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Predictive value of general movements' quality in low-risk infants for minor neurological dysfunction and behavioural problems at preschool age

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ABSTRACT

Background: General movement (GM) assessment is a well-established tool to predict cerebral palsy in high-risk infants. Little is known on the predictive value of GM assessment in low-risk populations.
Aims: To assess the predictive value of GM quality in early infancy for the development of the clinically relevant form of minor neurological dysfunction (complex MND) and behavioral problems at preschool age.
Study design: Prospective cohort study.
Subjects: A total of 216 members of the prospective Groningen Assisted Reproductive Techniques (ART) cohort study were included in this study. ART did not affect neurodevelopmental outcome of these relatively low-risk infants born to subfertile parents.
Outcome measures: GM quality was determined at 2 weeks and 3 months. At 18 months and 4 years, the Hempel neurological examination was used to assess MND. At 4 years, parents completed the Child Behavior Checklist; this resulted in the total problem score (TPS), internalizing problem score (IPS), and externalizing problem score (EPS). Predictive values of definitely (DA) and mildly (MA) abnormal GMs were calculated.
Results: DA GMs at 2 weeks were associated with complex MND at 18 months and atypical TPS and IPS at 4 years (all $p < 0.05$). Sensitivity and positive predictive value of DA GMs at 2 weeks were rather low (13%–60%); specificity and negative predictive value were excellent (92%–99%). DA GMs at 3 months occurred too infrequently to calculate prediction. MA GMs were not associated with outcome.
Conclusions: GM quality as a single predictor for complex MND and behavioral problems at preschool age has limited clinical value in children at low risk for developmental disorders.

1. Introduction

The assessment of the quality of general movements (GMs) is one of the best methods to predict developmental outcome in high-risk infants [1,2]. GMs are spontaneous movements involving all body parts [3]. They are present during fetal life and early infancy and they disappear around 4 months postterm, when goal-directed motor behavior emerges. Concurrent with the developmental changes in the brain, the form of GMs changes. Around term age, GMs have a 'writhing' character and in the last phase – present at 2 to 4 months postterm – GMs have a 'fidgety' character. Multiple studies in high-risk infants have demonstrated that in particular the presence of definitely abnormal (DA) GMs at 'fidgety age' is associated with a high risk for cerebral palsy (CP) [4–8]. DA GMs are characterized especially by a lack of movement complexity and variation. DA GMs in high-risk infants are also associated with minor neurological dysfunction (MND), especially with the clinically relevant form complex MND, and with behavioral problems in later life [9–11].

In contrast to the well-documented predictive validity of GM assessment in high-risk infants, little is known on the predictive value of GM quality in infants with a low risk for developmental disorders. The information available is limited to the study of Bouwstra et al. [12]. In 450 3-month-old infants, Bouwstra et al. studied the ability of DA GMs to predict serious neurodevelopmental disorders and behavioral problems in preschoolers from the general population. The results showed an association between DA GMs and major neurodevelopmental disorders, but the association was less strong than that in the high-risk populations. DA GMs were not associated with behavioral problems.

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The present study aims to assess the predictive value of definitely and mildly abnormal GMs at 2 weeks and 3 months for the development of complex MND and behavioral problems at preschool age, i.e., at 18 months and 4 years, in a group of low-risk infants. When positive or negative predictive values are good, early detection and exclusion of MND and behavioral problems may provide options for early intervention or reassurance, respectively.

To this end, we used the data collected in the Groningen Assisted Reproductive Techniques (ART) cohort study. This study aims to assess the effect of in vitro fertilization (IVF) on the child's development by comparing outcome of children born after IVF with those having been conceived naturally. The data revealed that IVF did not affect neurological and behavioral outcome up until the age of 4 years [13–18].

On the basis of the study of Bouwstra et al. [12], we hypothesize that the predictive value of DA GMs at 3 months for complex MND and behavioral problems in our group of low-risk infants is lower than that in high-risk infants. We expect that also mildly abnormal (MA) GMs are associated with complex MND and behavioral problems at preschool age, but less strongly than DA GMs. In addition, we expect that prediction of DA GMs at 2 weeks is better than that of DA GMs at 3 months, as neonatal neurological dysfunction in relatively low-risk infants often is followed by neurological normalization in infancy, to be followed by complex MND in later years [19]. Finally, we hypothesize that persistently abnormal GMs, i.e., the presence of abnormal GMs at 2 weeks and at 3 months, have the best predictive value for neurobehavioral problems, as a persistently abnormal quality of GMs during the first months after term age in high risk is associated with the highest risk for CP [8].

