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Atypical knee jerk responses in high-risk children: A longitudinal EMG-study

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ABSTRACT

Introduction: We previously found that atypical responses to the knee jerk reflex, i.e., tonic responses (TRs), clonus and contralateral responses in very high-risk (VHR) infants were associated with cerebral palsy (CP) at 21 months. The current study aimed for a better understanding of pathophysiology of atypical knee jerk responses by evaluating whether infant atypical knee jerk responses are associated with CP and atypical knee jerk responses at school-age.

Methods: 31 VHR-children, who had also been assessed longitudinally during infancy, and 24 typically developing children, were assessed at 7–10 years (school-age). We continuously recorded surface EMG of thigh muscles during knee jerk responses longitudinally during infancy and once at school-age. Neurological condition was assessed with age-appropriate neurological examinations. It included the diagnosis of CP at 21 months corrected age and school-age. CP's type and severity (Gross Motor Function Classification System (GMFCS)) were reported.

Results: Persistent TRs in infancy were associated with CP at school-age. TR prevalence decreased from infancy to childhood. At school-age it was no longer associated with CP. Clonus prevalence in VHR-children did not change with increasing age; it was significantly higher in children without than those with CP. Reflex irradiation was common in all school-age children, and its prevalence in contralateral muscles in VHR-children decreased between infancy and childhood.

Conclusions: In infancy, TRs indicated an increased risk of CP, but at school-age TRs were not associated with CP. In general, spinal hyperexcitability, expressed as reflex irradiation and TRs, decreased between infancy and school-age.

1. Introduction

Assessment of the knee jerk response is an integral part of the neurological examination. An absent knee jerk response indicates an abnormality in the reflex arc, an asymmetry points to peripheral or central dysfunction, and hyperreflexia reflects neural dysfunction above the level of the reflex arc, i.e., a lesion of the corticospinal tract [1–3]. Damage to the corticospinal tract, for example due to an early brain lesion, may result in loss of inhibitory activity from descending motor pathways, causing hyperexcitability of the motoneuronal spinal system as often seen in children with cerebral palsy (CP). CP is the most common neuromotor disability in childhood with a prevalence in most high-income countries of 1 in 500 live births [4]. Key symptoms of CP are - regardless of subtype - hyperreflexia, atypical muscle tone and motor and/or postural control impairments [5]. Most children diagnosed with CP have the spastic form (60–80%) [5,6].

In infants later diagnosed with CP it usually takes time before the specific signs of CP emerge [7]. For example, hypertonia and spasticity are seldomly present in early infancy in children who are later diagnosed with CP, and will become more evident during childhood [8]. Due to the complex development of the nervous system during infancy, early diagnosis of CP is challenging. At the same time, early detection of infants at risk is highly recommended since the plasticity of the nervous system during this phase of life offers the possibility of early intervention [7,9].

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Abbreviations

CA	corrected age
CI	confidence interval
CP	cerebral palsy
EMG	electromyography
GMFCS	Gross Motor Function Classification System
L2M	LEARN2MOVE
MND	minor neurological dysfunction
PIC	persistent inward current
PR	phasic response
TD	typically developing
TR	tonic response
VHR	very high-risk

The present paper focuses on associations between atypical knee jerk responses and the later diagnosis of CP. We were especially interested in the tonic response, as we previously had found that the presence of a tonic response, i.e., a long-lasting contraction as a response to the knee jerk, was associated with the diagnosis of CP at 21 months [10,11]. It was hypothesized that tonic responses may be one of the preliminary expressions of hypertonia. High-risk infants who later got diagnosed with CP also showed more often clonus and contralateral responses than their peers who did not develop CP.

