Research in Developmental Disabilities 62 (2017) 69–80

Contents lists available at ScienceDirect

Research in Developmental Disabilities

Predictive value of General Movement Assessment for preterm infants' development at 2 years – implementation in clinical routine in a non-academic setting

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ARTICLE INFO

Article history:
Received 29 July 2016
Received in revised form 2 January 2017
Accepted 9 January 2017
Available online 20 January 2017
Number of reviews completed is 2

Keywords:
General movements
Preterm infant
Motor development
Mental development
Clinical routine
Sensitivity

ABSTRACT

Background: General movements (GM) are used in academic settings to predict developmental outcome in infants born preterm. However, little is known about the implementation and predictive value of GM in non-academic settings.
Aims: The aim of this study is twofold: To document the implementation of GM assessment (GMA) in a non-academic setting and to assess its predictive value in infants born preterm.
Methods and procedures: We documented the process of implementing GMA in a non-academic outpatient clinic. In addition, we assessed the predictive value of GMA at 1 and 3 months' corrected age for motor and cognitive development at 2 years in 122 children born <33 weeks' gestation. Outcome at two years was based upon the Bayley Scales of Infant Development-II (mental/psychomotor developmental index (MDI, PDI)) and a neurological examination. The infants' odds of atypical outcome (MDI or PDI ≤70 or diagnosis CP) and the predictive accuracy of abnormal GMA were calculated in a clinical routine scenario, which used all available GM information (primarily at 3 months or at 1 month, when 3 months were not available). In addition, separate analysis was undertaken for the samples of GMA at 1 and 3 months.
Outcomes and results: Tips to facilitate GMA implementation are described. In our clinical routine scenario, children with definitely abnormal GM were more likely to have an atypical two-year outcome than children with normal GM (OR 13.2 (95% CI 1.56; 112.5); sensitivity 55.6%, specificity 82.1%). Definitely abnormal GM were associated with reduced MDI (−12.0, 95% CI −23.2; −0.87) and identified all children with cerebral palsy (CP) in the sample of GMA at 3 months only.

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http://dx.doi.org/10.1016/j.ridd.2017.01.012

GMA can be successfully implemented in a non-academic outpatient setting. In our clinical routine scenario, GMA allowed for adequate prediction of neurodevelopment in infants born preterm, thereby allaying concerns about diagnostic accuracy in non-academic settings.

What this paper adds

For nearly a decade, the assessment of general movements (GM) at 3 months' corrected age has been well recognised as a clinical, non-invasive method to predict neurodevelopment and cerebral palsy (CP) in infants born preterm. Yet GM assessment (GMA) tends to be used in academic contexts rather than in non-academic out-patient centres, which in contrast see the majority of infants born preterm for follow-up. This could be because the organisational effort behind GMA is perceived as high for a relatively small group of patients. Moreover, the implementation of GMA in non-academic settings has not been evaluated up to now, and thus little is known about the diagnostic accuracy of GMA in such settings.

Based on documentation of organisational structures in our Social Paediatric Centre, a non-academic outpatient centre, we developed a series of useful and standardised tips for implementing GMA in non-academic routine. Our analysis of more than one hundred infants born at <33 gestational weeks additionally showed that GMA reliably predicts neurodevelopment and CP in high-risk infants, thereby allaying concerns about diagnostic accuracy in non-academic settings.

1. Introduction

Worldwide, 5–18% of infants are born preterm (Romero, Dey, & Fisher, 2014). Yet while modern neonatology care enables even the very preterm of these infants to live, this survival is often associated with increased morbidity in later life. For instance, 5–10% of children born preterm are diagnosed with cerebral palsy (CP) (Sellier et al., 2016). In addition, children born preterm have increased risks for minor cognitive and motor developmental problems (Crump, Sundquist, Winkleby, & Sundquist, 2013).

Early interventions may reverse or ameliorate risk profiles during the first years of life (Einspieler & Prechtl, 2005; Guralnick, 2012; Nordhov et al., 2012; Spittle, Orton, Anderson, Boyd, & Doyle, 2015) as they rely on the plasticity of potentially injured brains. However, to ensure that such interventions are as efficient and cost-effective as possible and to avoid unnecessary treatment, methods are needed that identify children with high developmental risks at an early age. Recent years have demonstrated that when infants are evaluated in academic settings, the assessment of general movements (GM, spontaneous infant movements) is a reliable method to identify children at high risk for CP and other developmental problems (Bosanquet, Copeland, Ware, & Boyd, 2013; Burger & Louw, 2009; Hadders-Algra, 2004; Oberg, Jacobsen, & Jorgensen, 2015). GM assessment (GMA) is based on pattern recognition of spontaneous movements of young infants that are video-recorded.