2. Materials and methods

2.1. Participants

The 216 participants (110 males, 106 females) were the members of the prospective Groningen ART cohort study, a prospective, assessor-blinded, follow-up study that monitors child development after ART. They were recruited between March 2005 and December 2006 at the Department of Reproductive Medicine of the University Medical Center Groningen (UMCG). The children were born following IVF with or without ovarian hyperstimulation or to subfertile couples who conceived naturally while waiting for fertility evaluation or treatment. Information on the prenatal, perinatal, and neonatal periods, parental characteristics, and socioeconomic conditions were collected from medical records and on standardized charts at the first follow-up assessment 2 weeks postterm. Table 1 provides an overview of the perinatal and social characteristics of the study group. The ethics committee of the UMCG approved the study design, and all parents provided written, informed consent for participation of their children in the study.

GM quality was assessed at 2 weeks and 3 months, neurological follow-up at 18 months and 4 years. Included in the current study were the infants with at least one appropriate recording of GMs and one follow-up assessment at preschool age. At 2 weeks, data of 6 infants were missing: 2 had missed their appointment and another 4 had been crying. At 3 months, data of 4 infants were missing, 7 children did not show up at 18 months, and at 4 years, 21 children were lost to follow-up. Attrition was mainly due to logistical problems or assessment burden. One girl died at 3 weeks of age from the consequences of a congenital heart disorder. Background characteristics of the infants included in the study did not differ from those of the children who were excluded from the analyses (data not shown).

2.2. GM assessment

GM quality was assessed at 2 weeks and 3 months postterm by two assessors (K.M. and M.H.-A; for details see Middelburg et al. [14]). Spontaneous movements in supine position were videotaped for 5–10 min. The aim was to record the infant's motility in an awake, active, and not-crying behavioral state. Quality of GMs was classified into four different categories: two normal types and two abnormal types [9]. The two subtypes of normal GMs are normal–optimal GMs, which are characterized by abundant variation, complexity, and fluency, and normal–suboptimal movements, which have a sufficient degree of variation and complexity, but lack fluency. Abnormal GMs also lack fluency; they are subdivided into MA GMs, which are characterized by insufficient variation and complexity and DA GMs, which are virtually devoid of variation and complexity. The reliability of the GM assessment is good, including for this study [9,13].

Table 1
Participant characteristics.

Characteristics	Study group, $n = 216$
Male/female	110/106
Birth characteristics	
Gestational age (weeks), median (range)	39.9 (30–43)
Preterm birth <37 weeks, *n* (%)	20 (9)
Birth weight (g), mean (SD)	3453 (568)
Low birth weight <2500 g, *n* (%)	12 (6)
Small for gestational age,* *n* (%)	5 (2)
Signs of fetal distress,** *n* (%)	77 (36)
Caesarean section, *n* (%)	49 (23)
Neonatal characteristics	
Apgar score 5 min <7,[a] *n* (%)	1 (1)
Neonatal intensive care admission, *n* (%)	10 (5)
Parental characteristics	
Maternal age at conception in years, median (range)	32.9 (22–41)
Paternal age at conception in years,[b] median (range)	35.1 (26–56)
High education level mother,*** *n* (%)	85 (39)
High education level father,[c,***] *n* (%)	81 (38)

* Birth weight for gestational age is below 2 standard deviations compared with the Dutch reference population (Dutch reference tables, perinatal Registration Netherlands).
** Signs of fetal distress denoted by meconium stained amniotic fluid and/or cardiotocographic signs and/or acidosis.
*** University education or vocational colleges.
[a] Missing data $n = 6$.
[b] Missing data $n = 5$.
[c] Missing data $n = 4$.

