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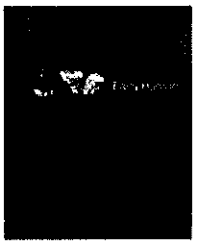

Movement analysis in neonates with spina bifida aperta

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Abstract

Introduction: In neonates with spina bifida aperta (SBA), leg movements by myotomes caudal to the meningomyelocele (MMC) are transiently observed. It is unclear whether these leg movements relate to functional neural conduction through the MMC. For optimal therapeutical intervention, pathophysiological insight in these transient leg movements seems relevant. If leg movements by myotomes caudal to the MMC concur with the execution of general movements (GMs), functional neural conduction through the MMC is implicated.
Objective: In neonates with SBA, we aimed to determine whether the transiently present leg movements caudal to the MMC indicate functional neural conduction through the MMC.
Methods: During the perinatal period, fetuses and neonates with SBA ($n=7$ and $n=13$, respectively) were longitudinally analysed for concurrency between leg movements caudal to the MMC and GMs. To address the integrity of the reflex arc in spinal segments (at, or) caudal to the MMC, tendon leg reflexes were assessed during the first postnatal week.
Results: At postnatal day 1, leg movements caudal to the MMC concurred with GMs in 12 of 13 infants. Isolated leg movements were observed in only 3 of these 12 infants (isolated vs. concurrent; $p<0.005$). Leg movements concurring with GMs lasted longer than isolated leg movements (median duration=11 s vs. 2 s; $p<0.05$). Between days 1 and 7, tendon leg reflexes (at, or) caudal to the MMC had disappeared in all but 1 neonate. However, leg movements caudal to the MMC remained concurrently present with GMs in all five neonates available for follow-up after day 7. Comparing these leg movements between days 1 and 7 indicated a decreased duration (−44%, $p<0.05$).

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Conclusions: In neonates with SBA, leg movements caudal to the MMC concur with GMs, indicative of functional neural conduction through the MMC. The disappearance of these leg movements is caused by lower motor neuron dysfunction at the reflex arc, whereas neural conduction through the MMC is still functional.

1. Introduction

Spina bifida aperta (SBA) is characterised by absent motor function in myotomes caudal to the meningomyelocele (MMC) [1–3]. Perinatally, however, leg movements in myotomes caudal to the MMC are still present [4–7]. These leg movements tend to disappear during the first weeks after birth [4,5]. In an attempt to preserve these leg movements caudal to the MMC, innovative neuroprotective strategies have been initiated [8]. In a fetal sheep model with surgically inflicted vertebral injury, it has been shown that limb movements can be preserved after prenatal coverage of the spinal cord [9–11]. In analogy with these sheep, it was presumed that prenatal coverage of the MMC in human fetuses with SBA could improve motor outcome [12,13]. Thus far, however, prenatal coverage of the MMC in human fetuses with SBA did not convincingly preserve leg movements caudal to the MMC [13–18]. For the interpretation of these findings, characterisation of neural structures involved in the presence and subsequent disappearance of leg movements caudal to the MMC seems relevant.

Leg movements caudal to the MMC may be activated by (upper- or inter-)neurons cranial to the MMC, or by neurons caudal to the MMC (Fig. 1). If neurons cranial to the MMC maintain conductance through the MMC, leg movements caudal to the MMC might ultimately become voluntary in character. In contrast, leg movements that are entirely activated by neurons caudal to the MMC would become reflex-like in character. In this perspective, distinction between presence and absence of functional neural conduction through the MMC seems therapeutically relevant.

We reasoned that analysis of general movements (GMs) and leg movements could discriminate between presence and absence of functional neural conduction through the MMC. GMs consist of gross movement patterns of variable speed and amplitude [19] that involve muscle contractions by all myotomes of the body. If leg muscle contractions by myotomes caudal to the MMC concur with the execution of GMs, functional neural conduction through the MMC is present (Fig. 1). In contrast, if conduction through the MMC is absent, leg muscle contractions by myotomes caudal to the MMC will entirely appear in isolated fashion (Fig. 1).

