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Early motor and pre-linguistic verbal development in Prader-Willi syndrome – A case report

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ABSTRACT

Background: Prader-Willi syndrome (PWS) is a rare genetic disorder. Infants with PWS show a neurodevelopmental dysfunction which entails a delayed motor and language development, but studies on their spontaneous movements (i.e. general movements) or pre-linguistic speech-language development before 6 months of age are missing so far.
Aim: To describe early motor and pre-linguistic verbal development in an infant with PWS.
Methods and procedures: Prospective case report; in addition to the assessment of general movements and the concurrent movement repertoire, we report on early verbal forms, applying the Stark Assessment of Early Vocal Development-Revised.
Outcomes and results: General movements were abnormal on days 8 and 15. No fidgety movements were observed at 11 weeks; they only emerged at 17 weeks and lasted until at least 27 weeks post-term. The movement character was monotonous, and early motor milestones were only achieved with a delay. At 27 weeks the infant produced age-adequate types of vocalisations. However, none of the canonical-syllable vocalisations that typically emerge at that age were observed. Early vocalisations appeared monotonous and with a peculiarly harmonic structure.
Conclusions and implications: Early motor and pre-linguistic verbal behaviours were monotonous in an infant with PWS throughout his first 6 months of life. This suggests that early signs of neurodevelopmental dysfunction (i.e. abnormal general movements) might already be diagnosed in infants with PWS during their first weeks of life, potentially enabling us to diagnose and intervene at an early stage.

What this paper adds

- General movements were abnormal on days 8 and 15, and at 11 weeks post-term. Fidgety movements and concurrent movements emerged with a delay, at 17 weeks.

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- At 27 weeks, no age-adequate canonical syllables were vocalised. Vocalisation was monotonous and of a peculiarly harmonic structure.

1. Introduction

Prader-Willi syndrome (PWS) is a rare genetic disorder that occurs in 1:10.000–30.000 births (Cassidy, Schwartz, Miller, & Driscoll, 2012). It can be caused by the absence of paternally inherited genes on chromosome 15q11-q13 (deletion, 65–75%), by loss of the entire paternal chromosome 15, the presence of two maternal homologues – a disorder that is referred to as uniparental maternal disomy (UPD, 20–30%), or by imprinting defects (1–3%; (Cassidy et al., 2012)). Familial inheritance has been described in a few cases, but most cases are de novo (Cassidy et al., 2012).

The neonatal period is characterised by typical craniofacial features (e.g., prominent forehead, narrow face, almond-shaped eyes, small and downturned mouth, thin upper lip, and micro mandible), as well as hypotonia, poor arousal, absent or weak crying, transient bradycardia, thermolability, paleness and/or intensely mottled skin with acrocyanosis, hypogonadism (e.g. undescended testicles), and feeding difficulties which require tube feeding (Oiglane-Shlik et al., 2006). In early childhood, the symptoms include hyperphagia with consequent obesity, growth hormone deficits resulting in short stature, behavioural problems (e.g. skin picking, obsessive-compulsive disorder), intellectual disability (average IQ = 65), and neurodevelopmental delay (e.g., infants with PWS begin to sit at 12 months and to walk at 24 months of age; (Cassidy et al., 2012; Gunay-Aygun, Schwartz, Heeger, O´Riordan, & Cassidy, 2001; Holm et al., 1993)).

Language development has been investigated from 6 months onwards, with reports on peculiar vocalisation, especially weak crying, and reduced babbling (Lewis, Freebairn, Heeger, & Cassidy, 2002). First words are uttered with a delay, co-occurring with poor oral motor skills, flat intonation, and an abnormal pitch of the voice, leading to unintelligible speech (Lewis et al., 2002).

Growth hormone treatment of children with PWS not only has an effect on body composition, linear growth, physical strength, and adaptive functioning, but has also yielded neurodevelopmental benefits (Festen et al., 2008; Reus et al., 2013). Growth hormone treatment was even more beneficial to the mental and motor development when initiated at a younger age, as demonstrated in a prospective cohort study on 63 infants and toddlers with PWS, in which the growth hormone therapy started at a median age of 1.0 year (IQR 0.7–1.6 years; (Donze, Damen, Mahabier, & Hokken-Koelega, 2018). The growth hormone therapy also improved language development in 25 infants and toddlers with PWS aged 4–37 months (Myers et al., 2007).