2.3. Assessment of neurological condition at 18 months and 4 years

At 18 months and 4 years, the standardized and age-specific neurological examination according to Hempel (1993) was used to assess MND [20]. The Hempel examination has been developed to evaluate MND at preschool age. It assesses MND in five domains of functions: fine motor function, gross motor function, posture and muscle tone, reflexes, and visuomotor function [21]. Each of the domains can be scored as typical or deviant. Findings are classified as major neurological dysfunction, complex MND, simple MND, or neurologically normal. Major neurological dysfunction implies the presence of a distinct neurological syndrome, such as CP. Complex MND implies the presence of two or more deviant domains; simple MND implies the presence of one deviant domain. Neurologically normal implies the absence of deviant domains or the presence of only deviant reflexes [21]. Simple MND has limited clinical significance and reflects the presence of a normal, but non-optimally wired brain. On the other hand, complex MND represents the clinically relevant form of MND and is associated with behavioral and learning disorders [19]. The reliability of the Hempel examination is satisfactory (κ scores for various items: 0.62–1.00). Information on the predictive validity is lacking thus far [21]. The assessments were carried out by trained assessors supervised by M.H.-A. All assessors and the supervisor were blind to prenatal and perinatal history, and to GM quality.

2.4. Assessment of child behavior at 4 years

Child behavior at 4 years was evaluated with the Dutch version of the Child Behavior Checklist (CBCL) for children aged 1½ year to

5 years [22]. The CBCL includes 100 items that address emotional and behavioral problems, which are scored by parents on a three-point scale: not true, somewhat or sometimes true, and very true or very often true. The sum of all questions results in the total problem score (TPS), an internalizing problem score (IPS: emotionally reactive, anxious or depressed, somatic complaints, and withdrawn), and an externalizing problem score (EPS: attention problems and aggressive behavior). Raw scores are normalized into *T*-scores (mean: 50, SD: 10). Higher *T*-scores represent more problematic behavior. *T*-scores below 60 are in the normal range, *T*-scores of 60 to 63 (84th to 90th percentile) are in the borderline range, and *T*-scores above 63 (above 90th percentile) are in the clinical range. The *T*-scores were dichotomized into typical (scores in the normal range) and atypical (scores in the borderline and clinical range). The reliability and validity of the CBCL are good [22].

2.5. Statistical analysis

Fisher's exact tests and Pearson's chi-square tests were applied to assess associations between the quality of GMs on the one hand and neurological outcome and atypical behavior on the other hand. Predictive values, i.e., sensitivity, specificity, positive predictive value, and negative predictive value, were calculated in case of statistically significant associations. In addition, differences in behavioral *T*-scores of children with and without abnormal (DA or MA) GMs were calculated with Student's *t*-test for independent samples.

The IBM Statistical Package for Social Science (SPSS), version 20, was used for the analyses. *P*-values <5% were considered statistically significant.

3. Results

3.1. Neurobehavioral outcome in infancy and preschool age

At 2 weeks, 5 infants (2%) showed DA GMs and 75 infants (36%) MA GMs. At 3 months, only one infant showed DA GMs – he had shown MA GMs at 2 weeks – and 88 infants (42%) had MA GMs. At 18 months, 18 of the 209 children assessed showed complex MND (9%); at 4 years, the prevalence of complex MND had increased to 48 out of 195 children (25%). None of the children was diagnosed with major neurological dysfunction, such as CP.

Completed CBCL questionnaires were available for 194 children. Fifteen children (8%) had an atypical total problem score (i.e., a score in the borderline or clinical range), 19 children (10%) had an atypical internalizing problem score, and 15 children (8%) had an atypical externalizing problem score.

3.2. GM quality and neurological outcome at preschool age

The presence of DA GMs at 2 weeks was associated with the development of complex MND at 18 months: 2 of the 5 infants with DA GMs had complex MND compared to 13 of the 200 (7%) infants without DA GMs (Fisher's exact test, $p = 0.044$; see Table 2). The presence of DA GMs at 2 weeks was not associated with the development of complex MND at 4 years: 2 of the 5 infants with DA GMs developed complex MND compared to 45 of the 187 (24%) infants without DA GMs (Fisher's exact test, $p = 0.598$). The presence of MA GMs at 2 weeks was not associated with the development of complex MND at 18 months and 4 years (Table 2).