Already during the first postnatal week, leg movements caudal to the MMC are known to disappear in SBA patients [4,5,20]. The disappearance of these leg movements is contrasted by the constant frequency of motor behaviour in neonates with an intact neural tube [21]. In SBA, leg movements caudal to the MMC could disappear by cranial impairment (hydrocephalus and Arnold Chiari [13,18,22]) or by spinal impairment (neural damage (at, or) caudal to the MMC). Since only preserved activity by neurons cranial to the MMC could relate to voluntary leg muscle activity, identification of initial neural impairment seems relevant. In neonatal SBA, longitudinal comparison of quantitative trends between GMs (all myotomes) and leg movements (myotomes caudal to the MMC) may help to distinct between initial neural impairment cranial to the MMC or (at, or) caudal to the MMC. If leg movements caudal to the MMC decline simultaneously with GMs, initial neurological dysfunction is localised cranial to the MMC (Fig. 1, line a). In contrast, if leg movements caudal to the MMC disappear in an isolated fashion, neurological dysfunction is localised (at, or) caudal to the MMC (Fig. 1, lines c–e).

In the present study in human neonatal SBA, we aimed to determine the relationship between the transient presence

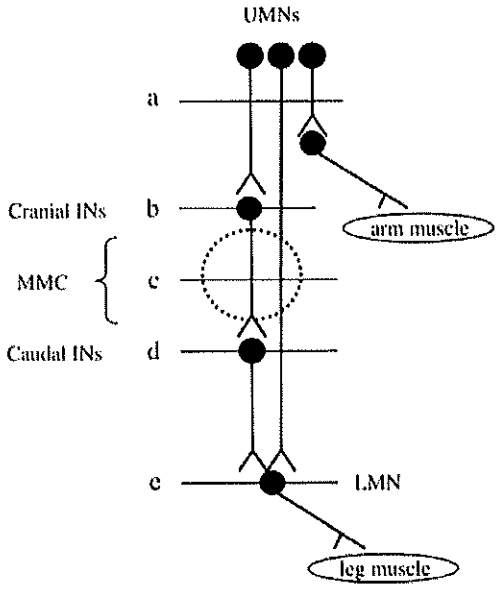

Figure 1 Potential neural involvement in the (dis)appearance of leg movements caudal to the MMC. Schematic model illustrating potential neural involvement in the presence and subsequent disappearance of leg movements caudal to the MMC. Leg movements caudal to the MMC can be characterised according to present or absent concurrence with GMs. If cranially located neurons conduct through the MMC, leg muscle contractions caudal to the MMC will occur in the execution of GMs (concurrent leg movements and GMs). If conduction through the MMC is absent (lines b–d), leg muscle contractions caudal to the MMC occur in an isolated fashion. If the subsequent disappearance of leg movements caudal to the MMC concurs with the disappearance of GMs, neurological dysfunction is located cranial to the MMC (line a). If leg movements caudal to the MMC disappear in an isolated fashion, neurological dysfunction is located (at, or) caudal to the MMC (lines c–e). UMN = upper motor neuron; IN = interneuron; MMC = meningomyelocele; LMN = lower motor neuron.