Currently two variants of GMA exist: the one developed by Prechtl (Einspieler, Prechtl, Bos, Ferrari, & Cioni, 2005; Prechtl, 1990; Prechtl et al., 1997) and the one by Hadders-Algra (Hadders-Algra, 2007; Hadders-Algra et al., 2004). Both variants measure essentially the same construct, i.e. they assess with Gestalt perception the variation, complexity and fluidity of GM (Hadders-Algra & Prechtl, 1992; Prechtl, 1990). Nevertheless, there are differences. Hadders-Algra, for instance, pays more attention to the presence of minor abnormalities – in line with the tradition of Groningen research. Through such detailed scoring on the non-pathological part of the GM spectrum, it was possible to demonstrate adverse effects of, for example, hyperbilirubinaemia (Lunsing, Pardoen, & Hadders-Algra, 2013; Soorani-Lunsing, Woltil, & Hadders-Algra, 2001) and subfertility (Middelburg, Haadsma, Heineman, Bos, & Hadders-Algra, 2010). In addition, at 6–18 weeks' corrected age (CA), Hadders-Algra pays attention primarily to the general aspects of GM, i.e. movement variation and complexity (Hamer, Bos, & Hadders-Algra, 2011; Hamer, Bos, & Hadders-Algra, 2016) – and does not consider merely the presence or absence of fidgety movements. The similarity of the two variants of GMA, however, implies that their prediction of CP is largely comparable. –

GMA is most predictive at 3 months of CA (Guzzetta et al., 2007; Hadders-Algra, 2004; Prechtl et al., 1997; Spittle et al., 2013). The predictive value of GM depends, as in any diagnostic test, on the age and prevalence of risks at follow-up. For instance, in high-risk children born at <30 weeks of gestation, GMA evaluated in an academic centre at 3 months' CA had a high sensitivity and specificity for adverse neurological outcome (100% sensitivity and 84% specificity for CP), a moderate-to-good prediction of cognitive problems (41% and 85% specificity for cognitive impairment at 2 and 4 years, respectively) and moderate prediction of language problems at 2 years (58% sensitivity and 83% specificity) (Spittle et al., 2013). GMA in low-risk groups, however, yields lower predictive values. For instance, a study in the Dutch general population indicated that GMA at 3 months had a sensitivity of 67% and a specificity of 97% to predict CP (Bouwstra et al., 2010).

Only a handful of publications have reported on the use of GM in non-academic settings (Brown, Greisen, Haugsted, & Jonsbo, 2016; Palchik, Einspieler, Evstafeyeva, Talisa, & Marschik, 2013; Yuge et al., 2001). Besides an anecdotal report in a German-language journal (Seme-Ciglenecki, 2007) and a small follow-up study of 37 children born preterm in Brazil (Manacero, Marschik, Nunes, & Einspieler, 2012), a study used GMA in Dutch well-child clinics (Bouwstra et al., 2009, 2010), however without specifically reporting on the process GMA implementation. Another report studied the applicability of GMA

in a Serbian non-academic Paediatric Rehabilitation Centre (Dimitrijevic et al., 2016), but in a highly vulnerable population of preterm infants (prevalence of cramped synchronised movements at GMA at 1 month >10%). Consequently its results might not be transferable to current preterm populations from Western European countries with high-quality neonatal care (Sellier et al., 2016).

Most infants with developmental concerns in Europe are referred to and guided by such non-academic centres. Yet, regrettably only little is known about how GMA can be successfully implemented in such settings and whether it has the same predictive value and reliability (Brown et al., 2016) as in academic settings. Simultaneously, the fact that GMA is a very effective tool in academic settings does not automatically imply that this is also true for non-academic settings. This is because non-academic settings are subject to constraints that may interfere with effective implementation: e.g. fewer personnel, less research-motivated staff and inadequate third-party funding.

Germany has 153 non-academic outpatient centres for children at risk of developmental problems, including infants born preterm. Up until now, GMA has been used in fewer than 5% of these centres, mostly because the efforts for its implementation have been seen as too high in relation to the only 2–5% of referrals potentially profiting from GMA. Therefore, the aim of this paper is two-fold. First, we describe the implementation of GMA in a non-academic outpatient centre and the lessons learned during this process. Second, we study the diagnostic accuracy of GMA for predicting neurodevelopmental outcome at two years' CA in high-risk preterm children treated in the outpatient centre. In addition to separately analysing predictive values of GMA at 1 and 3 months, we applied a clinical routine scenario using all available GM information for prediction (primarily GM at 3 months or at 1 month, when 3 months were not available).

2. Methods

2.1. Description of the non-academic setting and participants

The study draws on routine clinical data collected in a non-academic outpatient centre in Frankfurt, which serves about 2600 children per year with neurological, muscular, genetic and socially based developmental problems. The centre also features a specialised neurodevelopmental follow-up program for infants born preterm. Starting in 2008, we performed GMA on all children born preterm who were routinely referred to our centre from two perinatology clinics in Frankfurt for neurodevelopmental follow-up. Their gestational age was less than 33 weeks, and neurological abnormalities included intraventricular haemorrhage (IVH), periventricular leukomalacia (PVL), seizures and microcephaly. After this pilot year and a streamlining of GMA processes, infants recruited from 2009 to 2011 were eligible to participate in the prediction study. Parents of all study participants gave informed written consent to the research, including the publication of the results. Ethical approval for the study was given by the Medical Ethics Review Board of the Landesärztekammer Hessen.

2.2. Implementation of GMA in non-academic clinical routine and lessons learned

After our first year of GMA (2008), we distilled our experiences to develop the following streamlined process, which we embedded in our clinical routine:

- GM are videotaped during the first and/or second medical visit (at 1 and 3 months' CA) by the paediatrician before the neurological examination or by a physiotherapist during a counselling appointment; the recording lasts about five minutes.
- Eight of the centre's paediatricians (three child neurologists, five child neurology fellows) and four paediatric physiotherapists received training in GM monitoring (e.g. video conditions and duration, importance of adequate behavioural state). Three to five trained GM assessors evaluate weekly all GM recordings of the preceding week without knowing the infants' clinical history. In case of disagreement, evaluations are discussed until consensus is reached. The rating of a video recording during the weekly conferences takes 5–8 min per infant, allowing GMA in 4 infants within the 30-min weekly time slot.
- Currently, all procedures involved in GM recording and assessment take about 10–18 min per infant.