The only infant with DA GMs at 3 months had not developed complex MND at 18 months. The child was not assessed at 4 years due to complex family problems. MA GMs at 3 months were not associated with the development of complex MND at 18 months and 4 years (Table 2).

Thirty-eight infants showed MA GMs at 2 weeks and at 3 months. One of these infants was not assessed at 18 months and 4 years. In the children re-assessed at preschool age, the consistent presence of MA GMs was not associated with increased risk for complex MND (Table 2). Five infants showed DA GMs at 2 weeks and MA GMs at 3 months. The prevalence of complex MND in this group at 18 months was significantly higher than that in the infants with normal and/or MA GMs (40% vs 7%, Fisher's exact test, $p = 0.045$), but at 4 years, the difference in complex MND did not reach statistical significance (40% vs 24%, $p = 0.598$; Table 2). These results are similar to those of the infants with DA GMs at 2 weeks as they involve the same five infants. One infant showed MA GMs at 2 weeks and DA GMs; at 3 months, she showed simple MND at 18 months, but she was not assessed at the age of 4 years.

Table 2
GM quality and complex MND at preschool age.

	Neurodevelopmental outcome at 18 months[#]		Neurodevelopmental outcome at 4 years[#]	
	No complex MND, *n* (%)	Complex MND, *n* (%)	No complex MND, *n* (%)	Complex MND, *n* (%)
GM assessment at 2 weeks				
	$n = 190$	$n = 15$[a]	$n = 145$	$n = 47$
NO GMs	10 (100)	0	10 (100)	0
SO GMs	110 (94)	7 (6)	82 (74)	29 (26)
MA GMs	67 (92)	6 (8)	50 (76)	16 (24)
DA GMs	3 (60)	2 (40)[*]	3 (60)	2 (40)
GM assessment at 3 months				
	$n = 189$	$n = 18$	$n = 146$	$n = 48$
NO GMs	7 (100)	0	6 (100)	0
SO GMs	104 (90)	11 (10)	82 (74)	29 (26)
MA GMs	77 (92)	7 (8)	58 (75)	19 (25)
DA GMs	1 (100)	0	n.a.[a]	n.a.[a]
Longitudinal GM assessment (2 weeks and 3 months)[†]				
2× normal GMs	79 (94)	5 (6)	66 (80)	17 (21)
1× normal GMs and 1× MA GMs	70 (92)	6 (8)	46 (67)	23 (33)
2× MA GMs	35 (95)	2 (5)	29 (85)	5 (15)
MA GMs at 2 weeks and DA GMs at 3 months	1 (100)	0	n.a.[a]	n.a.[a]
DA GMs at 2 weeks and MA GMs at 3 months	3 (60)	2 (40)	3 (60)	2 (40)

GM, general movement; MND, minor neurological dysfunction; NO, normal–optimal; SO, normal–suboptimal; MA, mildly abnormal; DA, definitely abnormal.
Normal GMs include normal–optimal and normal–suboptimal GMs.
[a] The only child with DA GMs at 3 months was not assessed at 4 years. n.a. = not applicable.
[*] $p = 0.044$.
[†] Presence of normal and/or MA GMs versus development from DA to MA GMs: complex MND at 18 months, Fisher's exact test, $p = 0.045$; complex MND at 4 years: Fisher's exact test, $p = 0.598$.
[#] Note that the total numbers vary: at 18 months 209 children had been assessed, in 4 of those children the GM assessment at 2 weeks was missing (3 infants were crying, 1 was not assessed), in 2 of them the GM assessment at 3 months was missing (those 2 were not assessed). At 4 years, 195 children had been assessed; in 3 of those children, the GM assessment at 2 weeks was missing (the 3 infants that had been crying); in 1 of them, the GM assessment at 3 months was missing (this infant was not assessed).