Table 1 Clinical data of included patients

Case	Level MMC	Other congenital defects	g.a. at birth (wks)	Mode of delivery	Apgar at 1 and 3 min	Outcome
1	Th6–Th10	Ch, Hy	39	CS	8 and 9	†
2	Th9–Th10	Ch, Hy	37	Vaginal	6 and 7	†
3	Th10–Th11	Ch, Hy	38	Vaginal	6 and 7	Wheel chair
4	Th11–Th12	Ch, Hy, CCA	39	CS	9 and 10	Wheel chair
5	Th12	Ch, Hy, Sy Th1–Th6, SA	38	CS	8 and 9	†
6	Th12–L3	Ch, Hy	39	Vaginal	8 and 10	†
7	Th12–L3	Ch, Hy, CCA, SLH	39	Vaginal	8 and 9	†
8	Th12–L5	Ch, Hy	39	Vaginal	9 and 10	†
9	L2–L3	Ch, Hy	40	Vaginal	8 and 9	Wheel chair
10	L2–S1	Ch, Hy, CCA	36	Vaginal	6 and 8	†
11	L3	Ch, Hy, CC	38	CS	8 and 9	No data
12	L3–L5	Ch, Hy, Diastem. at Th10	38	Vaginal	8 and 9	Wheel chair
13	L4–L5	Ch, Hy, FA	39	Vaginal	9 and 10	Ambulant

The level of the MMC was assessed according to the anatomical defect.
Abbreviations: MMC = meningomyelocele, Th = thoracal, L = lumbal, S = sacral, Hy = hydrocephalus, Ch = Arnold Chiari, CCA = corpus callosum agenesis, Sy = syringomyelia, SA = sacral agenesis, SLH = semi-lobar holoprosencephaly, Diastem = diastematomyelia, CC = choroideus cyst, CS = caesarean section, g.a. = gestational age, wks = weeks, † = neonatal death.

of leg movements and the functionality of neural conduction through the MMC.

2. Patients

2.1. Study group

The Medical Ethical Committee of the University Hospital Groningen, the Netherlands, approved the study protocol. In order to select exclusively leg movements generated by myotomes caudal to the MMC, only children with a spinal defect cranial to S1 were included in the study. After informed consent by the parents, 13 patients with SBA were included in the study at postnatal day 1. Table 1 summarises the clinical data of these patients. Seven fetuses with SBA were diagnosed before birth and intra-uterinely transported to our hospital. Ultrasound recordings in these seven fetuses had been performed between 1 and 4 weeks prior to delivery (median = 3 weeks). All neonates were born at term with appropriate weight for gestational age (defined as ± 1 S.D. of the mean birth weight [23]). The MMC was at thoracic level in eight neonates, or at lumbar level in five neonates. Additional spinal malformations consisted of syringomyelia in one neonate, sacral agenesis in one neonate and diastematomyelia in one neonate. Cerebral malformations consisted of Arnold Chiari malformation and hydrocephalus in 13 neonates, hypoplasia of corpus callosum in 3 neonates, plexus choroideus cyst in 1 neonate, falx agenesis in 1 neonate and semi-lobar holoprosencephaly in 1 neonate.

After the first recording, five infants (cases 3, 4, 9, 12 and 13, Table 2) were available for longitudinal assessment. In these infants, the MMC had been surgically closed during the first postnatal week (at postnatal day 3, median age). At neither time point during the inclusion, indications for infection were present.

2.2. Control group

At postnatal day 1, the quantity (frequency and duration) of leg movements in eight neonates with SBA with thoracic MMC (in which all leg movements are innervated by spinal segments caudal to the MMC) was compared with a control group (in which all leg movements are innervated by intact spinal segments). All nine infants of the control group were born full-term after an uncomplicated pregnancy and delivery, with a birth weight appropriate for gestational age.

3. Methods

3.1. Presence and categorisation of leg movements caudal to the MMC

To assess fetal leg movements caudal to the MMC, prenatal ultrasound recordings during the last trimester of pregnancy were performed in 7 of 13 included patients. In these seven fetuses with SBA, the presence of leg movements caudal to the MMC was assessed by means of continuous real-time ultrasound registrations that were recorded on videotape for off-line analysis. Due to the small size of the transducer compared to the body size of the fetus, quantification of GMs was postponed until after birth. In all 13 patients, neonatal motor behaviour was recorded on videotape and scored off-line for the presence of leg movements caudal to the MMC at postnatal days 1 and 7. Subsequently, leg movements caudal to the MMC were assessed for present or absent concurrence with GMs. During the execution of a GM, leg movements caudal to the MMC were separately assessed. This implicates that one GM could theoretically concur with more than one leg movement.