Only recently has research on early motor and pre-linguistic development proved valuable for our understanding of the early development of infants with rare genetic disorders. Especially in infants with a late clinical onset, prodromal features or symptoms might facilitate earlier diagnosis in the future (Marschik et al., 2017). In order to get a better understanding of specific developmental profiles, we need to delineate peculiarities of different developmental disorders so as to effect earlier detection and intervention (early motor development: Cornelia de Lange syndrome (Marschik, Soloveichick, Windpassinger, & Einspieler, 2015), Smith-Magenis syndrome (Einspieler, Hirota, Yuge, Dejima, & Marschik, 2012), Rett syndrome (Einspieler, Kerr, & Prechtl, 2005), Down syndrome (Mazzone, Mugno, & Mazzone, 2004; Herrero, Einspieler, Panvequio Aizawa, Mutlu, & Yang, 2017), and pre-linguistic verbal development: Angelman syndrome (Grieco, Bahr, Schoenberg, Conover, Mackie & Edwin, 2018), Rett syndrome (Marschik, Pini, Bartl-Pokorny, Duckworth, Gugatschka & Vollmann, 2012, Marschik, Kaufmann, Sigafoos,Wolin, Zhang & Bartl-Pokorny, 2013; Pokorny, Bartl-Pokorny, Einspieler, Zhang,Vollmann & Bölte, 2018; Roche, Zhang,Bartl-Pokorny, Pokorny, Schuller & Esposito, 2018).

To enhance our knowledge on the early development of PWS, we report the early motor and pre-linguistic verbal development of an affected infant, observed in a prospective, longitudinal study between his second week of life and 27 weeks post-term age (PTA).

Apart from assessing the global general movement categories, we conducted a detailed general movement assessment (GMA), applying age-specific detailed scores: the general movement optimality score (GMOS [Einspieler, Marschik, Pansy, Scheuchenegger, Krieber, & Yang, 2016]) at term age and the motor optimality score (MOS, [Einspieler, Prechtl, Bos, Ferrari, & Cioni, 2004]) at 3 to 5 months. Moreover, we report on early verbal capacities, applying the Stark Assessment of Early Vocal Development-Revised (SAEVD-R, (Nathani, Ertmer, & Stark, 2006)) at 27 weeks PTA.

2. Method

2.1. Case report

A two-day-old boy, born by caesarean section due to breech presentation at a gestational age of 39 + 0 weeks, with an Apgar Score of 9/10/10, a birth weight of 2996 g (10th percentile), a birth length of 52 cm (50th percentile), and a head circumference of 36 cm (74th percentile), was referred to the Division of Neonatology at the Medical University of Graz, Austria. He presented with muscle hypotonia and feeding problems. Further investigations revealed hypoglycaemia (a blood glucose of 35 mg/dl (1.9425 mmol/l)). Electrolytes, bilirubin and blood gas check were normal. The blood glucose level stabilised after parenteral glucose infusion. Early examinations included cranial ultrasound to exclude central nervous causes, and metabolic work-up to exclude inborn errors of metabolism. Both the cranial ultrasound and the metabolic work-up were unremarkable. Ultrasound of the kidneys was normal. Echocardiography revealed a cribriform atrial septal defect without haemodynamic relevance. Blood tests were negative for bacterial infection.

The boy only cried every once in a while in a low voice and persistently showed insufficient feeding interest, which necessitated tube feeding. Feeding by nasogastric tube had to be continued for 14 days. He had a small forehead, narrow face, almond-shaped eyes, a small mouth, thin lips, undescended testicles, and bilateral hip valgus. Because of persistent hypotonia he received

physiotherapy.

Clinical problems such as muscle hypotonia, feeding difficulties, and the need for nasogastric tube became more evident over time, which, along with the boy's hypoglycaemia, undescended testicles and craniofacial features (small forehead, narrow face, almond-shaped eyes, small mouth, thin lips, etc.), were indicative of Prader-Willi syndrome (Oiglane-Shlik et al., 2006).

Genetic testing confirmed the suspected clinical diagnosis of PWS on day 24 (deletion on the long arm of chromosome 15 (arr [hg19]15q11.2q13.1(23179948 × 2,23699701_28525460 × 1,29213402 × 2) with array-comparative genomic hybridisation and multiplex ligation-dependent probe amplification.

The ethical board of the Medical University of Graz approved an early motor analysis, i.e. GMA, and assessment of the pre-linguistic verbal development (29-060 ex 16/17). The parents gave their written informed consent.

