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Highlighting the first 5 months of life: General movements in infants later diagnosed with autism spectrum disorder or Rett Syndrome

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Abstract

We review literature identifying an association between motor abnormality in the first 5 months of infancy and later diagnosis of autism spectrum disorder (ASD) or Rett syndrome (RTT). The assessment of the quality of early spontaneous movements (also known as the assessment of general movements; GMs) is a diagnostic tool that has repeatedly proven to be valuable in detecting early markers for neurodevelopmental disorders. Even though the rate of occurrence of abnormal GMs is exceedingly high in infants later diagnosed with ASD, we endorse further studies using this method either based on family videos or its prospective implementation in high-risk sibling studies to evaluate the power of GM assessment as one potential marker for early maldevelopment in this cohort.

Keywords

Autism spectrum disorder; Family videos; General movement assessment; Infant; Rett syndrome; Spontaneous movements; Video analysis

1 Introduction

With an estimated prevalence of autism spectrum disorder (ASD) of 1 in 88 children (Centers for Disease Control and Prevention, 2008), and with the growing evidence of the efficacy of earlier intervention (Dawson et al., 2010; Landa, Holman, O'Neill, & Stuart, 2011), there is a need for the early identification of individuals at increased risk for ASD. However, very early detection of ASD is a considerable challenge due to an extended prodromal period through mid- to late infancy (Deconinck, Soncarrieu, & Dan, 2013; Landa, Gross, Stuart, & Faherty, 2013; Yirmiya & Charman, 2010; Zwaigenbaum, Bryson, &

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Garon, 2013). One of the developmental domains that has been retrospectively and prospectively studied is motor development (for a recent review see Zwaigenbaum et al., 2013). Apart from behavioral and neurodevelopmental assessments, a recent diffusion tensor imaging study adds to the body of knowledge on early motor dysfunctions in ASD by reporting an aberrant white matter fibre tract development (from higher to lower fractional anisotropy values) from 6 to 24 months of age (Wolff et al., 2012).

But what are the early motor abnormalities? In one of the first systematic analyses of home videos (recorded prior to diagnosis), Adrien and colleagues (1991, 1993) reported that hypotonia, hypoactivity and unusual postures were common findings in the ASD group. Since then, poor postural control and postural asymmetries were the most frequently discussed early markers for ASD (Baranek, 1999; Esposito, Venuti, Apicella, & Muratori, 2011; Esposito, Venuti, Maestro, & Muratori, 2009; Flanagan, Landa, Bhat, & Bauman, 2012; Iverson & Wozniak, 2007; Teitelbaum et al., 1998; 2004). Already during the first half a year of life the following signs were observed in individuals with a later ASD diagnosis: postural asymmetries during lying (Esposito et al., 2009; Teitelbaum et al., 1998), head-lag during the pull-to-sit transition (Flanagan, et al., 2012), fluctuating muscle tone (Dawson, Osterling, Meltzoff, & Kuhl, 2000), oral-motor abnormalities and insufficient opening of the mouth in anticipation of the approaching spoon during feeding (Brisson, Warreyn, Serres, Foussier, & Adrien-Louis, 2012; Gernsbacher, Sauer, Geye, Schweigert, & Hill Goldsmith, 2008). Other researchers, however, have not found any abnormalities at 6 months of life when prospectively testing young infants later diagnosed with ASD using the Mullen Scale of Early Learning (Mullen, 1995). Only from 12 months onwards, infants and toddlers with ASD had both lower gross motor and fine motor scores when compared to other high-risk groups (Brian et al., 2008; Landa & Garrett-Mayer, 2006; Landa, Gross, Stuart, & Bauman, 2012; Landa et al., 2013; Zwaigenbaum et al., 2005). Home video analyses, carried out during the second half of the first year of life or even later, again revealed postural abnormalities such as a persistent asymmetric tonic neck reflex, abnormal rolling, asymmetrical sitting with unequal weight distribution, or asymmetries in unsupported gait (Esposito et al., 2011; Teitelbaum et al., 1998; 2004). Esposito et al. (2011) speculated that a continuity of static (referring to a single frame analysis) and dynamic (coded over 4 frames) asymmetries during the first year of life could result from atypical hemispheric asymmetry or an impairment of brain connectivity (Hadders-Algra, 2008). Other researchers, however, have not confirmed higher rates of postural abnormalities in infants and toddlers with ASD (Ozonoff et al., 2008; Provost, Lopez, & Heimerl, 2007). Ozonoff and colleagues (2008) reported some signs of slower motor development (e.g., weight bearing on arms while in prone, walking) in both individuals with ASD and individuals with global developmental delays of unknown origin suggesting that an early motor delay may be not specific to ASD. Also Iverson and Wozniak (2007) mentioned a delayed onset of independent sitting and walking in a group at high-risk for ASD.

