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General movements and magnetic resonance imaging in the prediction of neuromotor outcome in children born extremely preterm

Béatrice Skiöld [a,*], Christina Eriksson [a], Ann-Christin Eliasson [a], Ulrika Ådén [a], Brigitte Vollmer [a,b]

[a] Dept of Women's and Children's Health, Karolinska Institutet, Stockholm, Sweden
[b] Clinical and Experimental Sciences, University of Southampton, Southampton, UK

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ABSTRACT

Background: Extremely preterm (EPT) birth is a major risk factor for brain injury and neurodevelopmental impairment. Reliable tools for early prediction of outcome are warranted.
Aim: To investigate the predictive value of general movements (GMs) at "fidgety age" for neurological outcome at age 30 months in EPT infants, both in comparison and in combination with structural magnetic resonance imaging (MRI) at term equivalent age (TEA).
Study design: Fifty-three infants born <27 weeks of gestation were included prospectively. MRI was performed at TEA and images were evaluated for white and grey matter abnormalities. GMs were assessed at age 3 months corrected ("fidgety age").
Outcome measures: Neuromotor outcome was assessed at age 30 months corrected. Children were classified as having a normal neurological status, unspecific signs, or cerebral palsy (CP).
Results: Abnormal GMs were a common finding, seen in 32% (17/53) of infants. Of these, six infants (11%) had definitely abnormal GMs. Four infants (8%) had a diagnosis of CP at follow up. Definitely abnormal GMs were significantly associated to CP at 30 months (Fisher's Exact test $p = 0.03$, sensitivity 50%, specificity 92%). Moderate–severe white matter abnormalities on MRI were more strongly associated with CP (Fisher's Exact test $p < 0.001$, sensitivity 100%, specificity 98%) than GMs. Combining GMs with MRI-findings at TEA increased the predictive specificity to 100% (Fisher's Exact test, $p = 0.005$), whereas sensitivity remained unchanged.
Conclusions: The presence of definitely abnormal GMs was predictive of CP: prediction was significantly enhanced when the GMs assessment was combined with findings from MRI obtained at TEA.

1. Introduction

Extremely preterm (EPT) birth is a major risk factor for brain injury with potentially lifelong sequels. However, even in the absence of overt damage, many preterm infants suffer suboptimal brain growth [1] and a range of impairments [2]. Early identification of infants at risk is vital for counselling of parents regarding the prognosis of their child, both to enable appropriate support for the family and for individualized treatment of the child.

Early prediction of outcome is notoriously difficult. Heinz Prechtl developed a tool to assess the quality of an infant's spontaneous motor repertoire before goal directed movements emerge, the so-called general movements (GMs) observation [3,4]. The GMs assessment is based on the Gestalt evaluation of movement complexity, fluency and variation at different ages: "preterm age" (from gestational age 28 weeks up to around 36–38 weeks), "writhing age" (up to 6–9 weeks post term) and finally at "fidgety age" (up to 2–4 months post term) [5]. There is some evidence that abnormal GMs predict cerebral palsy (CP) [6,7] and that they may predict minor neurological dysfunction [8]. Abnormal GMs are frequently observed in preterm infants at "writhing age"; however, this may normalize within the first months of life [9] resulting in an intermediate specificity for these early assessments [10]. Later assessment of GMs (i.e. at "fidgety age") is a better tool for prediction of neuromotor outcome [11] although additional studies are warranted [12]. The predictive power may be enhanced when GMs observation is combined with other tools such as magnetic resonance imaging (MRI) at term equivalent age (TEA) [13] but reports are sparse, especially in EPT children.

The main objective of the present study was to investigate the predictive value of GMs at "fidgety age" for neurological status in EPT

Abbreviations: AIMS, Alberta Infant Motor Scales; CP, cerebral palsy; EPT, extremely preterm; GA, gestational age; GMs, general movements; GMFCS, Gross Motor Function Classification System; MRI, magnetic resonance imaging; TEA, term equivalent age; WM, white matter.