The aim of the current study was threefold. Our primary aim was to evaluate whether tonic responses to the knee jerk during infancy in very high-risk (VHR) children were associated with the presence and severity of CP at school-age. Secondly, we assessed whether in VHR-children the prevalence of specific knee jerk responses, such as tonic and contralateral responses, changes between infancy and school-age. The tertiary aim was to assess whether and how reflex organization at school-age, in terms of tonic response, clonus and contralateral phasic responses differs between VHR-children and their typically developing (TD) peers. Previous studies indicated that in TD-children the occurrence of phasic responses in antagonist and contralateral muscles decreases between infancy and adulthood [12–14]. Yet, we do not know to what extent a developmental decrease in excitability occurs in VHR-children. The information resulting from our study may contribute to a better understanding of reflex pathways in high-risk infants, in particular in terms of motoneuronal hyperexcitability, and its clinical expressions in children with CP.

2. Materials and methods

2.1. Participants

We assessed knee jerk responses in two groups of school-aged children: a group of VHR-children and a group of TD-children. The VHR-children were participants of the LEARN2MOVE 0–2 years trial (L2M0-2). L2M0-2 was a randomized controlled trial that evaluated the effect of two forms of early intervention in VHR-infants (for details see Refs. [15–17]). Most infants had an evident brain lesion on neuroimaging, that was performed as part of standard clinical care (mostly MRI, see Table 1). Infants were assessed at baseline (between 0 and 9 months corrected age (CA)), at 6 and 12 months after baseline and at 21 months CA. This resulted in a maximum of four EMG-assessments during infancy for each child. All L2M-0–2 participants were approached to participate in the current follow-up study when they were 7–10 years. There were no additional inclusion or exclusion criteria.

The TD-group consisted of healthy school-aged children. Recruitment took place via staff's acquaintances and social media. Inclusion criteria were: age between 7 and 10 years, attending mainstream primary education, and having caregivers with sufficient understanding of the Dutch language. Children were excluded from participation in the TD-group in case of a complicated perinatal history (for example preterm birth (gestational age <37 weeks), or admission to the neonatal ward), and atypical neurological function, such as CP or the complex form of minor neurological dysfunction.

Table 1
Characteristics of VHR-children and TD-children.

	VHR-children	TD-children	*p-value*
	n = 31	*n* = 24	
age at assessment in years, median (min-max)	8.4 (7–10.5)	8.0 (7.0–10.8)	0.734
sex (boys/girls), n	18/13	11/13	
gestational age in weeks + days, median (min-max)	30 + 6 (25 + 6–41 + 2)	40 + 3 (38 + 1–41 + 6)	**<0.001**
preterm birth (GA <37 weeks), n (%)	24 (77)	0	
birth weight in grams, median (min-max)	1550 (720–4410)	3525 (2488–4500)	**<0.001**
neonatal brain imaging, n (%)			
MRI/cranial ultrasound	25/6		
type of brain lesion			
periventricular leukomalacia	13 (42)		
cystic	10		
non-cystic	3		
cortical infarction	2 (6)		
posthemorrhagic porencephaly	7 (23)		
basal ganglia/thalamic lesion	3 (10)		
no/non-specific lesion	6 (19)		
neurological outcome at school-age[a], n (%)			
typical	2 (6)	24 (100)	
complex MND	11 (35)		
CP	17 (55)		
unilateral/bilateral	3/14		
GMFCS I/II/III/IV/V	3/5/0/7/2		
spastic/ataxic	16/1		

VHR: very high risk of cerebral palsy. TD: typically developing. MND: minor neurological dysfunction.
Note that Hamer et al. included the 34 infants who had undergone at least one proper knee jerk EMG during L2M0-2 and participated in the last assessment of L2M0-2 around 21 months CA.[11] For the current study, additional EMG data of 5 infants at 21 months were analysed.
[a] n = 1: no CP but type of MND unknown.

The work described has been carried out in accordance with the Declaration of Helsinki. For all participating children informed consent was obtained. The Medical Ethics Committee of the University Medical Center Groningen (UMCG) approved the follow-up study protocol under registration number METC 2017.321.