An infant may achieve a motor milestone but at the same time perform the milestone related behavior in a qualitatively abnormal manner. That is, qualitative abnormalities may not interfere with an infant achieving a score that is quantitatively within normal limits on a standardized motor assessment (Landa et al., 2013; Prechtl, 2001). Thus, alternative and more sensitive measures of motor behavior are needed. One possibility is Prechtl's method

of assessing infants' early spontaneous movements (Einspieler, Prechtl, Bos, Ferrari, & Cioni, 2004; Prechtl, 1990). This method has led to the identification of abnormality in infants with a variety of types of disorders such as cerebral palsy, minor neurological dysfunctions, psychiatric morbidities, but also metabolic and genetic disorders (e.g., Bruggink et al., 2008; Bruggink, van Spronsen, Wijnberg-Williams, & Bos, 2009; Einspieler, Hirota, Yuge, Dejima, & Marschik, 2012; Einspieler, Kerr, & Prechtl, 2005b, Hadders-Algra, Bouwstra, & Groen, 2009; Hadders-Algra et al., 2004; Marschik, Soloveichick, Windpassinger, & Einspieler, 2013; Prechtl, Einspieler, Cioni, Bos, Ferrari, & Sontheimer, 1997).

Prechtl (1990) introduced a novel approach to the field of motor assessment. Rather than presenting infants with a 'task' or set of examiner-imposed stimuli to determine their capacity to respond in a particular way, he endorsed the observation of infants' spontaneous behavior in contexts where the child is not being stimulated (Prechtl, 2001). The assessment of the quality of early spontaneous movements, also known as the assessment of general movements (GMs), has repeatedly proven to be a valuable tool in detecting early markers for neurodevelopmental disorders (Manual: Einspieler et al., 2004). The method is based on visual Gestalt perception of normal and abnormal GMs in preterm and term infants aged up to 5 months post-term (Einspieler et al., 2004; Einspieler & Prechtl, 2005). It predicts neurodevelopmental impairments, in particular cerebral palsy, with a sensitivity greater than 91% and a specificity greater than 81% (Bosanquet, Copeland, Ware, & Boyd, 2013; Burger & Louw, 2009; Einspieler, Marschik, Bos, Ferrari, Cioni, & Prechtl, 2012; Prechtl et al., 1997). Almost 20 studies have revealed an inter-observer agreement of (an average) kappa = 0.88 (Einspieler & Prechtl, 2005) and a test-retest reliability of 85 to 100% (Einspieler, 1994). Intra-individual consistency revealed a kappa = 0.90 for GMs during the preterm age, a kappa = 0.96 for GMs during term age, and kappa = 0.92 for GMs during 3 to 4 months postterm age (Mutlu, Einspieler, Marschik, & Livanelioglu, 2008).

Below, we review the literature that suggests a relation between abnormal GMs and a later diagnosis of ASD.