3.2. Qualitative impairment of leg movements caudal to the MMC

The diagnostic method Gestalt Perception applies global visual judgement of spontaneous motor behaviour to characterise movement quality (i.e. the way in which movements are performed; see for review of the method [19]). In the unstimulated fetus and infant, application of

Table 2 Pre- and postnatal discrepant leg movements and the level of the defect

Case	MMC and spinal lesions	Level of postnatal sensory deficit	Level of prenatal LM	Level of postnatal LM	Quality of prenatal LM	Quality of postnatal LM
1	Th6–Th10	Th6–Th7	L5–S1	L4–L5	**	**
2	Th9–Th10	Th9–Th10	L5–S1	Absent	**	*
3	Th10–Th11	Left Th10 Right Th7–Th8	L5–S1	L5–S1	****	***
4	Th11–Th12	L3–L4	L5–S1	L5–S1	****	***
5	Th12 SA, Sy Th1–Th6	Th7	¶	L5–S1	¶	**
6	Th12–L3	Th12	¶	L5–S1	¶	**
7	Th12–L3	Left Th11–12 Right L2–3	L5–S1	L5–S1	**	**
8	Th12–L5	Th11–12	¶	L5–S1	¶	**
9	L2–L3	L5–S1	L5–S1	L5–S1	****	**
10	L2–S1	L2–L3	¶	L4–L5	¶	***
11	L3	L3–L4	¶	L5–S1	¶	**
12	L3–L5 Diastem. Th10	L1–L2	L5–S1	L5–S1	***	***
13	L4–L5	L5–S1	¶	L5–S1	¶	***

Abbreviations: LM=leg movements by spinal segments caudal to the MMC, Ch=Arnold Chiari, CCA=corpus callosum agenesis, CC=choroideus cyst, SLH=semi-lobar holoprosencephaly, MMC=meningomyelocele, Th=thoracal, L=lumbal, S=sacral, Sy=syrinx, SA=sacral agenesis, Diastem.=diastematomyelia, ¶=no data, ****=normal, ***=poor repertoire, **=hardly discernible, *=absent.

this method enables noninvasive assessment of the integrity of the central nervous system [19,24–30]. The interscorer agreement of the method has been determined between 78% and 98% [19,26,28,29,31–33]. By application of Gestalt Perception in neonates with SBA, we previously showed that leg movements caudal to the MMC involve abnormal features, such as hardly discernible (minimal duration and amplitude) and poor repertoire (i.e. reduced variability) [5]. In the present study, we applied Gestalt Perception to characterise the integrity of leg muscle activation in myotomes caudal to the MMC. Three observers (D.A.S. and A.F.B.; and H.F.R. Prechtl, University of Graz) independently scored the quality of leg movements caudal to the MMC.

3.3. Quantitative impairment of leg movements caudal to the MMC

In addition to the quality of leg movements, the quantity (i.e. frequency and duration) of leg movements caudal to the MMC was assessed. For quantitative analysis, the frequency (median rate per 10 min) and median duration (in s) of leg movements caudal to the MMC were determined "off-line" from the videotapes (DAS and JLMB); see for review of the analysis [34]. To optimise reproducibility of quantification, a time window of 5 s was applied for movements (reliability >92% [35]). This means that, within a time interval of 5 s, two consecutive, identical movement patterns are considered as a single event. The duration was indicated by the exact time of on- and offset [36]. According to this method, frequency and duration were compared between leg movements concurring with GMs and isolated leg movements. Leg movements were also quantitatively compared between eight neonates with thoracic MMCs (in which all leg movements are innervated by spinal segments caudal to the MMC) and nine healthy neonates (in which all leg movements are innervated by intact spinal segments).