The lessons that we learned during the first year of using GMA are summarised in Table 1.

2.3. Assessments

2.3.1. GMA process

The medical visits at 1 and 3 months started with GMA. The infant was put in a supine position wearing only diapers and a one-piece. Care was taken that the infant was not crying or sucking on a pacifier and that caregivers did not interfere with the infant's behaviour (Hadders-Algra, 2004). GM in appropriate behavioural state were videotaped for three to five minutes, transferred from the camera to the centre's server and analysed according to the criteria of Hadders-Algra (Hadders-Algra, 2004).

The qualitative spectrum of GM (Hadders-Algra, 2004) can be divided into two normal and two abnormal categories. The normal GM are normal-optimal GM, which are characterised by abundant variation, complexity and fluency, and normal-suboptimal GM, which have sufficient variation and complexity but lack fluency. Abnormal GM also lack fluency. They

Table 1
Lessons learned during one-year implementation period of general movement assessment (GMA) in non-academic settings.

Barrier category	Barrier to implementation	Problem description	Solutions/tips to overcome barrier
Common to implementation of new diagnostic tools using videotaping	*Organising infant appointments at 1 and 3 months*	33% of appointments too late	• Training of staff, including importance of timely GMA • Integration of videotapes into physiotherapy appointments on infant handling, which appeared attractive for parents
	Implementing videotaping and GM video assessment into the daily routine	• 33% of videos not transferred to server • videotaping not performed on all appointments	• Two video cameras at central and easily accessible location • Fixed rules for labelling adopted • Shifting responsibility of video storage and labelling from medical doctors to physiotherapists • Physiotherapists also responsible for documenting GM rating results in a common document
	Video archiving according to the medical data protection law	German law demands archiving of video data for at least ten years	• Implementation of a separate terabyte hard disc, an automatic 24 h short storage system • a long-term archive protected by a firewall
	Getting informed consent of parents for videotaping and storage	Parents initially were not convinced about value of GMA	Information on GMA as • reliable indicator of the infant's neurological condition • indicator whether the infant needs early intervention or not
Specific for GMA	*Obtaining technically adequate video recordings of GMA*	15% of video recordings inadequate (infant <3 min in adequate behavioural state)	• Only GMA-trained staff members allowed to perform the video recording • Discussion of technical quality of the videos during weekly rating conferences
	Obtaining reliable GMA	20% staff rotation rate/year leads to many non-experienced raters in rating team	• Weekly group teaching on GMA by one experienced GM rater as regular part of the rating conferences • Introductory GMA course obligatory for all new staff members • Bi-annual refresher course for all staff members
	Reporting results to parents	• Reporting may confuse parents • Communication of results only possible some days after recording • Routine second short-term appointment not possible	• Instead of "mildly" and "definitely abnormal" use of numerical description, i.e., categories 1–4, with 4 denoting definitely abnormal GM • Communicating results by phone by paediatricians in case of normal or mildly abnormal results (category 1–3) as good results • Scheduling additional appointment only in case of definitely abnormal results (category 4) • Arranging early intervention in infants with category 4 as a chance for better development
	Reporting results to the referring paediatricians	Not all paediatricians familiar with GM interpretation	• Organization of information sessions for referring paediatricians • Addition of a short standardised summary of the GMA and its interpretation to medical reports sent to the paediatricians

are subdivided into mildly abnormal GM, which are characterised by insufficient variation and complexity, and definitely abnormal GM, which are virtually devoid of variation and complexity. Definitely abnormal GM are frequently also associated with absence of fidgety movements (Hamer et al., 2011). Mildly abnormal GM are considered to reflect a normal, but non-optimal function of the nervous system. They are only weakly associated with adverse developmental outcome (Hadders-Algra, 2004). Definitely abnormal GM are an indicator of significant dysfunction of the brain and are associated with neurodisability (Hadders-Algra, 2007; Hamer et al., 2016).

GMA according to Hadders-Algra, has a high reliability (interrater agreement: kappa 0.78-0.82 (Bouwstra et al., 2009; Hadders-Algra, 2004; Middelburg et al., 2010; van Iersel, Bakker, Jonker, & Hadders-Algra, 2009)), as well as a good construct and predictive validity. The value of GMA to predict CP, for instance, depends on the population studied. Sensitivity and specificity are highest for very preterm infants (88% and 100%, respectively) (Hadders-Algra, 2001) and substantially lower for full-term infants (van Iersel, Bakker, Jonker, & Hadders-Algra, 2016) and the general population (Bouwstra et al., 2010).

2.3.2. Neurodevelopmental assessment

At a mean CA of 24.4 months, all children born preterm were routinely scheduled for 1) a neurological and physical examination by a child neurologist and 2) a standardised Bayley Scales of Infant Development II (BSID-II) assessment. The BSID II is still one of the most widely used scales to measure cognitive and motor function in infants and toddlers. It has a moderate predictive validity for later cognitive functioning (r = 0.61 (95% CI: 0.57–0.64)) and later motor function (r = 0.34 (95% CI: 0.26–-0.42)) (Luttikhuizen dos Santos, de Kieviet, Konigs, van Elburg, & Oosterlaan, 2013). While the BSID-II Psychomotor Development Index (PDI) Scale was performed by the responsible paediatrician in an additional 20-min appointment, the Mental Development Index (MDI) Scale was conducted by an occupational therapist in 60–90 min.