2.2. Procedures

The children were assessed once between November 2017 and March 2021, either in the child's home or at the research lab of the Institute of Developmental Neurology of the UMCG, depending on families' preferences. The assessments were carried out by trained assessors and were video-recorded to facilitate supervision, which was performed by a neurodevelopmental expert (MH-A). Within the groups of VHR- and TD-children, both assessors and supervisor were not aware of clinical background of the children.

2.2.1. Neurological assessment

At school-age, children were assessed with the age-specific and standardized MND assessment[18]. The examination is organized into eight functional domains: posture and muscle tone, reflexes, dyskinesia, coordination, fine manipulative ability, associated movements, sensory

functioning and cranial nerve functioning. The examination results in a clinical classification in four categories: normal, simple MND (sMND), complex MND (cMND), and abnormal, for example the presence of cerebral palsy (CP). sMND implies the presence of one or two dysfunctional domains; it is considered a typical, but non-optimal form of typical brain function that is present in about 25% of children [18]. cMND denotes the presence of more than two dysfunctional domains; it is considered a clinically relevant form of brain dysfunction [18]. We classified the children with a normal neurological condition and with sMND as having a typical neurological condition. Children with cMND were excluded from the TD-group. In VHR-children with CP, a further classification was made based on type and distribution of CP [5] (for example: unilateral spastic CP), and gross motor function assessed with GMFCS [19].

2.2.2. Perinatal risk

Perinatal risk factors of the VHR-children were obtained from clinical records during L2M0-2. Caregivers of the TD-children filled out a short questionnaire on perinatal, childhood medical and social characteristics.

2.2.3. Knee jerk assessment and EMG data analysis

Our methodological set-up at school-age was comparable to that of the infant study of Hamer et al. [11] We continuously recorded surface EMG of the right and left quadriceps and hamstrings during the knee jerk response with bipolar electrodes placed over the muscles' bellies. An electro-physiological front-end amplifier (Twente Medical Systems International, Enschede, the Netherlands) recorded surface EMG signals with a sampling rate of 2000 Hz, as well as accelerations of the connected reflex hammer. The knee jerk reflex was elicited at least 10 times on each leg by tapping the patellar tendon with the reflex hammer. As described above, the EMG assessment was video-recorded.

Integrated analysis of signals of surface EMG and reflex hammer, and video recordings was performed with the software package PedEMG (Developmental Neurology, University Medical Center Groningen, the Netherlands) [20]. We started with video analysis to indicate when a tap was applied and whether it was applied to the left or right patellar tendon. Next, the EMGs of all four muscles (ipsilateral and contralateral quadriceps and hamstrings) were analysed without video in random order, implying that the assessor was masked for all child information. The hammer tap signal was used to define T0, i.e., the starting point of the calculation of onset latencies.

We defined a phasic response (PR) based on the following criteria: 1) occurrence within 30 ms (ms) after T0 in ipsilateral quadriceps, and within 35 ms in ipsilateral hamstrings and contralateral quadriceps and hamstrings, 2) duration between 10 and 35 ms, and 3) bi-, tri-, or pentaphasic form (Fig. 1, panel A). A response was considered tonic (tonic response; TR) when it 1) occurred within 150 ms after a phasic response, 2) had a minimal duration of 200 ms, and 3) had a prolonged activity of similar intensity throughout the response (Fig. 1, panel B). The presence of clonus (repetitive phasic responses) was reported (Fig. 1, panel C), as well as reflex irradiation to non-homonymous muscles, i.e., the presence of PRs in muscles other than the ipsilateral quadriceps.

In the VHR-group a persistent TR in infancy was defined as having had at least one TR during the last EMG assessment - for most children at 21 months CA - in combination with at least one TR during a previous EMG assessment at earlier ages (see Ref. [11]). Data of the last infant assessment were used for the comparison of the prevalence of clonus and reflex irradiation between infancy and school-age.

2.3. Statistical analyses

Statistical analyses were carried out using the software Statistical Package for Social Sciences (SPSS), version 26. In previous studies, no significant differences in developmental outcome of the VHR-infants between the two intervention groups at RCT-level were found [16,17].

