70)	7
	% clonus	29 (0–47)	7	27 (3 − 33)	7
	% contralateral quad	67 (11–95)	7	32 (24–55)	8
	% contralateral ham	76 (22 − 100)	7	41 (24–55)	7
4–6 months corrected age	% tonic responses	23 (3–45)	4	50 (13–95)	5
	% clonus	0 (0 − 10)	4	25 (0–35)	5
	% contralateral quad	48 (10 − 100)	4	54 (33 − 100)	4
	% contralateral ham	83 (40–100)	4	57 (22–76)	4
6–9 months corrected age	% tonic responses	8 (0–42)	8	48 (0–67)	11
	% clonus	0 (0–17)	8	13 (0–73)	11
	% contralateral quad	36 (8–73)	7	50 (0 − 100)	11
	% contralateral ham	58 (18–100)	7	60 (0–100)	11
9–12 months corrected age	% tonic responses	8 (5–35)	3	36 (0–82)	6
	% clonus	0 (0–0)	3	0 (0–45)	6
	% contralateral quad	23 (15–24)	3	50 (26–77)	5
	% contralateral ham	35 (20–62)	3	44 (33–100)	4
21 months corrected age	% tonic responses	0 (0–7)	11	9 (0–86)	15
	% clonus	0 (0 − 22)	11	0 (0–36)	15
	% contralateral quad	22 (0–57)	11	37 (5–86)	15
	% contralateral ham	22 (0–68)	11	52 (0–100)	15

Abbreviations used: quad for quadriceps muscle, and ham for hamstrings. We present the median percentages and their range per group, based on the percentages of occurrence of a specific response within one child at one measurement.

Table 3
Development of knee jerk responses in children with and without cerebral palsy.

	Variables in model	Fixed effects: (β)	Odds ratios exp.(β) (95% CI)	Significant difference between estimated group-mean-profiles (in months)
Tonic responses	CP	0.609	1.839 (0.629–5.490)	≥3.8
	Age	−0.178***	0.837 (0.800–0.874)	
	CP * age	0.105***	1.110 (1.057–1.170)	
	Intercept	−0.701	0.496 (0.210–1.120)	
Clonus	CP	−0.366	0.693 (0.183–2.430)	≥13.0
	Age	−0.245***	0.782 (0.718–0.841)	
	CP * age	0.121**	1.129 (1.038–1.240)	
	Intercept	−1.007*	0.365 (0.133–0.996)	
Phasic response contralateral quadriceps	CP	−1.165**	0.312 (0.143–0.656)	≤4.0 and ≥15.0
	Age	−0.133***	0.876 (0.850–0.902)	
	CP * age	0.119***	1.126 (1.087–1.168)	
	Intercept	0.813**	2.555 (1.274–4.063)	
Phasic response contralateral hamstrings	CP	−1.101**	0.332 (0.160–0.682)	≤4.0 and ≥14.6
	Age	−0.111***	0.895 (0.871–0.919)	
	CP * age	0.115***	1.122 (1.084–1.161)	
	Intercept	1.026***	2.790 (1.611–4.869)	

Results are presented of the four generalized linear mixed models with each of the EMG-parameters of interest as outcome variable, i.e. percentage of tonic responses, clonus, and contralateral phasic responses in quadriceps or hamstrings. Based on these results, time-profiles describing the average development of the outcome variables per group (CP versus non-CP, third column) and the age at which the difference between the groups became statistically significant could be calculated (last column, $p < 0.05$).

* < 0.05.
** < 0.01.
*** < 0.001.

infants was similar.

3.1. Tonic responses

There was a large variation in the occurrence of TRs (Fig. 2). Before the age of four months CA, TRs occurred in 34% (median value) and 24% of the trials in infants who were ($n = 7$) and infants who were not diagnosed with CP (n = 7, Table 2), respectively – a difference that was not statistically significant (Mann-Whitney U; $p = 0.535$). The generalized linear mixed models showed that throughout infancy, the percentage of occurrence of TRs decreased with increasing age (in children without CP OR 0.84, CI: 0.80–0.87, $p < 0.001$, in children with CP OR 0.93, CI: 0.91–0.95, $p < 0.001$). As a result, the median occurrence of TRs around 21 months CA was 9% (range 0–86, $n = 15$) in children with CP and 0% (range 0–12, $n = 12$, $p = 0.009$) in children without CP. The mixed models analysis indicated that the difference in occurrence of TRs between infants who would and who would not develop CP became significant after 3.8 months CA; from that age onwards infants later diagnosed with CP showed significantly more TRs than the other infants (Table 3). Persistence of TRs was observed in 13 out of the 26 children with a knee jerk assessment around 21 month CA: 11 of them (85%) had CP (Fisher's Exact test; $p = 0.015$). To assess the discriminating value of percentage of TR-occurrence for CP, the accompanying ROC curve based on the assessments of 30 different children between 4 and 12 months of age is presented in Fig. 3. The ROC curve illustrates the diagnostic ability by plotting the true positive rate (sensitivity) against the true negative rate (specificity) at various thresholds, i.e. percentages of occurrence of TRs. With an area under the curve of 0.72, the accuracy can be considered fair.