The MDI and PDI were used to define the outcome and entered into the prediction models. For both of them, standardisation means are 100 and standard deviations (SD) 15 points. Significantly delayed performance is defined as MDI/PDI <70 (-2 SD) and mildly delayed performance as MDI/PDI 70–84 (-1 SD). American norms were used as German norms are lacking.

2.3.3. Other medical variables

Information on the child's medical history was retrospectively extracted from the medical records and neonatology discharge. Specifically, we searched for information on gestational age, birth weight, retinopathy of the premature (ROP), intraventricular haemorrhage (IVH), periventricular leukomalacia (PVL) and necrotizing enterocolitis (NEC).

2.4. Statistical analysis to assess predictive value of GMA in a non-academic setting

Descriptive analysis of child characteristics according to GM status was performed for all relevant variables. The category outcome variable 'atypical development' was defined as the presence of an MDI and/or PDI $\leq$ 70 and/or diagnosis CP. In the case of CP, missing values of PDI were assigned a score of 50. Typical outcome was defined as the absence of atypical outcome. Children had complete data if they had GMA at either 1 or 3 months' CA and PDI/MDI/neurological examination results at 2 years (Fig. 1). Logistic regression models assessed the relationship between GMA category and the odds of atypical outcome, while linear regression models evaluated the relationship between GM and later MDI and PDI scores. Models were adjusted to the covariates PVL, IVH, NEC and ROP. Effect sizes were expressed by means of omega square statistics. An omega square value of 0.01 indicates a small effect size, 0.06 a medium effect size and 0.14 a large effect size (Field, 2013). Diagnostic test criteria were calculated for both the diagnostic cut-off at mildly and at definitely abnormal GM. As mentioned before, in addition to separately analysing predictive values of GMA at 1 and 3 months, we applied a clinical routine scenario which used all available GM information for prediction (primarily GM at 3 months or at 1 month, when 3 months were not available).

3. Results

Of the 256 infants born at <33 weeks' gestation referred to our outpatient centre from academic medical centres between 2009 and 2011, 121 received a GM rating at 1 month, 164 at 3 months and 190 were eligible to our clinical routine scenario, which used all GMA available (primarily at 3 months or at 1 month, when 3 months were not available). At 2 years, 133 children obtained MDI scores and 65 received PDI scores. Complete sets of data were available for 122 children, i.e. they had a GMA at 1 or 3 months and a 2-year outcome assessment, including a neurological examination. The relatively large proportion of infants who did not have a GMA were those who never showed up at our clinic. While we knew about their existence, we had no detailed clinical information. A flow chart of the infants included in each phase of the study is presented in Fig. 1. The major descriptive results of the study are listed in Table 2, which represents the sample of our "clinical routine scenario" (n = 122).

Cramped synchronised movements as a clinical marker of severe brain dysfunction were found only in one infant at 1 month GMA and in none at 3 month GMA. GMA at 1 month did not predict overall outcome at two years for mildly and definitely abnormal GM (OR 1.3 (p = 0.75; 95%CI: 0.24;6.9) and OR 1.8 (p = 0.55; 95% CI 0.24; 13.4), respectively). In contrast, GMA at 3 months significantly predicted outcome at two years. Linear regression revealed that infants with definitely abnormal GM at 3 months scored 12.4 index points lower on the MDI (p = 0.056, 95% CI:-25.12; 0.31; effect size: $\Omega^2 = 0.022$) and 12.7 index points lower on the PDI (p = 0.15; 95% CI: −30.4; 14.9; effect size: $\Omega^2 = 0.108$). These infants were also 11.9