During the early neonatal period, leg movements caudal to the MMC are known to disappear in neonates with SBA [4]. In order to assess longitudinal trends during the first postnatal week, frequency and duration of leg movements and GMs were assessed at days 1 and 7 in all five neonates with SBA (that were still admitted in our hospital and available for follow up).

3.4. Longitudinal assessment of tendon leg reflexes

During the first postnatal day and week, the integrity of the reflex arc (at, or) caudal to the MMC was assessed by the evaluation of tendon leg reflexes in supine position.

4. Statistical analysis

Statistical analysis was performed using SPSS version 10.0 (SPSS Inc. Chicago IL, USA). McNemar test for paired observations was used to analyse trends in isolated leg movements versus leg movements concurrent with GMs. For comparison of quantitative data of leg movements with the control infants, the Mann–Whitney *U* test was applied. Finally, to test differences between quantitative data of leg movements and GMs at postnatal days 1 and 7, the two-tailed Wilcoxon signed rank test was used. A p-value <0.05 was considered statistically significant.

5. Results

5.1. Presence and characterisation of pre- and postnatal leg movements caudal to the MMC

During the last trimester of pregnancy, prenatal ultrasound recordings indicated leg movements caudal to the MMC in 7 of 13 included patients. In six of these seven fetuses,

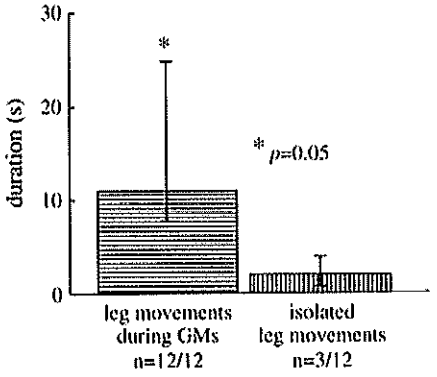

Figure 2 Characterisation of leg movements caudal to the MMC, at neonatal day 1. At postnatal day 1, leg movements caudal to the MMC were characterised according to concurrence with GMs. In 12 of 13 neonates, leg movements caudal to the MMC were present. In 12 of these 12 neonates, leg movements caudal to the MMC concurred with GMs. In only 3 of these 12 infants, isolated leg movements were observed (isolated vs. concurrent, $p<0.005$). The median duration of leg movements concurring with GMs was longer than that of isolated leg movements ($p<0.05$).

prenatally observed leg movements remained present after birth. During the first 24 h after birth, videorecordings of spontaneous leg movements had been made in all ($n=13$) included patients. In 12 of 13 neonates, leg movements caudal to the MMC were observed. These spontaneous leg movements were not provoked by trunk displacements or by other visible tactile stimulation. Presence of pre- or postnatal leg movements caudal to the MMC was independent of the segmental sensory or morphological defect (thoracic ($n=8$) or lumbar lesions ($n=5$); see Table 2).

In accordance with the assumption that conduction through the MMC must be present if GMs involve leg movements caudal to the MMC, all leg movements caudal to the MMC were characterised. At postnatal day 1, leg movements concurred with GMs in all 12 neonates with leg movements caudal to the MMC. Additionally, the combination of concurrent leg movements and isolated leg movements was observed in three of the 12 neonates. Leg movements concurring with GMs were observed in more neonates than isolated leg movements ($p<0.005$). Leg movements concurring with GMs lasted longer than isolated leg movements (median = 11 and 2 s, respectively; range = 3–25 and 2–5 s, respectively; $p<0.05$; Fig. 2). In five neonates at day 7, leg movements by myotomes caudal to the MMC were re-assessed for concurrence with GMs. In all five neonates, leg movements caudal to the MMC were still concurrently present with GMs, whereas isolated leg movements were not observed anymore.