* Corresponding author at: Neonatal Research Unit, Astrid Lindgren Children's Hospital, Q2:07, S-171 76 Stockholm, Sweden. Tel.: +46 41 7769717.
E-mail address: beatrice.skiold@karolinska.se (B. Skiöld).

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infants at age 30 months, in comparison as well as in combination with findings from visual assessment of structural MRI at TEA.

2. Methods

2.1. Participants

The participants were part of a prospective population-based study of EPT infants who had MRI at TEA and neurodevelopmental follow-up at age 30 months corrected [14]. All infants born in Stockholm (2004–2007) with a gestational age (GA) of <27 weeks + 0 days were eligible for inclusion. Between December 2005 and June 2007, 53 infants were prospectively enrolled in the sub-study which is the subject of this paper. Children with malformations, chromosome aberrations, malignant disorders or congenital infections were excluded. The Regional Ethics Committee in Stockholm approved the study and informed consent was obtained from all parents of the participating infants.

The 53 included infants had a mean GA of 25 weeks + 4 days (SD ± 1 day, range 23 + 1–26 + 6) and a mean birth weight of 812 grams (SD ± 152 g, range 499 g–1161 g). Sixty percent were boys, and 53% were delivered with caesarean section. Clinical characteristics and perinatal data are shown in Table 1.

2.2. General movements

One videotaped assessment of GMs was obtained on a single occasion at age 3 months corrected ("fidgety age"); mean corrected age at assessment was 53 weeks (SD ± 1.6, range 51–57 weeks). The observation was done during alert wakefulness, with the infant lying in supine position, wearing minimal clothing. One experienced investigator (CE), blinded to the perinatal history and the MRI results, rated the quality of GMs from 10 to 15 min of the video recordings.

GMs were assessed for complexity, variation and fluency, and then categorized according to Hadders-Algra et al., [15] as "normal optimal" (abundant variation and complexity, fluent), "normal suboptimal" (sufficiently variable and complex, non-fluent), "mildly abnormal" (insufficiently variable and complex, non-fluent) or "definitely abnormal" (variation and complexity virtually absent, non-fluent). This classification is mainly based on the amount of variation and complexity, whereas fluency is not considered in the distinction between normal and abnormal GMs. In cases of uncertainty, a second observer (BV) reviewed the films and consensus was reached after discussion.

2.3. Alberta Infant Motor Scales

On the same day as the GMs assessment, all infants underwent an assessment of motor development with the Alberta Infant Motor Scales (AIMS) [16], an observation of the infant in prone, supine, sitting and standing position. A raw score is calculated and a percentile rank is given. All scores ≤5th centile are considered as indicating delayed motor development.

2.4. Neurological examination

At age 30 months corrected, a structured neurological examination was performed by a paediatric neurologist (BV) for assessment of posture, reflexes, muscular tone and movements. The neurologic status was categorized as 'normal' (completely normal neurologic status), 'unspecific signs' (e.g., asymmetric muscle tone or reflexes, muscular hypotonia, or muscular hypertonia without definite signs of cerebral palsy, CP), or 'abnormal' (signs of CP were present, as defined by the Surveillance of Cerebral Palsy in Europe working group [17]).

For children who did not attend the research follow up assessments, medical records from the child's routine clinical follow-up assessment (performed by either a neonatologist or a paediatric neurologist) were reviewed for information regarding CP and/or abnormal motor development.

2.5. Magnetic resonance imaging

All infants were scanned at Astrid Lindgren Children's Hospital in Stockholm. During the first six months of the study period, infants were scanned under light sedation (chloral hydrate 30 mg/kg orally or rectally). Conventional structural MRI data (T1 and T2 weighted images) were acquired on a Philips Intera 1.5 Tesla scanner (Philips International, Amsterdam, The Netherlands). Scanning procedure and protocol details have been published elsewhere [14,18].