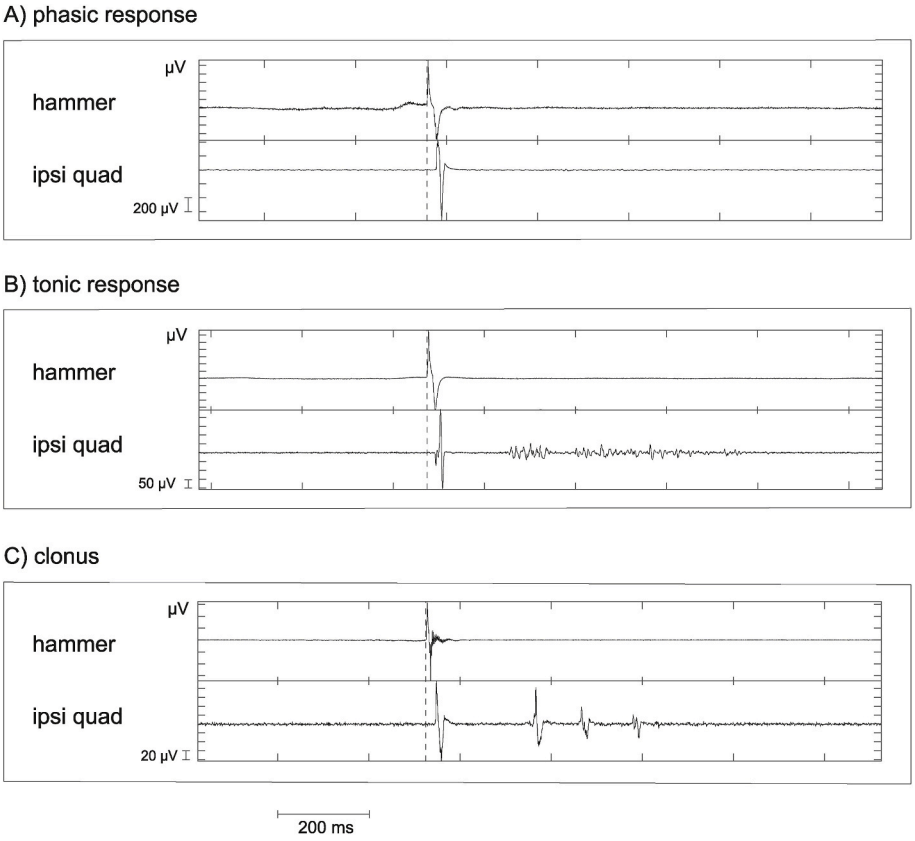

Fig. 1. Typical examples of phasic and tonic response and clonus
A) phasic response, B) phasic response followed by a tonic response, C) clonus, i.e., phasic response followed by 3 clonic beats. In each panel the upper signal indicates the hammer tap, whilst the lower signal shows the EMG of the ipsilateral quadriceps (ipsi quad). EMG amplitude units represent 200, 50 and 20 μv in panel A, B and C, respectively. T0 is indicated by the vertical dashed line.

This allowed for pooling of the two groups to study associations between the knee jerk response and neurological outcome. We calculated for the ipsilateral quadriceps the mean onset latency and duration of the phasic response. Differences in onset latency and duration were analysed with independent t-tests and one-way ANOVA. We also calculated the prevalence of a specific response (PR, TR or clonus) for each assessment as a percentage of the total amount of appropriate trials per child. We presented the median percentages and their range. Associations between dichotomic variables (for example between TR and CP) were analysed with Chi-square tests or Fisher's exact test. Odds ratios are presented with the 95% confidence interval (CI) between brackets. Mann-Whitney tests and Kruskal-Wallis tests were used for analysis of differences in prevalence of specific responses between subgroups (for example, children with and without CP). In case of a significant difference between the subgroups, post-hoc tests were applied. Throughout the analyses, differences and correlations with a p-value < 0.05 or 95%CI were considered statistically significant (two-tailed testing).