5.2. Qualitative and quantitative trends of leg movements caudal to the MMC

Three independent observers assessed the quality of pre- and postnatal leg movements caudal to the MMC. Inter-observer agreement was indicated by the κ value of 0.85. An abnormal quality of leg movements was assessed in four of seven fetuses (Table 2). In one neonate, prenatally present leg movements had disappeared after birth. In one other neonate, segmental involvement caudal to the MMC had partly disappeared (Table 2).

Comparing the median duration of leg movements at birth between neonates with thoracic MMC and healthy controls, indicated a shorter duration in SBA ($n=8$) compared to healthy controls ($n=9$) (median = 7 s (range = 3–25) and 91 s (range = 14–185); $p<0.001$).

From day 1 to 7, leg movements caudal to the MMC were quantitatively assessed in all neonates with SBA. Between days 1 and 7, leg movements concurring with GMs tended to decline in frequency (median frequency = 3 min^{-1} at day 1 and 1 min^{-1} at day 7; $p=0.08$) and in duration (median duration = 17.5 s at day 1 and 5 s at day 7; $p<0.05$). In contrast to this disappearing tendency of leg movements caudal to the MMC, frequency and duration of GMs did not

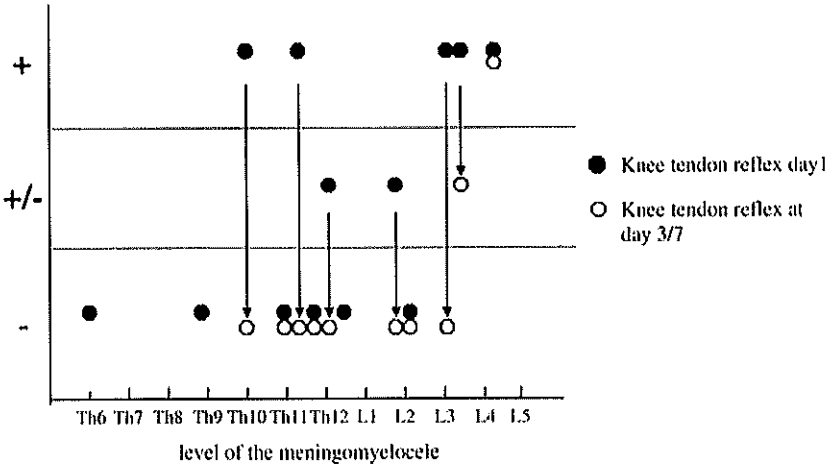

Figure 3 Knee tendon reflexes (L3–L4) between days 1 and 7. Graphical representation of present (+) or absent (–) knee tendon reflexes at day 1 (○), and day 3–7 (●), related to the spinal lesion (horizontal axis). If tendon leg reflexes differed between the left and right leg (+/–) is indicated. In ten neonates, knee tendon leg reflexes (at, or) caudal to the MMC were longitudinally compared between day 1 and days 3–7 (longitudinal assessments within the same individuals are interconnected by an arrow). Between day 1 and days 3–7, a decline in tendon leg reflexes was observed in six of seven neonates.

decline (median duration=35 s and 58 s; frequency=0.7 min^{-1} and 0.6 min^{-1} at days 1 and 7, respectively).

5.3. Longitudinal assessment of tendon leg reflexes

At day 1, tendon leg reflexes (at, or) caudal to the MMC were present in 7 of 13 neonates. At days 3 to 7 of follow-up, tendon leg reflexes (at, or) caudal to the MMC were present in 2 of 10 neonates. Between days 1 and 7, a decline in tendon leg reflexes was observed in six of seven neonates (Fig. 3). After day 7, tendon leg reflexes (at, or) caudal to the MMC were only present in one of five neonates, whereas leg movements caudal to the MMC were still concurrently present with GMs in all five neonates.

6. Discussion

In neonates with spina bifida aperta, leg movements by spinal segments caudal to the MMC are transiently observed. We aimed to determine whether the transient presence of leg movements caudal to the MMC reflects functional neural conduction through the MMC. In our data, the concurrent execution of leg movements by spinal segments caudal to the MMC and GMs indicates presence of functional neural conduction through the MMC.