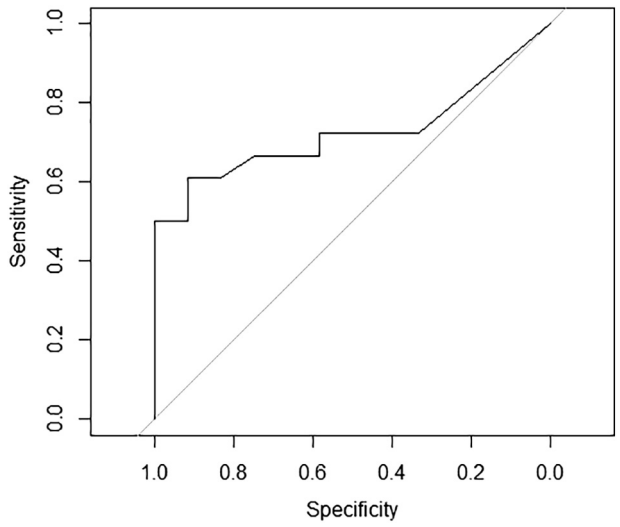

Fig. 3. ROC curve of tonic responses-percentage as indicator for CP in infancy
Based on assessments of 30 different infants between 4 and 12 months CA. The area under the curve was 0.72 (95% CI 0.54–0.91).

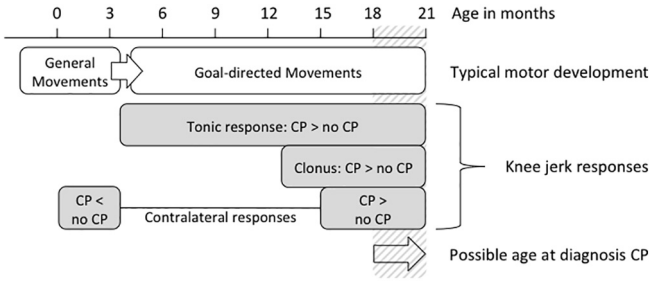

Fig. 4. Schematic overview of the development of knee jerk responses in infants at high risk of cerebral palsy.

3.2. Clonus

In the 14 infants assessed before four months CA, a clonus occurred in 28% of the trials (range 0–47). Throughout infancy, the occurrence of clonus decreased with increasing age (in children without CP OR 0.78, CI 0.72–0.84, $p < 0.001$, in children with CP OR 0.88, CI: 0.85–0.92, $p < 0.001$). Infants diagnosed with CP started to differ from the infants without CP from 13 months CA onwards, with the former group exhibiting more often clonus than the latter group (Table 3). Around 21 months CA, the median occurrence of a clonus was 0% in both groups (range CP 0–36, range no CP 0–22).

3.3. Contralateral phasic responses

Phasic responses in contralateral quadriceps and hamstring decreased throughout infancy (Table 3). Before four months CA, the median occurrence was 52% (range 11–95) for the contralateral quadriceps muscle and 50% (range 22–100) for the contralateral hamstring; at that time, infants who were not diagnosed with CP more often showed contralateral responses than the infants with CP (Table 2). From 15 months onwards, the difference reversed: contralateral responses were significantly more often observed in children diagnosed with CP than in the other children (Table 3, Fig. 2). Around 21 months CA, the median occurrence of PRs was 22% (CP 37%, range 4–86; no CP 22%, range 0–57) for the contralateral quadriceps muscle and 36% (CP 52%, range 0–100; no CP 22%, range 0–68) for the contralateral hamstring.

4. Discussion

The present study demonstrated several differences in knee jerk development over time between very high-risk infants with and without CP. Infants who later were diagnosed with CP showed more often than infants who were not diagnosed with CP a) TRs – from 4 months CA onwards, b) clonus - from 13 months CA onwards, and c) contralateral responses - from 15 months CA onwards.