The MR images were evaluated by visual inspection according to a standardized scoring system for structural abnormalities, which has

Table 1
Demographic data and neonatal clinical characteristics.

	All infants n = 53	Attending FU at age 30 months n = 35	FU info from clinical charts n = 18	p-Value
Gestational age, weeks + days mean ± SD (range)	25 + 4 ± 1 (23 + 1–26 + 6)	25 + 5 ± 1 (23 + 1–26 + 6)	25 + 2 ± 1 (23 + 2–26 + 6)	ns
Birth weight, grams mean ± SD (range)	812 ± 152 (499–1161)	852 ± 146 (561–1161)	736 ± 135 (499–917)	0.07
Gender, Nb of male infants	32/53 (60%)	21/35 (60%)	11/18 (61%)	ns
Mode of delivery, caesarean section	28/53 (53%)	19/35 (54%)	9/18 (50%)	ns
Continuous positive airway pressure, days mean ± SD (range)	35 ± 10 (19–60)	35 ± 10 (19–57)	36 ± 12 (20–60)	ns
Mechanical ventilation, days mean ± SD (range)	12 ± 13 (0–55)	10 ± 12 (0–55)	16 ± 15 (0–49)	ns
Bronchopulmonary dysplasia, oxygen required at 36 weeks GA	16/53 (30%)	9/35 (26%)	7/18 (39%)	ns
Retinopathy of prematurity, treated	11/52 (21%)	5/35 (14%)	6/17 (35%)	ns
Patent ductus arteriosus, surgical ligation	16/53 (30%)	8/35 (23%)	8/18 (44%)	ns
Necrotizing enterocolitis, Bell's grades 2–3	5/53 (9%)	4/35 (11%)	1/18 (6%)	ns
No intraventricular haemorrhage[a]	28/53 (53%)	20/35 (57%)	8/18 (44%)	ns
Intraventricular haemorrhage grades 1–2[a]	17/53 (32%)	11/35 (31%)	6/18 (33%)	ns
Intraventricular haemorrhage grade 3[a]	3/53 (6%)	1/35 (3%)	2/18 (11%)	ns
Parenchymal haemorrhagic infarction[a]	5/53 (9%)	3/35 (9%)	2/18 (11%)	ns
Periventricular leukomalacia[a]	1/53 (2%)	1/35 (3%)	0	ns

[a] Cranial ultrasound examinations were performed repeatedly during the hospital stay in all infants.

been shown to have high validity and reliability for prediction of adverse neurodevelopmental outcomes [19]. Five separate white matter (WM) items are assessed: abnormal WM signal, reduction in WM volume, cystic changes, myelination/thinning of the corpus callosum, and ventricular dilatation. From the summed individual item scores a composite score is derived. Based on this composite score, the study group was divided into four subgroups with 1) no WM abnormalities, 2) mild WM abnormalities, 3) moderate WM abnormalities or 4) severe WM abnormalities. Similarly, grey matter was assessed for abnormal signal in the cortical or deep grey matter, enlargement of the subarachnoid spaces and delayed gyral maturation. Infants were then divided into those with 1) normal or 2) abnormal grey matter based on the calculated composite score.

2.6. Statistics

Statistical analysis was performed with PASW Statistics® software 19.0 (SPSS Inc, Chicago, IL). Neurological outcome (normal, unspecific signs, or CP) at age 30 months corrected was compared between the EPT infants with normal ("normal optimal" and "normal suboptimal" pooled) versus abnormal ("mildly abnormal" and "definitely abnormal" pooled) GMs, as well as for infants with "definitely abnormal" GMs separately. In addition, neurological outcome was compared between the EPT infants with an AIMS score below or above the 5th centile. The same groupings were used for analyses investigating associations with MRI categories and individual scoring items.