3.3. GM quality and behavior at 4 years

The presence of DA GMs at 2 weeks was significantly associated with higher TPS, IPS, and EPS scores (Student's *t*-test: TPS $p = 0.002$; IPS $p = 0.001$; EPS $p = 0.019$; see Table 3). Infants with DA GMs at 2 weeks had significantly more often an atypical TPS ($n = 2$; 40%) and an atypical IPS ($n = 3$; 60%) than without DA GMs (atypical TPS; $n = 12$ (7%); Fisher's exact test, $p = 0.044$; atypical IPS ($n = 14$ (8%); Fisher's exact test, $p = 0.005$; see Table 3). The presence of DA GMs at 2 weeks was not significantly associated with an atypical EPS. The only child with DA GMs at 3 months was not assessed at 4 years.

The presence of MA GMs at 2 weeks and at 3 months was not associated with higher behavioral problem scores or atypical behavior scores, also not when MA GMs were consistently present at both ages (Table 3). Behavior of the five infants who presented with DA GMs at

Table 3
GM quality and behavioral outcome at 4 years.

	Behavioral outcome at 4 years ($n = 194$)					
	TPS		IPS		EPS	
	Mean *T* score (SD)	% atypical	Mean *T* score (SD)	% atypical	Mean *T* score (SD)	% atypical
GM assessment at 2 weeks ($n = 191$)						
NO GMs	46.80 (9.62)	1 (10)	47.40 (10.49)	2 (20)	47.30 (9.83)	0
SO GMs	46.16 (8.34)	9 (8)	46.65 (9.53)	7 (6)	48.14 (8.14)	8 (7)
MA GMs	45.41 (9.10)	2 (3)	46.18 (9.87)	5 (8)	46.56 (8.85)	5 (8)
DA GMs	58.20 (10.35)*	2 (40)#	60.20 (13.22) **	3 (60) ##	56.60 (7.60) ***	1 (20)
GM assessment at 3 months ($n = 193$)						
NO GMs	47.83 (9.37)	1 (17)	49.50 (8.38)	1 (17)	49.00 (8.63)	0
SO GMs	46.28 (8.79)	9 (8)	46.15 (10.26)	11 (10)	47.93 (8.67)	10 (9)
MA GMs	46.66 (9.56)	5 (7)	46.91 (10.06)	7 (9)	47.99 (9.11)	5 (7)
DA GMs	n.a.[a]	n.a.[a]	n.a.[a]	n.a.[a]	n.a[a]	n.a.[a]
Longitudinal GM assessment (2 weeks and 3 months) ($n = 190$)†						
2× normal GMs	46.98 (8.72)	9 (11)	46.34 (10.25)	8 (10)	48.74 (8.50)	8 (10)
1× normal GMs and 1× MA GMs	44.57 (8.19)	2 (3)	45.26 (8.98)	4 (6)	46.20 (8.16)	2 (3)
2× MA GMs	46.32 (9.31)	1 (3)	46.56 (9.74)	2 (6)	47.35 (8.96)	3 (9)
MA GMs at 2 weeks and DA GMs at 3 months	n.a.[a]	n.a.[a]	n.a.[a]	n.a.[a]	n.a.[a]	n.a.[a]
DA GMs at 2 weeks and MA GMs at 3 months	58.20 (10.35)	2 (40)	60.20 (13.22)	3 (60)	56.60 (7.60)	1 (20)

GM, general movement; TPS, total problem score; IPS, internalizing problem score; EPS, externalizing problem score; NO, normal–optimal; SO, normal–suboptimal; MA, mildly abnormal; DA, definitely abnormal.
Normal GMs include normal–optimal and normal–suboptimal GMs.
* Student's *t*-test, $p = 0.002$.
** Student's *t*-test, $p = 0.001$.
*** Student's *t*-test, $p = 0.019$.
\# Fisher's exact test, $p = 0.044$.
\#\# Fisher's exact test, $p = 0.005$.
[a] The only child with DA GMs at 3 months was not assessed at 4 years. n.a. = not applicable.
† Presence of normal and/or MA GMs versus development from DA to MA GMs: mean *T* scores: Student's *t*-test: TPS $p = 0.002$, IPS $p = 0.002$, EPS $p = 0.019$; atypical scores: Fisher's exact test: TPS $p = 0.044$, IPS $p = 0.005$, EPS $p = 0.150$.

2 weeks and MA GMs at 3 months was as reported in the above paragraph for infants with DA GMs at 2 weeks, as none of the infants with DA GMs at 2 weeks continued to show DA GMs.