3. Results

3.1. Study groups

Thirty-one of the 43 VHR-children included in L2M0-2 participated in the current knee jerk follow-up study. From the 12 children who did not participate, nine had insufficient infant EMG-assessments and three others were lost to follow-up (see flowchart in Fig. 2). The neurological risk profile (gestational age, birthweight, type of brain lesion) of the 12 children who did not participate at school-age was similar to that of the re-assessed children (data not shown). Also the prevalence of CP at 21 months was similar in participants and non-participants (known in 10 non-participants: 5 had CP). All 31 children had a neurological assessment at school-age, but in six we could not obtain an EMG-assessment due to technical or logistical reasons associated with the COVID-19 pandemic. Seventeen of the 31 children participating in the follow-up were diagnosed with CP at 21 months. In all the diagnosis of CP was confirmed at school-age. Their GMFCS level varied from I to V (Table 1). None of the children without CP at 21 months were diagnosed with CP at school-age. Eleven of the VHR-children without CP (n = 14) had cMND. All 24 TD-children had a typical neurological condition. Their age at assessment was not different from that of the VHR-children (Table 1).

3.2. EMG assessments

The 49 EMG assessments at school-age (VHR $n = 25$, TD $n = 24$) resulted in 1021 appropriate trials (median number per child 21, range 4–35). Preliminary analysis revealed differences in reflex activity between VHR-children with and without CP, and between children with CP with low and high GMFCS-levels. Therefore, we split the total group of children with an EMG assessment at school-age into four subgroups: a) TD-children ($n = 24$), b) VHR-children without CP ($n = 11$), c) VHR with CP functioning at GMFCS-levels I-II ($n = 6$), and d) VHR with CP functioning at GMFCS-levels IV-V ($n = 8$). The EMG knee jerk parameters are presented in Table 2 and will be discussed below in more detail.

3.2.1. Persistent tonic response in infancy and CP at school-age in VHR-children

Fifteen of the 31 VHR-children (48%) had shown a persistent TR in infancy; thirteen of them (87%) had developed CP. A persistent TR in infancy was associated with CP at school-age: OR 19.5 (95% CI 3.0–126.5). Also, the presence of TRs during the last assessment in infancy, i.e., independent of previous assessments, was associated with CP at school-age: OR 11.9 (95% CI 2.2–65.1; Supplementary Material S1). A persistent TR in infancy was not associated with GMFCS-level at school-age (Fisher's exact test; p = 1.000) (Supplementary Material S1).

3.2.2. Tonic responses at school-age

In the VHR-children, TR prevalence decreased significantly between infancy and school-age: at the last assessment in infancy 7 out of 31