The following variables were investigated for associations with outcome: GA, birth weight, gender, prolonged rupture of membranes, maternal signs of infection, prenatal steroids, mode of delivery, Apgar scores at ages 1, 5 and 10 min, postnatal steroids, sepsis episodes, number of days on mechanical ventilation or continuous positive airway pressure, bronchopulmonary dysplasia, medically or surgically treated patent ductus arteriosus, laser treatment for severe retinopathy of prematurity, and necrotizing enterocolitis Bell's grades 2–3.

The Student t-test was used for continuous variables, and the Pearson Chi Square test and Fisher's Exact test were used for categorical data. Because group sizes were unequal when based on MRI and GMs categories, nonparametric Mann–Whitney U test was used for these analyses. Diagnostic accuracy of the assessments methods was determined by calculation of sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV).

$P < 0.05$ was chosen as the cut off level for significance.

3. Results

Sixty-eight percent (36/53) of infants had normal GMs: 14/53 (26%) had normal optimal and 22/53 (42%) had normal suboptimal. Thirty-two percent (17/53) had abnormal GMs: 11/53 (21%) had mildly abnormal and 6/53 (11%) had definitely abnormal. Quality of GMs was not related to gender or associated with lower weight or gestation at birth; neither were any of the other perinatal factors or neonatal morbidities studied significantly associated with abnormal GMs at fidgety age.

In total, 66% of the infants (35/53) attended the follow-up assessment at age 30 months corrected. For the remaining 18 infants (34%), medical records from the child's routine clinical follow-up assessment (performed by either a neonatologist or a paediatric neurologist) were reviewed for information regarding CP and/or abnormal motor development (mean age of these children at clinical follow-up was 24 months, SD ± 8, range 11–36 months). Of the 35 infants attending the research follow up, 25 (71%) had a normal neurological exam. Three children were classified as having CP (9%). The corresponding rates in infants where information was retrieved from the paediatrician are shown in Table 2. In total, 4/53 children (8%) had a diagnosis of CP. Of these, one child was on level IV on the Gross Motor Function Classification System (GMFCS [20]), i.e. had CP with severely limited mobility, and the remaining three were on GMFCS level I, i.e. had mild CP with no limitations in mobility although somewhat different gate pattern. Clinical details of the infants with CP are shown in Table 3 and MR images are shown in Fig. 1.

Definitely abnormal GMs were associated with CP at 30 months (Fisher's Exact test, $p = 0.03$, sensitivity 50%, specificity 92%, PPV 33%, NPV 96%) see Table 4, but not with unspecific neurological signs. Abnormal GMs (grouping of mildly abnormal and definitely abnormal together) were not associated to either CP or unspecific neurological signs.

Findings on MRI in this cohort have been reported previously [18,21] and did not differ from the current sample. The majority of the EPT infants in this subset had no (23/53, 43%) or only mild (25/53, 47%) WM abnormalities. Three infants (6%) had moderate and two (4%) had severe WM abnormalities. Five infants (9%) had abnormalities in the grey matter.

Neither white nor grey matter abnormalities on MRI at TEA were associated with the quality of GMs at age 3 months. Associations between findings on MRI and outcome at age 30 months (neurological status and performance on the Bayley Scales of Infants and Toddler Development-III) in a population based cohort from the Stockholm region have previously been reported [14]. In the present smaller sample, moderate–severe WM abnormalities were highly predictive of CP (sensitivity 100%, specificity 98%, PPV 80%, NPV 100%), see Table 4. No associations between grey matter abnormalities and CP were found in the present study.

On the AIMS, 13 out of the 53 infants (25%) had scores below the 5th centile. Low AIMS scores were more common among male infants (Fisher's Exact test, $p = 0.04$) and infants treated for severe ROP (Fisher's Exact test, $p = 0.02$). AIMS scores below the 5th centile were associated with abnormal GMs (Fisher Exact test, $p < 0.001$) but showed no association with CP or unspecific neurological signs. Severe WM reduction (Fisher's Exact test, $p = 0.042$) and thinning of the corpus callosum (Fisher's Exact test, $p = 0.002$) were associated with AIMS scores below the 5th centile, but neither abnormal grey matter nor composite WM abnormality scores were associated with delayed motor development at age three months.