3.4. Predictive value of DA GMs

Only DA GMs at 2 weeks showed a statistically significant association with developmental outcome. Therefore, only predictive values of DA GMs at 2 weeks for complex MND at 18 months and atypical TPS and IPS scores at 4 years were calculated. The results are summarized in Table 4. The values indicate that the sensitivity and the positive predictive value of DA GMs at 2 weeks to predict these outcomes are moderate at best. On the other hand, the specificity and the negative predictive value of DA GMs at 2 weeks for complex MND at 18 months and atypical behavior at 4 years are high.

4. Discussion

The present study indicated that in relatively low-risk infants DA GMs at 2 weeks are associated with complex MND at 18 months and behavioral problems at 4 years. DA GMs at 3 months occurred too infrequently to calculate associations with neurodevelopmental outcome at preschool age. MA GMs were not associated with neurodevelopment at preschool age.

4.1. Clinical considerations

DA GMs at 2 weeks were significantly associated with complex MND at 18 months and behavioral problems, in particular internalizing behavioral problems at 4 years. The association remained notwithstanding the fact that the DA character of the GMs was temporarily only, as all DA GMs had changed into MA GMs at the age of 3 months. The specificity and negative predictive value of DA GMs at 2 weeks for behavioral problems was excellent. However, its positive predictive value was moderate at best and its sensitivity was low. The relatively low values for sensitivity and positive prediction contrast with the excellent predictive quality of GM assessment in high-risk populations [1,2]. It corresponds, however, to findings of Bouwstra et al. [12]. Most likely, this difference may be attributed to the differences in study populations. Our study and the study of Bouwstra et al. included low-risk, mostly full-term infants, whereas the infants of the high-risk populations mainly consisted of preterm infants. Neurodevelopmental disorders in preterm infants are mostly originating in pathology of the periventricular white matter; pathology underlying neurodevelopmental disorders in term infants is more heterogeneous in nature and often involves subcortical and cortical gray matter [1]. It has been hypothesized that the quality of GMs is largely based on the integrity of the cortical subplate and its efferent motor connections running through the periventricular white matter [23]. This may explain why neurodevelopmental disorders

Table 4
Predictive power (%) of DA GMs at 2 weeks for associated neurological and behavioral outcomes at preschool age.

Prediction of	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Complex MND at 18 months	13 (−4–31)	98 (97–100)	40 (−3–83)	94 (90–97)
Atypical TPS at 4 years	14 (−4–33)	98 (96–100)	40 (−3–83)	94 (90–97)
Atypical IPS at 4 years	18 (0–36)	99 (97–100)	60 (17–103)	92 (89–96)

DA, definitely abnormal; GM, general movement; MND, minor neurological dysfunction; TPS, total problem score; IPS, internalizing problem score.
Sensitivity, true positives/(true positives + false negatives).
Specificity, true negatives/(true negatives + false positives).
PPV, positive predictive value, true positives/all positives.
NPV, Negative predictive value, true negatives/all negatives.

in preterm infants are more closely connected to GM quality than in full-term infants.

Bouwstra et al. [12] did not find an association between DA GMs and behavioral problems at 4 years of age, whereas we did. This difference may be explained by the age of the GM-findings: Bouwstra et al. reported that GM quality at 3 months was not associated with behavioral outcome, whereas we found that GM quality at 2 weeks was associated with behavior. At 2 weeks of age, the contribution of cortical activity to functional performance is substantially lower than that at 3 months [24], leaving a larger role for subcortical and brainstem areas, in which monoaminergic neurotransmitter systems, such as the serotonergic system, play a prominent role. This might explain why DA GMs at 2 weeks were associated in particular to internalizing behavior [25]. Note also that the virtual absence of DA GMs at 3 months in our study did not allow for the assessment of an association with neurobehavioral outcome at 4 years. It also precluded the comparison of predictive validity of DA GMs at 2 weeks with that at 3 months and the evaluation of the predictive value of persistently DA GMs.