2.2. General movements

General movements are the most frequent movement patterns during early infancy. Prechtl's GM assessment is based on global visual Gestalt perception. Easy to acquire in standardised training courses (Einspieler & Prechtl, 2005; Einspieler et al., 2004), it is a widely applied tool and has been proven valuable for the detection of developmental disorders, genetic disorders, and cognitive dysfunction (Einspieler, Bos, Libertus, & Marschik, 2016, Einspieler, Kerr & Prechtl, 2005; Einspieler et al., 2012; Einspieler, Sigafoos, Bartl-Pokorny, Landa, & Marschik, 2014; Herrero et al., 2017; Marschik et al., 2015; Mazzone et al., 2004; Novak et al., 2017; Prechtl, 1997; 2001).

Normal general movements around term age involve the entire body with variable sequences of the arms, legs, neck, and trunk. They are characterised by variable speed, amplitude and intensity and give a complex, fluent and elegant impression. Abnormal general movements appear monotonous, lacking fluency and elegance: "poor repertoire" general movements are monotonous in terms of speed, amplitude and intensity; "cramped-synchronized" general movements appear rigid and stiff as the limb and trunk muscles contract and relax almost simultaneously; "chaotic" general movements are characterised by abrupt movements with a large amplitude and high speed (Einspieler et al., 2004).

While normal general movements – especially with regard to complexity, variability and fluency – stand for the integrity of the nervous system (Einspieler et al., 2004; Einspieler, Marschik, & Prechtl, 2008; Marschik et al., 2017), abnormal general movements are associated with later neurological dysfunction. One abnormal pattern – poor repertoire general movements – has an uncertain predictive value. Infants with this GM pattern might develop normally, have minor neurological dysfunctions, or develop cerebral palsy. Furthermore, poor repertoire general movements have also been described in infants with visual impairment, autism spectrum disorder, and genetic disorders (Einspieler et al., 2014; Marschik et al., 2015; Mazzone et al., 2004). In contrast, the occurrence of cramped-synchronised general movements is highly associated with the development of cerebral palsy (Novak et al., 2017; Prechtl, 1997; Prechtl, Einspieler, Cioni, Bos, Ferrari, & Sontheimer, 1997; Prechtl, 2001).

At three months post term, general movements change in character and are thenceforth called fidgety movements. Normal fidgety movements stand for a normal neurological outcome. While abnormal fidgety movements are associated with mild neurological dysfunction (Einspieler, 2005; Einspieler, Peharz,& Marschik, 2016; Einspieler et al., 2014; Herrero et al., 2017), the absence of fidgety movements is highly predictive of cerebral palsy (sensitivity of 98%, (Novak et al., 2017)). However, absence of fidgety movements is also attributable for genetic disorders with a late onset (Einspieler et al., 2012; Einspieler, Peharz, & Marschik, 2016 ; Herrero et al., 2017).

Apart from the global GMA we applied the following age-specific detailed scores: (a) at term age, the GMOS, focussing separately on the movement quality of the neck, trunk, upper and lower extremities, with a maximum score of 42 and a minimum score of 5 (Einspieler, Marschik et al., 2016) and (b) at 3 to 5 months PTA, the MOS, focussing on the repertoire and quality of movement and postural patterns, with a maximum score of 28 and a minimum score of 5 (Einspieler et al., 2004). The higher the total optimality score is the better is the quality of general movements. Monotony of the movement repertoire is defined as a lack of smoothness, fluency, and complexity. Typical movement patterns co-occurring with fidgety movements include hand-to-hand contact, hand-to-mouth contact, fiddling with clothes, reaching out and touching, leg lifting with or without hand-to-knee contact, wiggling-oscillating arm movements, and segmental movements. Wiggling-oscillating arm movements are defined as irregular, oscillatory, waving-like movements of small amplitude and moderate speed. They must not be confused with tremulous movements, which are less smooth in appearance and have a more regular rhythm (Einspieler et al., 2004). Abnormal wiggling-oscillating arm movements are waving-like movements with a high amplitude, either too slow or too fast, lacking smoothness. Segmental movements are distal movements of flexion, extension and rotation, occurring either in isolation or as part of general movements, but not as part of a global pattern of limb flexion or extension (Cioni et al., 2000; Guzzetta et al., 2003).

Video recordings of our patient were performed on days 8 and 15, and at 11, 17 and 27 weeks. The videos were evaluated by two experts in the field (J.P., C.E.) according to the Prechtl method of global and detailed assessment (Einspieler, Marschik et al., 2016; 2004). The scorers applied the GMA with full agreement.