When combining the finding of definitely abnormal GMs with findings of moderate–severe WM abnormalities on MRI, the prediction of CP was improved (Fisher's Exact test, $p = 0.005$, sensitivity

Table 2
Neurological status.

	All infants n = 53	Attending FU at age 30 months n = 35	FU info from treating paediatrician n = 18	p-Value
Normal	36/53 (68%)	25/35 (71%)	11/18 (61%)	ns
Unspecific signs	13/53 (24%)	7/35 (20%)	6/18 (33%)	ns
Abnormal, CP	4/53 (8%)	3/35 (9%)	1/18 (6%)	ns

Table 3
Infants with cerebral palsy.

Nb	Gender	GA	MRI	GMs	AIMS centile	CP	GMFCS
I	M	25 + 4	Severe WMA	Normal optimal	50	Bilateral	I
II	F	26 + 4	Severe WMA	Definitely abnormal	5	Bilateral	IV
III	M	25 + 1	Moderate WMA	Definitely abnormal	<5	Unilateral	I
IV	F	26 + 1	Moderate WMA	Normal suboptimal	25	Unilateral	I

GMFCS: the Gross Motor Function Classification System.

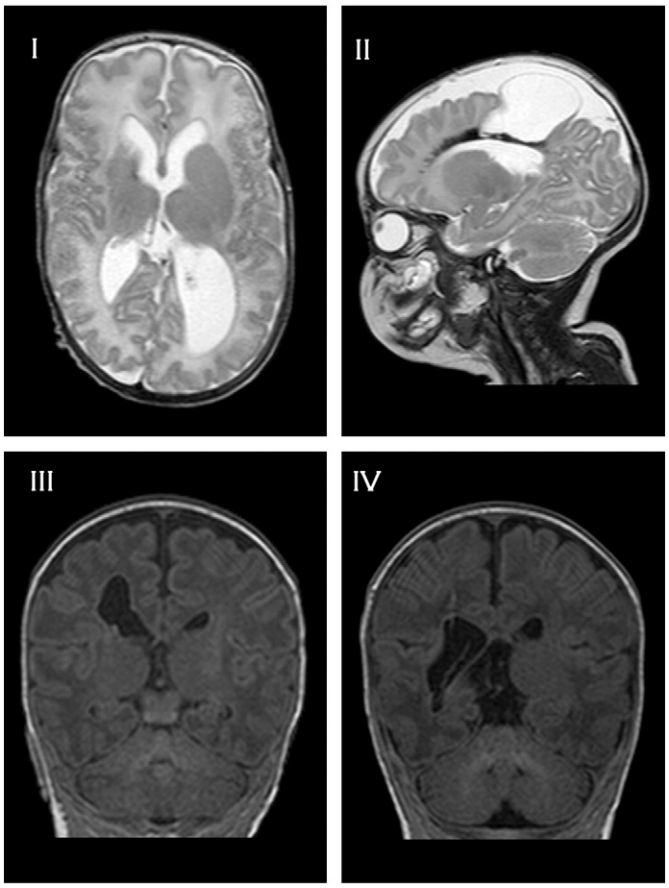

Fig. 1. Imaging findings in infants with cerebral palsy: For each child, one T1- or T2-weighted image in the axial, sagittal or coronal plane was chosen for best possible representation of abnormal findings. If not shown, additional abnormalities are described in the legend. I: Axial T2 weighted image of infant with bilateral CP (GMCFS I) showing abnormal deep grey matter (unilateral atrophy in the striatum and thalamus). This infant also had a global bilateral white matter reduction and a marked enlargement of the lateral ventricles. The myelination was delayed but no asymmetry was noted in the PLIC. No cysts were seen, and cerebellum and corpus callosum were normal. II: Sagittal T2 weighted image of infant with bilateral CP (GMCFS IV) showing a large parietal cyst affecting both surrounding white matter and the cortical grey matter. This infant also had multiple smaller cysts and gliosis bilaterally in the parieto-occipital regions, and marked enlargement of the lateral ventricles and of the subarachnoidal space. Global thinning was noted of the corpus callosum, and the myelination was delayed but no asymmetry was noted in the PLIC. The deep grey matter and cerebellum were normal. III: Coronal T1 weighted image of infant with unilateral CP (GMCFS I) showing a parietal cyst accompanied by white matter reduction and dilatation of the lateral ventricle on the same side. Abnormal myelination was noted unilaterally in the PLIC, whereas the cerebellum and grey matter was normal. IV: Coronal T1 weighted image of infant with unilateral CP (GMCFS I) showing a periventricular cyst accompanied by white matter reduction, abnormal deep grey matter and dilatation of the lateral ventricle on the same side. Abnormal myelination was noted unilaterally in the PLIC, whereas the cerebellum and corpus callosum were normal.

50%, specificity 100%, PPV 100%, NPV 96%). When combining the finding of definitely abnormal GMs with AIMS below the 5th centile, results were unchanged with regards to prediction of CP.