4.1. Tonic responses

We previously suggested that the presence of TRs could be considered a marker of a loss of supraspinal control, as a) 3-month-old very high-risk infants significantly more often exhibited TRs than their typically developing peers, and b) the presence of TRs was associated with definitely abnormal GM quality [8]. The presence of definitely abnormal GMs implies a high risk of CP but not a certainty of CP [18]. The current study shows that at group level, TRs can further differentiate between high-risk infants who will and who will not develop CP – but only after four months CA. Interestingly, around this age major developmental changes occur in the young nervous system. It is the phase in which GMs are replaced by goal-directed movements (see Fig. 4) [19], which coincides with the gradual disappearance of the cortical subplate and the emergence of the permanent cortical circuitry in the primary motor and sensory areas [10]. Conceivably perinatal damage of the subplate and its connections, results in early infancy in both an abnormal quality of GMs [20] and TRs. As the transient period of double circuitry lasts till about the age of one year [10], early neurological signs may slowly resolve or evolve into a clear neurological syndrome like CP. Which factors determine the nature of the resolution is largely unknown, but presumably the extent of the brain lesion contributes to both the presence and persistence of TRs and the risk of developing CP.

The first postnatal year is also important for refinement of corticospinal connections and muscle afferent projections in the spinal cord and dorsal column nuclei; a process depending on synaptic competition [21,22]. Consequently, damage to the developing corticospinal tracts results in an imbalance, which can lead to an increased excitability of spinal circuits that may induce a lowered threshold for long-lasting self-sustained firing of motoneurons by persistent inward currents [8,23].

4.2. Clonus

Before one year of age, the presence of clonus did not differ between high-risk infants who did and those who did not develop CP. The clonus phenomenon is likely to be a more general expression of neural hyperexcitability in infancy, as it is more frequently observed in high-risk infants than in typically developing infants [8]. Our results are in line with Futagi et al., who showed that about half of a group of 169 infants at risk for neurodevelopmental disorders with an ankle clonus before the age of 12 months, had a typical neurological outcome [24]. Our data indicated that after one year of age, clonus occurred more often in children with CP than in children without CP. Note, however, that in most children with CP the phenomenon was not observed.

4.3. Contralateral responses

In early infancy, contralateral responses in both quadriceps and hamstring muscles are present in both typically developing and high-risk infants. This suggests that these contralateral responses are part and parcel of typical early ontogeny [8]. The physiological hyperexcitability of the spinal circuitries, the increased sensitivity of muscles spindles, motoneuron pools and motor units, and the presence of excitatory projections, which is likely caused by extensive Ia afferent collaterals to motoneurons of non-homonymous muscles at this age all may contribute [6,25–28]. Our results are in line with those of

Myklebust and Gottlieb [26]. They demonstrated the presence of reciprocal responses, i.e., responses in the antagonist muscle, in healthy term born newborns. In addition, they reported that in typical development this pattern of reciprocal excitation resolves with increasing age and that it persists in children with CP. These human data correspond to findings in kittens that indicate a typical increase in spinal interneurons in early infancy, but a significant reduction of unilateral spinal interneurons after a lesion of the developing cortical spinal tract [21,29].

We previously demonstrated that in early infancy high-risk infants more often exhibit contralateral responses than typically developing infants [8]. Interestingly, the infants who developed CP showed at early age, i.e., prior to four months, less contralateral responses than the infants without CP. We previously hypothesized that the typical presence of contralateral responses in early infancy may be an expression of central pattern generator (CPG)-activity. The rhythmic motor activity produced by CPGs may be inhibited by tonic firing of CPG interneurons [30]. Possibly, the typical contralateral responses of early infancy occur at a higher rate in high-risk infants due to exaggerated hyperexcitability, but at a lower rate in infants with a severe brain lesion, due to increased tonic firing. Note, however, that the reported association prior to four months was based on a small number of observations.

4.4. Strengths and limitations

Strengths of this study are its longitudinal data collection in very high-risk infants and blinded EMG analysis. The advantages of the statistical models we used include the optimal use of all available data, while also taking into account the exact age of the child (instead of categorizing age groups) and correlation structures of the repeated measurements within children. Generalization of the results is limited due to the small sample size. The small group size also limited subgroup analysis, for example the exploration of the significance of the various brain lesions. The presence of CP was based on the assessment at 21 months corrected age: it is possible that milder forms of CP may be diagnosed at later age. The manual application of the tap to the patellar tendon can be considered a technical limitation, as this implies a variable force and frequency of the stimulus. However, this does correspond to a standard clinical assessment. Future research may address the question to what extent EMG responses and clinical observations correlate. Due to the small number of observations the ROC curve should be interpreted with caution. Therefore additional studies with more participants are necessary to confirm this potential diagnostically value of the knee jerk.

5. Conclusion

Our data on the development of the knee jerk response partially uncover the pathophysiology of the protracted trajectory of the “growing into a deficit phenomenon” of children with CP. Especially the assessment of tonic responses may be a valuable add-on to the clinical repertoire to indicate a high risk of CP, as the group of children who did develop CP already differed from the group of children without CP from four months CA onwards.

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Conflict of interest statement

None declared.

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