2.3. Pre-linguistic verbal development

The SAEVD-R provides a scheme for classifying early vocalisations (Nathani et al., 2006). It comprises 23 mutually exclusive vocalisation types assigned to five age-related levels of complexity in typically developing infants: level 1 (Reflexive, 0–2 months), level 2 (Control of Phonation, 1–4 months), level 3 (Expansion, 3–8 months), level 4 (Basic Canonical Syllables, 5–10 months), and level 5 (Advanced Forms, 9–18 months).

The absence of certain verbal behaviours may be an indicator of a general developmental delay, a deviant realization pattern or even peculiarities in the vocal repertoire may point to (specific) developmental disorders (Grieco et al., 2018; Marschik, Pini et al., 2012; Marschik et al., 2013; Pokorny et al., 2018; Roche et al., 2018) Among these patterns monotony, or the reduced variability of age-specific vocalizations, is discussed to be a reliable marker of maldevelopment (Brisson, Martel, Serres, Sirois, & Adrien, 2014; Marschik, Einspieler, & Sigafoos, 2012; Paul, Fuerst, Ramsay, Chawarska, & Klin, 2011; Pokorny et al., 2018).

At 27 weeks we analysed the infant's pre-linguistic verbal development on the basis of a 10-minute (audio-)video recording. A total of 62 pre-linguistic vocalisations (not including vegetative sounds) were identified, segmented, and annotated according to the SAEVD-R (Nathani et al., 2006). Two professionals in the field of early speech-language development (F.B.P., K.D.B.P.) conducted the annotation process. In case of disagreement, the annotators re-evaluated the vocalisation in question until consensus was achieved.

3. Results

3.1. General movements

A GMA on day 8 revealed hypokinesia. On day 15, general movements were scored as poor repertoire with a monotonous sequence, the neck hardly involved, and just a few rotations of the trunk. Movements of the upper extremities were monotonous and slow, with a limited space range, monotonous amplitude, few rotatory components, and minimal fluctuations of the onset and offset. Tremulous movements occurred in the left arm. Movements of the lower extremities were monotonous and slow, with a monotonous amplitude, limited space range, and few proximal rotatory components, no distal rotations, and minimal fluctuations of the onset and offset. Cramped components of his legs were occasionally present. The GMOS was 22/42 (52%).

At 11 weeks PTA the boy showed no fidgety movements. Detailed assessment revealed an age-inadequate movement repertoire, abnormal wiggling-oscillating arm movements, and asymmetrical segmental movements. The boy was unable to keep his head in midline and his body posture was asymmetrical. He fisted his right hand and showed only few finger postures with his left hand. His legs lay flat on the surface most of the time. The movement character was monotonous. The MOS was 6/28 (21%).

At 17 weeks the boy showed no age-adequate movements other than normal intermittent fidgety movements, normal side-to-side movements of the head, and visual scanning. His body posture was still asymmetrical, the head not in midline. Finger movements were sporadic in both hands. The overall movement character was still monotonous. The MOS was 20/28 (70%).

At 27 weeks we could still observe intermittent fidgety movements, as well as normal bursts of excitement, smiles, side-to-side movements of the head, hand-to-mouth contact, hand-to-hand contact, foot-to-foot contact, and visual scanning. However, there were also repetitive abnormal swipes of his arms. The movement repertoire was still not age-adequate, and the movement character monotonous. The MOS is not applicable beyond 20 weeks PTA.

3.2. Pre-linguistic verbal development

The infant primarily produced vowel glides representing vowel-like sounds exhibiting a slow change (> 200 ms) in vowel quality over time. Vowel glides are classified as level-3 vocalisations, which typically occur at 3 to 8 months of age. The distribution of vocalisations of the respective levels according to the SAEVD-R (Nathani et al., 2006) showed a predominance of level-3 vocalisations with 3 level-1, 22 level-2, 37 level-3, and 0 level-4 vocalisations, respectively. Although the high proportion of level-3 vocalisations was age-adequate, no level-4 vocalisation (characteristic for the period from 5 to 10 months) was noted. Moreover, vocalisation quality appeared partly monotonous and with a peculiar harmonic structure.

4. Discussion

This is the first report enhancing our knowledge on the early development of an infant with PWS. Early motor and pre-linguistic verbal behaviours were peculiarly monotonous during his first 6 months of life.