Table 4
Sensitivity and specificity of MRI and GMS in predicting cerebral palsy.

Assessment	Sensitivity	Specificity	PPV	NPV	p-value
Abnormal GMs	50%	69%	12%	94%	ns
Definitely abnormal GMs	50%	92%	33%	96%	$p = 0.029$
Abnormal AIMS	50%	78%	15%	95%	ns
MRI (moderate–severe WMA)	100%	98%	80%	100%	$p < 0.001$
MRI (moderate–severe WMA) and definitely abnormal GMs	50%	100%	100%	96%	$p = 0.005$

PPV: positive predictive value, NPV: negative predictive value.

4. Discussion

The present study investigates the early motor repertoire of EPT infants in relation to their neurological outcome at age 30 months and MRI findings at TEA. Abnormal GMs (i.e. the categories mildly abnormal and definitely abnormal considered together) at "fidgety age" were a common finding, but a poor predictor of CP. However, the presence of definitely abnormal GMs according to the categories of Hadders-Algra et al., [15] was a better predictor of CP, although not as good as using information from MRI at TEA.

Others have shown that clearly abnormal GMs at fidgety age indicate a high risk of CP [e.g. 22]. In the study by Stahlmann et al., 2007 [23], the sensitivity and specificity of abnormal GMs for CP is high; however, the positive predictive value remains fairly low (56%). The authors argue that this may be due to the low rates of CP (5%) in their very low birth weight cohort compared to other studies. For example, in the study by Hamer et al., 2011 [24] ten out of the 46 studied infants (22%) developed CP: five had a GMFCS level of II, three were on GMFCS level III and one had GMFCS I and V respectively. On the contrary, DeVries et al., 2011 [9] failed to show a relationship between abnormal GMs at "fidgety age" and impaired neurological outcome altogether, as none of their extremely low birth weight infants had CP on follow up. In the present study sample, only four infants (8%) developed CP, possibly explaining our low PPV and low sensitivity, however the specificity and NPV were high. In addition, we speculate that GMs may be less sensitive in the prediction of milder forms of CP, which was the case in the majority of the children in the current study, where three children were on GMFCS level I and only one was on GMFCS level IV.

In the present study, we used two motor assessment tools, the AIMS and observation of general movements. Performed on the same day, AIMS scores below the 5th centile were associated with abnormal GMs. However, AIMS scores below the 5th centile showed no associations with CP or unspecific neurological signs at age 30 months. Similar observations were made in a recent systematic review of different motor assessment tools for infants born preterm; GMs were the better predictor of CP around age 3 months corrected. The AIMS was a stronger tool at ages around 12 months corrected, a time when GM is no longer applicable [25].