2 What are general movements (GMs)?

General movements are among the earliest and most prevalent and complex patterns of movements. They emerge in the fetus at 8 to 10 weeks postmenstrual age and continue to be present until the 5th month postterm age (Einspieler et al., 2004). From their emergence until the 2nd month after term GMs comprise the entire body and manifest themselves in a variable sequence of arm, leg, neck and trunk movements. They come and go gradually, varying in intensity and speed. Rotations and frequent slight variations of the direction of motion make them look complex and smooth (Einspieler et al., 2004; Prechtl, 1990). At that age, GMs are labeled 'writhing movements' (Einspieler et al., 2004). Abnormal writhing GMs are classified as (a) 'poor repertoire GMs', whereby the sequence of movement components is monotonous, and the amplitude, speed, and intensity lack the normal variability; or (b) 'cramped-synchronized GMs', lacking the usual smoothness and fluent character, appearing rigid as the limb and trunk muscles contract almost simultaneously and relax almost simultaneously (Einspieler et al., 2004; Einspieler & Prechtl, 2005).

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At the beginning of the 3rd month, a new pattern of GMs, the so-called 'fidgety movements' emerge, and last until the end of the 5th month. Fidgety movements are small movements of the neck, trunk and limbs in all directions and of variable acceleration (Einspieler et al., 2004; Prechtl et al., 1997). If such fidgety movements are present and normal in their quality, infants develop normally, even if their clinical history may indicate a disposition to neurodevelopmental deficits (e.g., Burger & Louw, 2009; Prechtl et al., 1997). Fidgety movements of an abnormal quality (i.e., exaggerated amplitude, speed and jerkiness), are associated with an increased risk for minor neurological dysfunctions (Bruggink et al., 2008) or fine manipulative disabilities (Einspieler, Marschik, Milioti, Nakajima, Bos, & Prechtl, 2007). The absence of fidgety movements is usually related to the development of severe neurological deficits (Burger & Louw, 2009; Einspieler et al., 2012; Einspieler & Prechtl, 2005; Prechtl et al., 1997).

The neural mechanisms of GMs involve central pattern generators (CPGs) in the brainstem (Einspieler et al., 2004; Einspieler & Marschik, 2012; Hadders-Algra, 2007). CPGs are neural networks that are able to generate spontaneously and autonomously motor activity but are affected and modulated by signals from other parts of the brain (Grillner et al., 1995). Separate CPGs are assumed to be responsible for writhing and fidgety GMs, as both patterns may be seen simultaneously during a period of overlap from 6 to 8 weeks post-term age (Einspieler et al., 2004).

3 Family videos as a source for GM assessment

Although the assessment of GMs is typically applied prospectively and in multiple settings (i.e., at least two recordings from birth to 5 months after term; Einspieler et al., 2004), it has recently also been applied in home video analyses in children with ASD or Rett syndrome (RTT) (Einspieler, Kerr, & Prechtl, 2005a; Einspieler, et al., 2005b; Einspieler et al. 2013; Marschik, Einspieler, Oberle, Laccone, & Prechtl, 2009; Phagava et al., 2008). In order to assess GMs in home videos such clips need to meet essential criteria of GM assessment (i.e., have a minimum recording duration of 40 seconds of the unstimulated, awake, and non-crying infant, lying in supine position; Einspieler et al., 2004).

To date there are numerous studies on GMs that have focused on the quality of GMs in (mostly preterm) infants with and without acquired brain lesion (Bosanquet et al, 2013; Prechtl et al., 1997). Our retrospective studies on RTT (Einspieler et al, 2005a; Einspieler et al, 2005b) were among the first applications to infants with genetic disorders. That none of the individuals with RTT had a normal GM trajectory was certainly surprising as an apparently normal early development had been considered to be one of the initial criteria for typical RTT (Hagberg, Aicardi, Dias, & Ramos, 1983). Only two individuals of the study sample (Cases 1 and 2 in Table 1) had normal writhing GMs but their fidgety movements were abnormal or even absent. Additionally, some of the infants had tremulous movements (Einspieler et al., 2005a); others did not show the adequate motor repertoire usually seen at 3-5 months, such as movements to the midline or antigravity movements (Einspieler et al., 2005b).