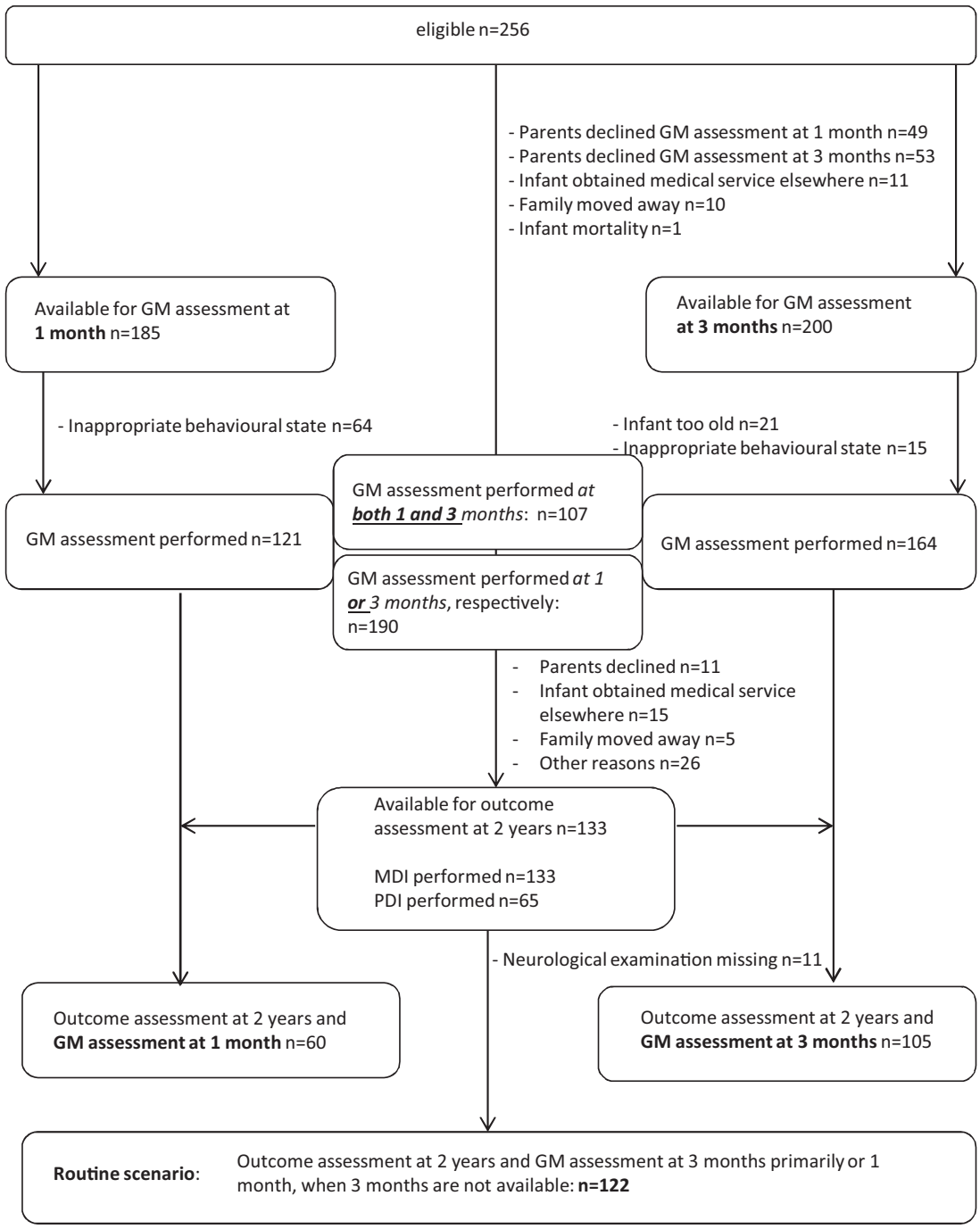

Fig. 1. Flow diagram of data collection.

times more likely to have an atypical neurological outcome at two years (p = 0.025, 95%CI: 1.4; 105.13) than infants with normal GM (Table 3a). Adjustment for different medical history parameters did not change these results substantially. In addition, sensitivity of definitely abnormal GMA at 3 months for CP was 100% (Table 4). In contrast, sensitivity of definitely abnormal GM at 3 months for atypical neurological outcome was only 58%, while specificity and negative predictive values were 82.7% and 87%, respectively (Table 4).

In our clinical routine scenario, which primarily included GMA at 3 months and, if not available, GMA at 1 month, 13.1% of infants had normal GM, 60.7% mildly abnormal and 26.2% definitely abnormal GM (Table 2). While the presence of abnormal GM at 1 or 3 months was not associated with birth weight, gestational age, IVH > grade 2 and ROP, it was significantly

Table 2
Description of "clinical routine scenario" analysis sample characteristics according to GM status at 3 months (or 1 month, when 3 months were not available).

	Total sample	GM quality normal	GM quality mildly abnormal	GM quality definitely abnormal	P-value
N[a]	122	16	74	32	
N per GM group in%		13.1%	60.7%	26.2%	
Mean birth weight [g] (SD)	1171 (366)	1279 (375)	1179 (367)	1101 (356)	0.35[b]
Gestation [weeks + days]	28.4 + 3.7	29.5 + 3.1	28.4 +4.1	27.8 + 3.0	0.08[b]
Prevalence of PVL n (%)	4 (3.3%)	0 (0%)	0 (0%)	4 (12.5%)	**0.011**[c]
Prevalence of ROP n (%)	16 (13.11%)	0 (0%)	9 (12.16%)	7 (21.9%)	0.13[c]
Prevalence of NEC n (%)	12 (9.84%)	1 (6.25%)	3 (4.1%)	8 (25%)	**0.005**[c]
Prevalence of IVH ≥ grade 3 n (%]	6 (4.9%)	0 (0%)	3 (4.1%)	3 (9.4%)	0.46[c]
Mean age at 3 month GMA [months] (SD)	3.15 (0.38)	3.1 (0.11)	3.16 (0.41)	3.15 (0.38)	0.87
Mean age at 1 month GMA[months] (SD)	0.98 (0.3)	0.9 (0.2)	1.03 (0.3)	0.91 (0.3)	0.17
Mean age at Bayley [months] (SD)	24.4 (1.0)	24.6 (0.6)	24.5 (1.0)	24.1 (1.1)	0.20[b]
Atypical neurodevelopmental outcome n (%)	27 (22.1%)	1 (6.3%)	11 (14.9%)	15 (46.9%)	**0.001**
Cerebral Palsy n (%)]	7 (5.7%)	0 (0%)	1 (1.4%)	6 (18.8%)	**0.004**[c]
Mean MDI (SD)	88.23 (18.21)	94.37 (9.27)	89.2 (18.9)	83.4 (19.1)	**0.08**[b]
Mean PDI (SD)	82.3 (18.4)	86.7 (12.4)	85.9 (16.9)	72.7 (20.6)	**0.03**[b]

Bold values indicate statistically significant differences.
Abbreviations: GMA (General Movements Assessment), IVH (intraventricular haemorrhage), MDI (mental developmental index, NEC (necrotising enterocolitis), PDI (psychomotor developmental index), PVL (periventricular leucomalacia), ROP (retinopathy of prematurity), SD (Standard Deviation).
[a] N total and within GM group can change according to which parameter is looked at, e.g. not all children had examinations regarding ROP.
[b] Kruskal-Wallis equality-of-populations rank test.
[c] Fisher's exact test and oneway anova.