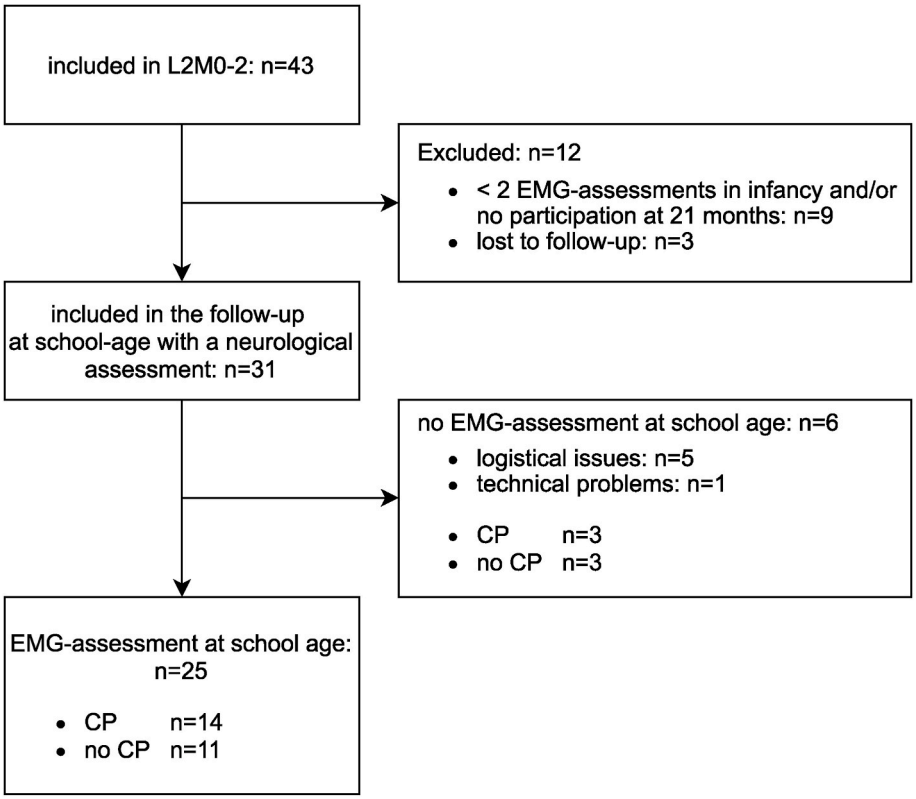

Fig. 2. Participation flow diagram of VHR-infants.

Table 2
EMG knee jerk parameters.

	TD *n=24*		VHR *n=25*						*p*-value[a]
			no cerebral palsy *n* = 11		cerebral palsy: GMFCS I-II *n* = 6		cerebral palsy: GMFCS IV-V *n* = 8		
	mean (SD) or median (range)	*n* (%)	mean (SD) or median (range)	*n* (%)	mean (SD) or median (range)	*n* (%)	mean (SD) or median (range)	*n* (%)	
ipsi quadriceps									
onset latency PR, ms	18 (2)	24 (100)	18 (2)	11 (100)	19 (5)	6 (100)	18 (2)	8 (100)	0.833
clonus, %	5 (0–53)	14 (58)	12 (0–40)	9 (82)	5 (0–23)	3 (50)	0 (0–8)	1 (13)	**0.031**
TR, %	0 (0–13)	5 (21)	0 (0–26)	4 (36)	2 (0–21)	3 (50)	0 (0–5)	2 (25)	0.418
irradiation - prevalence									
ipsi hamstrings: PR, %	86 (47–100)	24 (100)	91 (47–100)	11 (100)	76 (0–100)	5 (83)	93 (75–100)	8 (100)	0.152
contra quadriceps: PR, %	0 (0–69)	6 (25)	0 (0–5)	1 (9)	0 (0–0)	0	0 (0–26)	1 (13)	0.411
contra hamstrings: PR, %	0 (0–46)	10 (42)	0 (0–5)	3 (27)	2 (0–15)	3 (50)	0 (0–6)	2 (25)	0.470
irradiation - onset latency									
ipsi hamstrings: ms	23 (5–30)		24 (16–29)		21 (5–27)		22 (19–24)		0.489
contra quadriceps: ms	24 (15–31)		25 (–)		–		26 (–)		0.687
contra hamstrings: ms	22 (12–29)		25 (14–32)		25 (24–31)		22 (20–24)		0.829

TD: typically developing. VHR: very high risk of cerebral palsy. SD: standard deviation. PR: phasic response. TR: tonic response. Ipsi: ipsilateral. Contra: contralateral. *n* presents the number of children with at least 1 specific response (PR, TR or clonus). Note that the medians and ranges of the prevalence have been calculated in all children in the subgroup, while the medians and ranges of the onset latency were calculated only in the children that showed the relevant response. [a] Kruskal-Wallis or one-way ANOVA.
In the three children with a unilateral CP, we did not find significant differences in knee jerk parameters between the most and least affected side. Therefore, we pooled the trials of the left and right leg of all children in the analyses.

(23%) infants had a TR prevalence of at least 30% of trials, whereas its prevalence at school-age was consistently below 30% (OR 0.490 [95% CI 0.368–0.652]). The presence of at least one TR at school-age in VHR-children was not associated with CP (CP: 5/14; no CP: 4/11; OR 0.972 (95% CI 0.2–5.0)) nor with GMFCS level (Fisher's exact test; p = 0.880; Supplementary Material S1).