Our study indicated that DA GMs at 2 weeks were associated with complex MND at 18 months, but not with complex MND at 4 years. This is remarkable, as DA GMs were associated with behavioral problems at 4 years and behavioral problems are known to be associated with complex MND [19]. We hypothesize that a ceiling effect of the neurological examination according to Hempel at the age of 4 years caused the absence of a significant association between DA GMs at 2 weeks and complex MND at 4 years. The ceiling is reflected by the finding that none of the children showed dysfunctions in the domain of fine motor function [18]. Apparently, the Hempel assessment at 4 years is not sufficiently sensitive to pick up fine motor dysfunctions. From the study of Groen et al. [10], we know that abnormal GMs are especially related to fine manipulative disability; the Hempel assessment at 4 years was not able to detect this association. Notwithstanding the ceiling effect, a relatively high proportion of our study group showed complex MND at the age of 4 years: 25%, which is substantially higher than the prevalence of 6–7% in the general population. The relatively high prevalence of complex MND in our study presumably is caused by the subfertility of the parents, as subfertility is known to be associated with less favourable neurodevelopmental outcome of the offspring [18,26,27].

In the present study, MA GMs were not associated with neurological or behavioral outcomes. This indicates that MA GMs as a single sign in low-risk infants do not have predictive value. However, MA GMs may be used to evaluate neural integrity in terms of optimal versus non-optimal function of the young brain. For instance, it is known that MA GMs – reflecting a non-optimal neurological condition – in low-risk populations are associated with hyperbilirubinemia [28], infant formula with relatively little docosahexaenoic acid [29], and subfertility [13]. Yet our data may suggest that the significance of a non-optimal neurological condition in early infancy for developmental outcome is outweighed by the plasticity of the young brain.

4.2. Strengths and limitations

The major strength of the present study was its design, in which a substantial group of relatively low-risk infants mostly born at term had two GM assessments and two follow-up neurodevelopmental exams. Neurodevelopmental outcome was assessed with age-specific standardized tools. The blinding of the persons assessing neurodevelopmental outcome at preschool age to prenatal and perinatal history, and to GM quality add to the strength of the study.

A number of limitations need to be addressed. Inherent to the relatively low-risk nature of the study group, the prevalence of DA GMs was low. It precluded the assessment of associations between DA GMs at 3 months and neurodevelopmental outcome. However, the low prevalence of DA GMs in low-risk populations underlines the limited practical applicability of GM assessment in low-risk populations. The history of parental subfertility may be regarded as another limitation, as subfertility is associated with a higher prevalence of MA GMs and complex MND [13,18]. However, this might also be considered an advantage, as a higher prevalence of minor dysfunction would have increased the chance of finding associations. We expect that the predictive values of DA GMs in this subfertile population do not differ from those in the general population. The prevalence of atypical problem scores in our study group (8–10%) was lower than that in the general population (16%). Others suggested that a history of subfertility makes parents more tolerant with respect to their child's behavior [30]. This may have been advantageous to the study: parents only reported significant problems, with a higher likelihood of a significant neurobiological substrate. Finally, the previously mentioned ceiling effect of the Hempel assessment at 4 may be considered a limitation of our study.

5. Concluding remarks

Our study indicated that DA GMs at 2 weeks had a rather low sensitivity and positive predictive value for complex MND at 18 months and behavioral problems at 4 years, but a good specificity and negative predictive value for these problems. This implies that the absence of DA GMs at 2 weeks in low-risk infants is associated with a very low risk of neurodevelopmental problems. Our study was not able to evaluate the predictive value of DA GMs at 3 months. MA GMs in relatively low-risk infants were not associated with non-optimal neurodevelopmental outcome at preschool age, even when the MA GMs were consistently present at 2 weeks and 3 months.

Further studies in larger populations of low-risk infants are needed to determine (a) the predictive value of DA GMs at 3 months and (b) the predictive value of MA and DA GMs at 2 weeks and 3 months at school age in this population.

Conflict of interest statement

All authors, Anne N. Bennema, Pamela Schendelaar, Jorien Seggers, Maaike L. Haadsma, Maas Jan. Heineman, and Mijna Hadders-Algra declared no conflict of interest in the paper by Bennema and colleagues entitled Predictive value of general movements' quality in low-risk infants for minor neurological dysfunction and behavioral problems at preschool age.

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