Table 3a
Odds ratios for the association between GM assessment at 3 months only and atypical neurological outcome at 2 years of age from logistic regression.

Logistic regression		1 OR raw (95%CI)	2 Adjusted for ROP OR adj_{ROP} (95%CI)	3 Adjusted for IVH OR adj_{IVH} (95%CI)	4 Adjusted for PVL OR adj_{PVL} (95%CI)	5 Adjusted for NEC OR adj_{NEC} (95%CI)
	GM definitely abnormal	**12.0 (1.36;105.1)**	8.5 (0.9;77.9)	**10.6 (1.2;94.6)**	9.33 (0.9;76.7)	**10.18 (1.1;95.0)**
	GM mildly abnormal	1.96 (0.22;17.0)	1.4 (0.15;12.7)	1.74 (0.2;15.3)	1.87 (0.21;16.5)	2.2 (0.24;20.36)
	Constant	0.08 (0.01;0.64)	0.1 (0.01;0.8)	0.08 (0.01;0.64)	.1 (0.012;0.78)	0.08 (0.01;0.7)
	Variance explained (PseudoR)	13.3%	20.4%	18.6%	9.0%	16.05%
	N	105	94	103	90	94

Column 1 represents raw odds ratios, columns 2–5 present odds ratios adjusted to the presence of ROP, IVH, PVL and NEC.
Abbreviations: PVL (periventricular leucomalicia), ROP (retinopathy of prematurity), NEC (necrotising enterocolitis), IVH (intraventricular haemorrhage), MDI (mental developmental index, PDI (psychomotor developmental index. **Bold values** indicate statistically significant different.

associated with the presence of PVL and NEC (Table 2). Neither the age at GMA nor at BSID-II assessment differed among GM categories.

Of the 32 infants with definitely abnormal GM at 1 or 3 months (Table 2, "clinical routine scenario"), 15 (46.9%) had an atypical neurodevelopmental outcome at two years. This rate was significantly higher than that in infants with mildly abnormal GM (11 out of 74 (14.9%)) and normal GM (1 out of 16 (6.3%); Fisher exact: p = 0.001). Linear regression revealed that infants with definitely abnormal GM at 1 or 3 months scored 12.0 index points lower on the MDI (p = 0.035, 95% CI: −23.2; −0.86; effect size: $\Omega^2 = 0.025$) and 14.0 points lower on the PDI (p = 0.079; 95% CI: −29.8; 1.7; effect size: $\Omega^2 = 0.079$). They were also 13.2 times more likely to have an atypical neurological outcome at two years (p = 0.018, 95% CI 1.6; 112.5)

Table 3b
Odds ratios for the association between GM assessment at *1 or 3 months* ("clinical routine scenario") and atypical neurological outcome at 2 years of age from logistic regression.

Logistic regression		1 OR raw (95%CI)	2 Adjusted for ROP OR adj_{ROP} (95%CI)	3 Adjusted for IVH OR adj_{IVH} (95%CI)	4 Adjusted for PVL OR adj_{PVL} (95%CI)	5 Adjusted for NEC OR adj_{NEC} (95%CI)
	GM definitely abnormal	**13.2 (1.56;112.5)**	**10.05 (1.14;88.55)**	**11.6 (1.34;99.8)**	**9.53 (1.1;84.1)**	**10.95 (1.24;96.95)**
	GM mildly abnormal	2.6 (0.31;21.89)	2.1 (0.24;17.87)	2.2 (0.25;18.38)	2.6 (0.30;21.58)	2.7 (0.24;6.87)
	Constant	0.07 (0.01;0.50)	0.1 (0.01;0.8)	0.08 (0.01;0.64)	0.1 (0.012;0.7)	0.08 (0.009;0.67)
	Variance explained (PseudoR)	11.7%	14.69%	18.9%	8.0%	14.2%

Column 1 represents raw odds ratios, columns 2–5 present odds ratios adjusted to the presence of ROP, IVH, PVL and NEC.
Abbreviations: PVL (periventricular leucomalicia), ROP(retinopathy of prematurity), NEC (necrotising enterocolitis), IVH (intraventricular haemorrhage), MDI (mental developmental index, PDI (psychomotor developmental index. Bold values indicate statistically significant differences.

Table 4
Predictive properties of GM quality at *1 or 3 months* for atypical neurological outcome and CP at 2 years.