Fourteen of the 49 VHR- and TD-children (29%) showed at least one TR during the school-age assessment. The prevalence of at least one TR was highest in the children with CP GMFCS-levels I or II (3 out of 6 children; 50%), followed by VHR-children without CP (4 out of 11; 36%) and VHR-children with CP GMFCS-levels IV or V (2 out of 8; 25%). The TD-children had the lowest prevalence of TR (5 out of 24; 21%); the neurological condition of the 5 children who showed an occasional TR was classified as sMND. The differences between the subgroups were not statistically significant (ANOVA; p = 0.510).

3.2.3. Clonus

In the VHR-group, the prevalence of clonus did not differ between infancy and school-age (median percentages per assessment 0% in infancy versus 5.6% at school-age; p = 0.104). Twenty-seven of all 49 assessed children (55%) had at least once a clonus in the ipsilateral quadriceps at school-age. VHR-children without CP most often showed this phenomenon (9 out of 11; 82%), followed by TD-children (14 out of 24; 58%), children with CP functioning at GMFCS levels I-II (3 out of 6; 50%) and children with CP functioning at GMFCS levels IV-V (1 out of 8; 13%). The prevalence of clonus in VHR-children without CP was significantly higher than in VHR-children with CP (p = 0.009), and in particular higher than in the children with CP functioning at GMFCS level IV-V (p = 0.004; Table 2).

3.2.4. Phasic responses in ipsilateral and contralateral muscles (reflex irradiation)

The prevalence of PRs in the ipsilateral hamstrings of VHR-children did not differ between infancy and school-age (96.3 and 83.3%, respectively; p = 0.134). However, PRs in contralateral muscles occurred significantly less often at school-age than in infancy (quadriceps: 16.8% in infancy and 0% at school-age; p < 0.001, and hamstrings: 37.5% in infancy and 0% at school-age; p < 0.001).

At school-age, most assessed children (48/49) showed PRs in the ipsilateral hamstrings. In the 48 children, the prevalence varied between 19% and 100% (median value 85%; Table 2). Eight children (16%) showed PRs in the contralateral quadriceps and eighteen children (37%) in the contralateral hamstrings. The prevalence of reflex irradiation and the latencies to the PRs in the four recorded muscles did not differ between the four groups at school-age (Table 2).

4. Discussion

The present study indicates that a persistent tonic response to the knee jerk in infancy is associated with the diagnosis of CP at school-age, but not to its severity in terms of GMFCS-level. At school-age, TRs occurred significantly less often than in infancy, their presence was no longer associated with the diagnosis of CP, and their prevalence was now similar in VHR- and TD-children. At school-age, clonus was more often observed in VHR-children who had not developed CP than in VHR-children who had developed CP. In VHR-children the prevalence of reflex irradiation to the contralateral muscles decreased between infancy and school-age, reaching the low rates observed in TD-children. Reflex irradiation to the ipsilateral hamstrings was a common finding in both groups, and in VHR-children at both ages.

4.1. Clinical and pathophysiological considerations

The association between a persistent TR during infancy and CP at school-age confirmed earlier findings of Hamer and colleagues. Hamer et al. had diagnosed CP at 21 months CA [10,11]. The latter age is relatively early as it may take up until the age of 5 years before the diagnosis of CP can be made [21]. The current study indicates that our children with an early evident lesion of the brain did not grow into or out of their diagnosis of CP after the age of 21 months CA. The assessment at school-age did not only allow for the confirmation of the diagnosis of CP, but also for a better determination of the subtype and severity of CP than

at 21 months. At school-age most children with CP were diagnosed with spastic CP (16/17; 94%). Our findings therefore support the hypothesis that tonic responses in infancy and CP's spasticity may share the pathophysiological mechanism of reduced supraspinal inhibition [13], resulting in increased motoneuron excitability [22,23].