Similar to the findings of Spittle et al., 2009 [13], who examined a slightly more mature cohort with regards to GA at birth, all infants in the present study underwent MRI at TEA. Both the incidence of moderate–severe WM abnormalities and the rate of CP were comparable, and the strong associations between MR findings and CP at age one year shown by Spittle et al. were confirmed to be excellent in the present study. In both studies, the prediction of unspecific neurological signs was less accurate. Importantly, we demonstrate that these associations are true also in the extremely preterm group as our study was restricted to infants born <27 weeks, and that results are robust given our higher age at follow up.

When combining the two measures (definitely abnormal GMs and moderate–severe WM abnormalities on MRI), the specificity and PPV for predicting CP reached 100% and there were no false positive results. On the other hand, sensitivity was only 50% as 2 infants with CP were missed, i.e. the rate of "false negatives" was similar to assessment of GMs used on its own. Conversely, MRI on its own identified all infants who developed CP and yielded only one false positive result. This infant had severe ventricular dilatation, WM loss and delayed myelination but no focal abnormalities such as cysts or lesions in the basal ganglia, possibly explaining the favourable outcome. Thus, the combination of the two assessments decreased the number of infants unnecessarily identified being at high risk of CP; yet two infants who developed mild CP (GMCFS I) were not identified. As noted previously, the present study suggests that GMs are less sensitive in the prediction of very mild forms of CP, compared to neonatal MRI.

Understanding the strengths and weaknesses of the different assessment tools available is important for the clinician who aims at

identifying infants at risk of adverse outcome. General movements observation is a non-intrusive, reproducible and cost-effective tool, and it is possible to perform it in the home setting, but it requires considerable experience in order to reach high accuracy [26]. MRI provides detailed high quality anatomical data but is more expensive and also needs specific expertise in interpretation of the images. Hence, the present study agrees with existing studies regarding the potentially complementary roles of these assessment methods for high risk infants in the early prediction of outcome, providing important data about the extremely preterm group where reports are very sparse.

We found no associations between early WM damage and abnormal GMs in the present study, nor with any of the investigated perinatal characteristics or neonatal morbidities. In contrast, Spittle et al., found WM abnormalities [27] as well as reduced cerebellar diameter [28] at TEA to be associated with abnormal GMs. Whether this discrepancy is explained by the somewhat smaller sample size in our study is uncertain. However, neither Spittle et al. nor we could demonstrate associations between grey matter abnormalities on MRI and abnormal GMs. A hypothesis about damage of the subplate being a potential cause of abnormal GMs [29] has been proposed, as the time-line of evolution and dissolution of these transient neurons match the GMs very neatly. This theory has to our knowledge not been confirmed, and the neurobiological and anatomical basis for abnormal GMs is still largely unknown.

The population-based design with a homogenous sample of high risk EPT infants is a strength of the present study. Moreover, the age at follow up was higher than in most other reports [13,23,24]. A higher follow up rate would have strengthened our study, however, for all children not attending the formal research follow up program, we obtained information on neurological outcome from medical records. Eight of these children (15%) were assessed before age 24 months corrected, making the diagnosis of CP less certain. Another possible limitation of our study was the analysis of one single GMs assessment instead of serial assessments, which would allow identifying a trajectory.

5. Conclusion

The present study investigated the early motor repertoire in EPT infants in relation to their neurological outcome. The presence of definitely abnormal GMs was predictive of CP. Prediction was, however, significantly enhanced when GMs assessment was combined with findings from MRI obtained at TEA.

Conflict of interest

The authors do not have any potential, perceived, or real conflict of interest relevant to this article to disclose, especially no financial arrangement with a company whose products are discussed in the manuscript.

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