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Encouraged by the feasibility to use the assessment of GMs for the analysis of family videos, Phagava et al. (2008) analyzed the footage of 20 children who had a diagnosis of ASD. Unfortunately, only four individuals were recorded several times to allow for the assessment of a GM trajectory (Cases 3, 11, 12, 20 in Table 2); all others could only be assessed either for writhing or fidgety GMs. However, the GM trajectories of those four individuals varied substantially: Case 3 had normal writhing movements but deteriorated over time expressed by the absence of fidgety movements; Cases 11 and 12 showed abnormal writhing movements but improved to normal fidgety movements; and Case 20 exhibited a consistent abnormal GM trajectory (Table 2). A limitation of this study is the lack of detailed information about outcome and severity of the phenotype in motor and cognitive domains. This limitation was evident for 16 participants who were either recorded and assessed for writhing GMs (n = 3; Case 1 with normal GMs; Cases 13, 14 with abnormal GMs) or solely for fidgety movements (n = 13; Cases 4 to 9 with normal fidgety movements; Cases 16 to 19 with abnormal fidgety movements, and Cases 23 to 25 with no fidgety movements at all; Table 2): again, nothing is known about the severity of their phenotype and no explanation was provided for the diversity of the results.

4 Prospective assessment of GMs in infants later diagnosed with ASD

Out of three different prospective studies that applied the assessment of GMs in populations at high risk for maldevelopment, five participants were diagnosed with ASD (two of them with pervasive developmental disorder not otherwise specified, PDD-NOS) 3 to 5 years later (Hadders-Algra et al., 2009; Palchik, Einspieler, Evstafeyeva, Talisa, & Marschik, 2013; Yuge et al., 2011). Recently, Palchik et al. (2013) reported on three children with ASD who were prospectively assessed for their GMs because they were prenatally exposed to HIV and maternal opiate abuse (the total sample comprised 77 children). All three individuals with a later diagnosis of ASD had abnormal writhing and fidgety GMs (Cases 15, 21, 22 in Table 2). It has to be noted, however, that approximately half of the 77 study cases showed abnormal GMs, most likely related to a prenatal exposure to neurotoxins (Palchik et al., 2013).

In a group of 41 infants, who were at high risk for neurodevelopmental problems due to their perinatal history, one girl (Case 10, Table 2) was diagnosed with PDD-NOS at age 5 years. She had normal fidgety movements but her overall motor repertoire was not age-adequate (Yuge et al., 2011). Hadders-Algra et al. (2009) described another child with PDD-NOS (Case 2 in Table 2) whose writhing GMs were normal but the GMs at 3-5 months were classified as ‘mildly abnormal’ (i.e. insufficiently variable, complex, and not fluent). This finding is hardly comparable with the other cases as a different approach of assessing GMs was applied (Hadders-Algra, Klip-van den Nieuwendijk, Martijn, & van Eykern, 1997).

While there is mounting evidence to support a link between GMs and ASD, the studies described above were not designed specifically to examine the association between abnormal GMs and later ASD diagnosis. If a link does exist, that link may exist only in some subgroups of individuals with ASD. This tentative conclusion is based on the fact that in some cases of the above mentioned studies, GMs were within normal limits. Thus, there would seem to be a need for more research to determine the relation between abnormal GMs

and later ASD features or diagnosis, and associations between degree of abnormality in GMs and severity of later ASD symptoms.

5 Conclusions

The rate of occurrence of abnormal GMs in infants who were later diagnosed within the ASD or related neurodevelopmental disorders appears to be common. Specifically, 17 out of 25 individuals with ASD (68%; Table 2), and 100% of individuals with RTT (Table 1) had abnormal GMs during their first months of life. However, the early motor abnormality as expressed by qualitatively deviant GMs cannot be regarded as specific sign for any of these disorders. Similar atypical GM patterns occur in infants with acquired brain lesions resulting in later functional impairments such as cerebral palsy or minor neurological dysfunctions. That is, whenever the integrity of the nervous system is impaired, the variability of GMs is reduced (Einspieler et al., 2004; Prechtl et al., 1997). In line with Zwaigenbaum et al. (2013), we conclude that there is a need for further studies using the assessment of GMs in individuals with ASD. Two types of studies would seem relevant: (a) retrospective analysis of home videos for children diagnosed with ASD, and (b) prospective studies of high-risk siblings of children with ASD. We are well aware that more and standardized data are necessary to evaluate the potential power of GM assessment as one component of an assessment designed to identify infants at heightened risk for ASD. In addition to the global assessment of GMs (feasible for home video analysis), standardized video recordings would allow for more detailed analysis of GMs and concurrent motor and postural patterns in order to gain information about pace, range of motion, velocity, intensity, spatial character and amount of rotations of the spontaneous early motor repertoire. One could even think of combining the classic Gestalt-based video assessment with computer-based GM analysis as a complementary approach (Einspieler & Marschik, 2013).