The boy moved very little from birth onwards, which might be attributable to muscle hypotonia. In general, muscle hypotonia during the first weeks of life is not a specific sign of later neurological deficits (Prechtl, 1997, 2001), and might even be a transient phenomenon. However, in infants with PWS, muscle hypotonia is a distinctive feature, but may vary in severity (mild to severe; (Whittington, Butler, & Holland, 2008)).

At 2 weeks, movements increased in terms of quantity, but remained monotonous, which reveals a significantly reduced GMOS (22/42). A similarly monotonous movement pattern has been reported for other genetic disorders such as Cornelia de Lange syndrome (Marschik et al., 2015), Rett syndrome (Einspieler et al., 2005), and Down syndrome (Mazzone et al., 2004), which is indicative of an impaired integrity of cortical-subcortical networks (Hadders-Algra, 2018).

While fidgety movements normally emerge between 4 and 8 weeks PTA with a continual appearance between 12 and 14 weeks and a gradual ending at 20 weeks PTA (Ferrari et al., 2016), our infant showed no fidgety movements at 11 weeks. His fidgety movements did not appear before 17 weeks, and lasted until 27 weeks.

Infants with Down syndrome, have normal, abnormal, or absent fidgety movements at 3–5 months of age (Herrero et al., 2017). As muscle hypotonia is a distinctive feature not only of Prader-Willi syndrome but also of Down syndrome (Tudella, Pereira, Basso & Savelsbergh, 2011), it remains unclear whether abnormal general movements are related to muscle hypotonia or the underlying genetic disorder.

Hadders-Algra recently hypothesised that "the emergence of fidgety movements reflects a developmental transition from

widespread to fragmented cortical network activity" (Hadders-Algra, 2018). We should like to add that the delayed emergence of fidgety movements in our infant might be an early indicator of a developmental delay which was also confirmed by a delay in acquiring early motor milestones such as midline and antigravity movements, as reflected in his reduced MOS.

We may also hypothesise that the absence of level-4 vocalisations at 27 weeks PTA might be the first sign of delay in early verbal development and a precursor to speech-language dysfunction. While we are fully aware that our analysis of verbal development was based on a single 10-minute audio recording, we would like to stress that both early motor and pre-linguistic verbal behaviours were monotonous throughout all our observations.

Encouraging brain plasticity (Ismail, Fatemi, & Johnson, 2017), counselling of the parents, enhanced handling, and early multidisciplinary interventions in the first days to weeks after birth may improve the early development and quality of life for infants with PWS, particularly if initiated at a younger age (Bachere et al., 2008; Donze et al., 2018; Myers et al., 2007; Reus et al., 2013).

Although the majority of infants with PWS (90%) are diagnosed within the first 3 months of life, some neonatal cases are missed because of unrecognized clinical signs (Bar et al., 2017). Bar et al. recently reported of two infants, who were diagnosed with a remarkable delay, at 11 and 17 months, respectively. Assessments of general movements, age-specific detailed scores (GMOS around term age (Einspieler, Marschik et al., 2016), and MOS at 3–5 months post-term age (Einspieler et al., 2004)) and pre-linguistic verbal assessments (applying the SAEVD-R (Nathani et al., 2006)) may help to define symptom clusters related to specific disorders, essential for fine grained recognition approaches of infants without apparent or significant features. GMA and early pre-linguistic assessments may enhance early diagnosis in infants with and without distinctive features. Early diagnosis is mandatory for initiation of early intervention. GMA and pre-linguistic verbal assessments may not only enhance early diagnosis, but also identify improvements and deteriorations in development after initiation of interventions.

Because of the great variability in psychomotor development in infants and toddlers, our findings cannot be generalized and have to be reassessed in bigger cohorts of infants with PWS. Special attention should be given to trajectories of general movements (Manacero, Marschik, Nunes, & Einspieler, 2012) and of pre-linguistic verbal behaviours in infants with PWS. Providing comparative data of early motor and pre-linguistic verbal behaviour may help to define potential specific patterns and precursors of later development.

5. Conclusion

Apart from typical characteristics of Prader-Willi syndrome such as hypotonia, feeding problems and craniofacial characteristics, early motor and pre-linguistic verbal behaviours were peculiarly monotonous in an infant with PWS throughout his first 6 months of life. Our findings might shed some light upon early pathomechanisms of PWS and show once more that the "how" outweighs the "if", since the behavioural monotony was obvious before its lack of age-adequacy. Obviously our findings need to be verified in a larger cohort.

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Declarations of interest

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