The decrease in prevalence of both TR and reflex irradiation to contralateral muscles between infancy and school-age in VHR-children may be attributed to the general decrease in excitability of the spinal circuitries from infancy to school-age [24]. The latter is in line with findings of O'Sullivan and colleagues, who studied spread of reflex activity in healthy individuals from early infancy into adulthood [14]. They found that in typical development redundancy of excitatory projections to motoneurons of non-homonymous muscles gradually reduces with increasing age. Our study illustrates that a similar decrease is also present in children who were perinatally at very high risk of CP. Our observation that the prevalence of reflex irradiation did not differ between the four subgroups at school-age extends to our previous hypothesis that contralateral responses are part of typical early ontogeny [10], thus that their presence does not necessarily indicate atypical development.

Both TRs and clonus are signs of increased neuronal excitability. Nevertheless, the pathophysiology of both signs is not identical. In TRs an additional mechanism is activated: the spinal hyperexcitability - and in particular a monoaminergic drive - induces activation of persistent inward currents (PICs) in the motoneurons [25]. The latter results in sustained activity in the motoneurons. Indeed, our results illustrate that the two signs are not identical. First, TRs were found with the highest prevalence in VHR-children with CP GMFCS levels I-III, whereas clonus occurred in particular in the VHR-children without CP. Second, TRs in VHR-children decreased with increasing age, but clonus did not. Yet, it should be realized that in our small subgroups, TR prevalence at school-age did not differ between the four subgroups, presumably also due to its general low prevalence at school-age. The VHR-children with CP in the highest GMFCS-levels had a lower prevalence of clonus than the VHR-children without CP. Also the prevalence of TRs was relatively low in the VHR-children with the highest GMFCS-levels. It is conceivable that two mechanisms prevented the expression of both TR and clonus in the children with the highest GMFCS levels. First, it is known that in these children the serious loss of supraspinal control results in long-lasting hypertonia [26]. In this hypertonia, PICs of the motoneurons may play a role, as PICs – activated by the long-term loss of supraspinal control – may result in prolonged high self-sustained firing activity of the motoneurons [27]. This relative overactivity of the motoneurons may have masked the expression of TR and clonus. Second, it is possible that the children's persisting hypertonia had induced long-term transformation of the muscles' morphology [28,29], leading to less compliant muscles. The latter does not only give rise to contractures leading to a decreased range of motion of the knee joint, but also may result in less compliant muscle fibres, therewith reducing the effective transmission of the stretch to the muscle spindle, resulting in a low prevalence of both TRs and clonus in the group of children with the highest GMFCS levels [30].

4.2. Methodological considerations

A unique property of the study is that it documented EMG activity of the knee jerk response in infancy and at school-age in a well-documented group of VHR-children [10,11]. Another strength of the study is the inclusion of a group of age-matched typically developing school-aged children. This allowed us to compare reflex activity between VHR- and TD-children. The study's main limitation is the small size of the study groups and subgroups. Additionally, the group of VHR-children was heterogeneous in terms of GMFCS-level and brain lesion. However, this heterogeneity is typical for CP, which is an umbrella diagnosis covering a wide variety of aetiologies, types, and severity of motor impairments and accompanying problems [5].

4.3. Concluding remarks

In conclusion, our findings indicate that a tonic response (TR) to the knee jerk *in infancy* is associated with the diagnosis of CP, but not with its severity in terms of GMFCS. The study also indicates that the presence of a TR *at school-age* is part of typical development. We did not find that the presence of TR or clonus at school-age in children with CP was associated with higher GMFCS-levels. We hypothesized that the lack of associations may have been caused by the long-lasting hypertonia in the children with higher GMFCS-level, resulting in (a) masking of TR and clonus, and (b) changed muscle morphology. Finally, our study indicated that in very-high risk children reflex irradiation to contralateral muscles decreases between infancy and childhood – just as is known for typically developing children.

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Declaration of competing interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejpn.2022.07.003.

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