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Highlights

Einspieler, Marschik, Landa, Bölte - Highlight

Home video analyses and prospective case studies demonstrated that the rate of occurrence of abnormal general movements in infants who were later diagnosed with autism spectrum or related neurodevelopmental disorders was exceedingly high.

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Table 1

Quality of writhing and fidgety GMs in 17 children later diagnosed with typical or atypical Rett syndrome; 10 children were recorded longitudinally and could be assessed for writhing and fidgety movements. All assessments were based on family videos (Einspieler et al., 2005b; Einspieler et al., 2013; Marschik et al., 2009).

Case / Mutation	Writhing GMs (Term Age to 2 Months)	Fidgety GMs (3 to 5 Months)	Comments
1/ R168X	N	AF	
2 / del exon 3-4	N	F-	
3 / c.378-43_964delinsGA	–	AF	PSV
4[a] / *	PR	–	
5[a] / *	PR	–	
6 / *	PR	–	
7 / *	PR	AF	
8 / R168X	PR	AF	
9 / P152R	PR	AF	
10 / T158M	PR	AF	
11/ R255X	–	AF	
12 / truncation deletion 1116-1201	–	AF	
13 / S134 C	–	AF	
14 / Q244X	CS	AF	
15 / R255X	–	F-	
16 / R168X	–	F-	
17 / **	PR	F-	

Abbreviations: N = Normal; PR = Poor Repertoire GMs, CS = Cramped Synchronised GMs, AF = Abnormal Fidgety movements; F- = Absence of Fidgety movements, – = not assessed during this epoch; [a] = twins; * = not mutation tested; ** = MECP2 mutation positive but not further specified; PSV = Preserved Speech Variant of Rett syndrome.

Table 2

Quality of writhing and fidgety GMs in 25 children later diagnosed with ASD (including two children diagnosed with PDD-NOS). Ten individuals were recorded longitudinally and could be assessed for writhing and fidgety movements. Assessments were carried out either retrospectively using family videos ([a]Phagava et al., 2008) or prospectively on various at risk groups for maldevelopment ([b]Hadders-Algra et al., 2009; [c]Palchik et al. 2013; [d]Yuge et al., 2011)

Case[Reference]	Writhing GMs (Term Age to 2 Months)	Fidgety GMs (3 to 5 Months)	Comment
1[a]	N	–	Family video
2[b]	N	Mildly abnormal*	Prospective study, PDD-NOS
3[a]	N	F-	Family video
4[a]	–	N	Family video
5[a]	–	N	Family video
6[a]	–	N	Family video
7[a]	–	N	Family video
8[a]	–	N	Family video
9[a]	–	N	Family video
10[d]	–	N	Prospective study, PDD-NOS
11[a]	PR	N	Family video
12[a]	PR	N	Family video
13[a]	PR	–	Family video
14[a]	PR	–	Family video
15[c]	–	AF	Prospective study
16[a]	–	AF	Family video
17[a]	–	AF	Family video
18[a]	–	AF	Family video
19[a]	–	AF	Family video
20[a]	PR	AF	Family video
21[c]	PR	AF	Prospective study
22[c]	CS	AF	Prospective study
23[a]	–	F-	Family video
24[a]	–	F-	Family video
25[a]	–	F-	Family video

Abbreviations: N = Normal; PR = Poor Repertoire GMs, CS = Cramped Synchronised GMs, AF = Abnormal Fidgety movements; F- = Absence of Fidgety movements, – = not assessed during this epoch; PDD-NOS = pervasive developmental disorder not otherwise specified; *= according to Hadders-Algra et al. (1997) ‘mildly abnormal GMs’ lack fluency but still show some movement complexity and variation.