Despite declined duration of these leg movements during the first postnatal week, functional neural conduction remained present in all infants available for follow up, which was indicated by persistent concurrence of all leg and general movements. These findings, indicative for maintenance of functional neural conduction through the MMC, are in accordance with intra-operatively derived responses after electrical stimulation at the MMC [37].

During the first postnatal week, tendon leg reflexes caudal to the MMC disappeared, whereas concurrent leg movements and GMs were still present. We conclude that lower motor neuron damage (instead of interrupted neural conduction through the MMC) initiates the disappearance of leg movements caudal to the MMC.

In fetuses with SBA, leg movements caudal to the MMC are present from the first trimester onwards and persist throughout pregnancy [5,6]. In uncomplicated pregnancies, fetal leg movements are already present at about 6 weeks gestational age [38,39], which is well before segmental sensory and cortico-motoneuronal projections become functional [40–42]. This early activation of leg movements has been attributed to functional networks by spinal interneurons [43]. The concept of generating interneuronal networks, or so-called central pattern generators, was originally discovered in vertebrates such as spinal cats and monkeys [44]. This concept was translated to human motor behaviour after injury of the brainstem [45] and spinal cord [46–48].

As indicated by our data, neurons cranial to the MMC persistently conduct through the MMC. These projections may both consist of upper- and inter-neuronal projections. In human fetuses, upper motor neuron projections to spinal interneurons are usually present from 28 weeks gestational age onwards [42,49,50]. In perspective of these projections, it seems apprehensive that input by both upper motor neurons and interneurons cranial to the MMC is involved in the activation of leg movements. This implicates that leg movements caudal to the MMC could ultimately become voluntary in character.

Leg movements caudal to the MMC show a tendency to disappear. In accordance with the qualitative deterioration of leg movements from pre- to postnatal life, it seems likely that initial neural dysfunction is already present before birth. At neonatal day 1, the concept of prenatally initiated neural dysfunction is also supported by the shorter duration of leg movements in SBA compared to healthy control neonates.

Theoretically, neurological dysfunction could be caused by both cerebral deterioration (hydrocephalus and Arnold Chiari malformation [13,18]) and by spinal deterioration ((at, or) caudal to the MMC). However, in perspective of the exclusive disappearance of leg movements caudal to the MMC, initial neural dysfunction seems located (at, or) caudal to the MMC. Given the persistent conduction through the MMC from day 1 to 7, the question emerges why leg movements caudal to the MMC disappear at all. According to our data, leg and general movements remained concurrently present, whereas tendon leg reflexes meanwhile disappeared. The obviously impaired reflex arc integrity indicates that segmental lower motor neuron dysfunction is already initiated at this stage. Previously, we reported histological data of motor forehorn cell death (at, and) caudal to the MMC. In corresponding myotomes, structural lower motor neuron damage caudal to the MMC was also reflected by the presence of muscle fibre atrophy (predominantly type 1) [4]. Altogether, present functional data in neonatal SBA support earlier histological findings indicative for lower motor neuron damage in well-covered spinal segments caudal to the MMC. Since this lower motor neuron damage cannot be attributed to disrupted neural conduction through the MMC, fetal coverage of the MMC (alone) is not likely to revert it.

Although the number of included patients is limited, leg and general movements clearly concurred, indicating persistence of functional neural conduction through the MMC. At least theoretically, these leg movements may ultimately become voluntary in character. In the early postnatal period, the disappearance of these leg movements is preceded by lower motor neuron dysfunction caudal to the MMC, whereas neural conduction through the MMC is still functional. Our present data in neonatal SBA implicate that therapeutical strategies aiming to preserve leg movements, should be targeted at lower motor neuron protection caudal to the MMC.

Acknowledgements

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