	Atypical neurological outcome		CP	
	Presence of *mildly or definitely* abnormal GM	Presence of *definitely* abnormal GM *at 1 or 3 months*	Presence of *definitely* abnormal GM	Presence of *definitely* abnormal GM at *3 months only*
Sensitivity (95% CI)	96.3% (81;99.9)	55.6% (35.3;74.5)	85.7% (42.1; 99.6)	100% (54.1; 100)
Specificity (95% CI)	15.8% (9.12;24.7)	82.1% (72.9;89.2)	77% (68.1;84.4)	77.6 (68; 85.4)
Positive predictive value (95% CI)	24.5% (16.7;33.8)	46.9% (29.1;65.3)	18.8% (7.21;36.4)	21.4% (8.3; 41)
Negative predictive value (95% CI)	93.8% (69.8;99.8)	86.7% (77.9;92.9)	98.9% (93.8; 100)	100% (95.3; 100)
Accuracy (correct classification rate)	33.6%	76.2%	77.5%	78.8%

than infants with normal GM (Table 3b). The latter association was still relevant and significant when adjusting for medical history parameters such as ROP, IVH, PVL and NEC (Table 3b).

Only 18.8% of children with definitely abnormal GM in our "clinical routine scenario" were diagnosed with CP, implying a sensitivity of definitely abnormal GMA for CP of 85.7% (Table 4). Sensitivity of definitely abnormal GMA at 1 or 3 months' CA for atypical neurological outcome was 55.6%, while specificity and negative predictive values were 82.1% and 86.7%, respectively. Further diagnostic test criteria for the presence of either mildly or definitely abnormal GM can be found in Table 4.

4. Discussion

This study shows that it is possible to implement GMA in a non-academic setting, with predictive values for neurodevelopmental outcome and CP at two years comparable to those in academic settings. Furthermore, we demonstrate that prediction of atypical neurological outcome remained sufficiently accurate when we applied a clinical routine scenario which used all available GM information for prediction (primarily GMA at 3 months, or at 1 month, when 3 months were not available). However, for the prediction of CP, GMA at 3 months outperforms the assessment based on the clinical routine scenario.

Our study is unique in its detailed analysis of organisational factors necessary for the successful and efficient implementation of GMA in a non-academic outpatient centre. Moreover, the numerous practical solutions that we provide to problems encountered as we established efficient GMA in our centre may be easily taken over by other centres (Table 1). These solutions include management of the appointments at 1 and 3 months' CA, communication with the parents, video storage, and the way to report GMA results to paediatric colleagues. Our experiences lead us to conclude that the most important element might be the team: GMA by a team of professionals rather than by an individual allows for continuous self-calibrating and quality assurance. In addition, our study suggests that GMA results may facilitate the clinical dialogue with parents. For example, about three-fourths of parents (those of infants with normal and mildly abnormal GM, see Table 2) feel relief as they expect a favourable outcome, while one-fourth (those of infants with definitely abnormal GM) appreciate the offer of early intervention and feel reassured by starting therapy as soon as possible.

When comparing tools to predict developmental outcome at an early age, predictive accuracy, costs, risks and resources should be taken into account. MRI scans and cranial ultrasound exams are costly and time-consuming, in addition to requiring the attention of experts and occasionally anaesthesia (Malec, Sidonio, Smith, & Cooper, 2014). A neurological assessment at term also necessitates a specially trained and experienced neonatologist or neuropaediatrician. In contrast, the totally non-invasive GM videotaping and assessment may be performed by trained physiotherapists in less than 20 min per infant.

Simultaneously, we showed that this practical method was highly predictive for later neurodevelopmental outcomes: Besides a 100% sensitivity for CP (Table 4, GMA at 3 months), our clinical routine scenario showed that definitely abnormal GM were associated with substantially lower MDI and PDI and a largely increased odds of atypical neurological outcome at two years of age, irrespective of the presence of neonatal risk factors such as IVH and ROP. These results underline the predictive value of GMA as implemented in non-academic outpatient settings. Although not all children with definitely abnormal GM in the clinical routine scenario developed CP (sensitivity 85%, Table 4), they still had a high risk of other forms of atypical neurodevelopmental outcome. This means that also the "clinical routine scenario" use of GMA is a powerful tool to provide guidance to families of at-risk infants in non-academic settings.

In addition, our study suggests that GMA in non-academic outpatient centres might be quite cost-effective: Given that early risk detection and risk stratification is key for the wise distribution of limited budgets, infants with the highest risk profiles should have the highest priority to receive early interventions that may reduce the risk of unfavourable neurodevelopmental outcome (Guralnick, 2012; Nordhov et al., 2012). If, however, risk is only based on the presence of traditional neonatal risk factors such as PVL, IVH or NEC, it may be easy to miss or underestimate the effect of important postnatal influences affecting neurological recovery and brain plasticity (e.g. postnatal social environment (Latal, 2009), socioeconomic status (Largo et al., 1989) and parental attachment and care (Head, 2014)). In this line, studies have shown that e.g. low levels of postnatal parental stress may buffer the negative influence of neonatal distress (Voigt et al., 2013). The advantage of GMA for risk assessment thus is that, if performed at 3 months' CA, when most infants have left the neonatal intensive care unit and are at home, it integrates the influences of prenatal, early postnatal and first home periods on neurological recovery. This fact might also explain the greater sensitivity of GMA if assessed at 3 months for later CP as compared to if using all available GMA (1 or 3 months, Table 3b).

When comparing the prevalence of abnormal movements in our study with that in other studies on GMA, our estimate was partly higher (Romeo et al., 2008; Stahlmann et al., 2007), but also similar to that in previous studies (Spittle et al., 2013) using the Prechtl classification (Einspieler & Prechtl, 2005; Prechtl et al., 1997). Despite these differences, the prediction of CP and atypical neurodevelopmental outcome in our study by GMA at 3 months as well as by our clinical routine scenario are within the range of those published in previous reports (Bosanquet et al., 2013; Burger & Louw, 2009; Kodric, Sustersic, & Paro-Panjan, 2010; Stahlmann et al., 2007).

If compared with the few existing reports on GMA in clinical routine, our study differs in some aspects: While some of them were much smaller than ours (e.g. systematic review(Burger & Louw, 2009): in 9 of 13 studies n <100; Kodric et al., 2010: n = 26; Stahlmann et al., 2007 n = 103), they also differed with respect to age at GMA as well as outcome assessment, the outcome assessment method chosen and the gestational age of children eligible for the study (e.g. <33 gestational weeks in our study, ≤36 weeks in Kodric et al., 2010).

Definitely abnormal GM at 3 months (as well as at 1 or 3 months) in our study significantly and consistently predicted cognitive outcome (MDI) but not motor outcome (PDI). This differential finding might be explained by the low number of children with PDI measurement in our study, but it is also in line with previous results (Stahlmann et al., 2007) (Butcher et al., 2009). While this may be surprising at first sight, the neurobiological concept of GM (Hadders-Algra, 2007) suggests that they are the clinical correlate of the functional complexity and variation of neuronal networks. Such networks can be assumed to be a prerequisite for successfully solving the cognitive items of the MDI at two years (Hadders-Algra, 2007). In the case of a reduced neuronal network and reduced complexity and variation of GM, cognitive performance will be limited.

In contrast to cognitive BSID-II items, the motor items at two years (e.g. walking back and forth or up and down the stairs) can successfully be managed, even with a qualitatively reduced motor repertoire. Thus, the BSID-II at two years is relatively insensitive to motor disorders.

Previous studies indicate that the specificity of predicting unfavourable neurological outcome for mildly abnormal GM at 3 months is rather low (Hadders-Algra, 2004). The present study confirms this finding. Mildly abnormal GMA at 3 months as stand-alone parameter may therefore not be useful in preterm aftercare. Additional clinical data like neurological status, cranial ultrasound and neurological follow-up may be helpful to further refine mildly abnormal as a developmental risk category (Hadders-Algra, 2004; Setanen et al., 2014). Also, GMA at 1 month CA in our study shows limited predictive capacity, as in previous literature (Burger & Louw, 2009).

4.1. Strengths and limitations

Our study has a number of strengths. It is, to the best of our knowledge, the first study to describe the problems encountered during the implementation of GMA as well as potential solutions in a non-academic outpatient centre. It is also the first study to evaluate the predictive values of GMA in a non-academic paediatric outpatient centre and to analyse these values using a clinical routine scenario, which combines all available GMA (at 3 months primarily or 1 month, when 3 months are not available). This is significant because our approach approximates the situation in clinical routine environments, where follow-up of children born preterm is not ideal due to limited resources. Despite potential constraints in non-academic

outpatient centres, we were able to establish quality standards in implementing GMA (e.g. blinding GM assessors regarding the results of the neurological examination status and the infant's medical history), which could be easily transferred to other outpatient centres.

A further strength is that our evaluation was performed on a study population with less brain damage and lower CP rates than those in many previous studies, which better reflects the current populations of children born preterm after high-quality neonatal care (Sellier et al., 2016).

Besides these strengths, our study also has limitations. First, the sample size is limited due to attrition. However, the sample itself is typical for preterm referrals to our centre and to non-academic clinical settings. While 40% of eligible infants were lost early during transition from the neonatology clinic to the social paediatric centre, only 15% of children were lost to follow-up once the infant had shown up at the GM appointment. The latter attrition rate might be improved by informing the parents about the value of GMA when close to discharge from the hospital. A second limitation was that we applied a single-centre approach, meaning that we could not assess the effect of different clinical settings and organisations on the implementation of GMA. With our approach, we give a best practice example of the implementation of GMA in clinical routine. We achieved this notwithstanding many missing values in PDI assessment, which was difficult to perform in all children due to the length of the two-year examination (MDI and PDI; neurological and physical examination; counselling of the parents). Third, our results are limited to a high-risk preterm population (<1500 g or gestational age <33 weeks with neurological abnormalities) and therefore cannot be generalised to other populations of at-risk infants. Fourth, it might be considered a limitation that we used American norms for the BSID-II. However, the study of Westera et al. (Westera, Houtzager, Overdiek, & van Wassenaer, 2008) showed that Dutch and American norms of the BSID-II are similar, implying that the norms for German and American infants would most likely be similar, too.

5. Conclusion

Our study demonstrated how GMA can be successfully implemented in a non-academic outpatient clinic. It also showed that if *all available* GMA (primarily at 3 months or 1 month, when 3 months are not available) are used in a non-academic setting, atypical neurological outcome in high-risk infants born preterm can be predicted with diagnostic accuracy comparable to previous studies. Thus, the capacity of GMA to identify risk in non-academic settings does not seem to differ from that in academic settings. As primary follow-up service providers for infants born preterm, non-academic outpatient centres should therefore use GMA as an efficient way to stratify developmental risk in these infants. We hope that our example will inspire other non-academic outpatient centres to implement GMA as part of their clinical routine.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

The authors have no financial relationships nor conflicts of interest relevant to this article to disclose. Nobody was given a grant, or other form of payment to produce the manuscript.

Acknowledgements

We thank the parents, children and families for their cooperation.

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