Early behavioural manifestation of Smith-Magenis syndrome (del 17p11.2) in a 4-month-old boy

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Abstract
Objective: There is little systematic data on early neurodevelopmental functioning of infants with Smith-Magenis syndrome, since early diagnosis is rare.
Methods: A boy with cytogenetically confirmed Smith-Magenis syndrome was videotaped at 4 months and 1 week of age. His posture and spontaneous movements were analysed without knowing the diagnosis.
Results: The motor repertoire appeared significantly reduced; fidgety general movements, which are typical of that age, were missing. Posture was abnormal and overall movements were jerky and monotonous. The findings indicate a severe motor impairment by no more than 4 months of age.
Conclusion: It was concluded that an absence of fidgety movements that goes along with subtle dysmorphic features indicates an increased risk of maldevelopment and justifies the need to refer for genetic evaluation with the potential of facilitating earlier diagnosis.

Keywords: Fidgety movements, general movements, infant, posture, video analysis

Introduction
Smith-Magenis syndrome is a distinct and clinically recognizable multiple congenital anomaly caused by an interstitial deletion of chromosome 17p11.2 or mutations in the RAI1 gene [1, 2]. The phenotype displays a characteristic pattern of physical features (brachycephaly, mid-face hypoplasia, a prominent forehead, upslanting palpebral fissures, epicantal folds, brachydactyly, short stature), developmental delay (especially in the speech/language domain), cognitive deficits, clinical signs of peripheral neuropathy and neurobehavioural problems including sleep disturbances and maladaptive, self-injurious behaviours [1]. The prevalence is estimated to be as high as 1 in 25 000 births [3].

Despite increased clinical awareness as well as improved cytogenetic technologies, many children are not definitely diagnosed until early childhood or even school age, when the phenotypic features become more prominent [4–7]. Facial dysmorphology can be quite subtle during infancy: a broad, square-shaped face; mild mid-face hypoplasia; a short, upturned nose; a fleshy, everted upper lip; and micrognathia are usually observable but do not necessarily point to Smith-Magenis syndrome [5, 8]. Parents often describe their infant as ‘perfect baby with a cherubic appearance, who cries infrequently’ [5]. In fact vocalizations, especially babbling, are markedly decreased, but usually do not worry parents before an age of 12–18 months, for the social behaviour is still inconspicuous [5, 7]. At that age, the delay in gross motor function also becomes obvious and parents notice significant sleep disturbances, although actigraphies suggest that the disrupted sleep pattern sets in by as early as 6–9 months of age [5].

In a recent study on the natural history of Smith-Magenis syndrome, Wolters et al. [7] prospectively assessed 11 children at an age between 5–34 months. Nine patients—one of whom was 5.5 months old—were examined neurologically; all infants had a mild or moderate generalized hypotonia that affected their motor development; only two children exhibited depressed deep tendon reflexes.
the others had normal reflexes; three children had fine motor tremor. The authors summarized that the motor functioning of the four infants near 1 year of age or younger varied from normal to mildly or moderately delayed [7].

As diagnosis of the syndrome is rare during infancy, the main sources of information regarding early development and behaviour are retrospective parental descriptions and chart reviews. However, parental reports of this kind may be biased. An objective way of evaluating behavioural abnormalities is the analysis of video recordings [9]. Recent analyses of family videos proved a valuable source for an assessment of early signs of disorders. Previously, early development (e.g. in the case of regressive autism or Rett syndrome) had often appeared normal but was not [10–12].

It is almost impossible to carry out prospective behavioural analyses of rare disorders. The authors were recently conducting a longitudinal study on the predictive value of infantile movements and postures (videotaped at 3–5 months of age) for later neurological deficits [13]. The study group consisted of 40 high-risk infants admitted to the Department of Paediatric Neurology and Rehabilitation, St. Joseph’s Hospital, Kyoto (Japan). One of the infants happens to have been diagnosed with cytogenetically confirmed Smith-Magenis syndrome. Since the diagnosis was not known at the time of analysis, the results are considered to be obtained prospectively. The aim of the study was to meticulously describe the motor behaviour at age 3–5 months.

Methods

Participant

The patient, a boy, was born in 2004, at 40 + 3 weeks’ gestation. He was the second child of a 35-year-old healthy mother. Pregnancy, delivery and development of the first child were uneventful. The index pregnancy was complicated by vaginal bleeding (first trimester) and oedema (third trimester). A decrease of foetal movements had not been recognized. The delivery was uneventful; Apgar scores were normal; birth weight (3204 grams), length (49 cm) and head circumference (34 cm) were within the normal ranges. The neonatal period was complicated by long-lasting apnoeas (during the first 2 days of life) and hyperbilirubinemia. Brain ultrasound revealed mild ventricular dilatation. Due to atrial septal defect, inguinal hernia, small hands and feet and mildly malformed ear lobes, the boy was referred to standard cytogenetical testing, which revealed a deletion in 17p11.2 (Smith-Magenis syndrome) at the age of 1 month.

Conductive hearing impairment was diagnosed at 10 months of age. Gross motor development was delayed: the boy only started to ambulate at 20 months. Language development was significantly impaired: aged 4 years, he merely spoke three words (‘yes’, ‘Mum’, ‘Dad’); during the subsequent year he acquired a number of additional words, but could not combine them.

Procedure

At the age of 4 months and 1 week, the boy’s spontaneous motor behaviour was videotaped in a standard setting [14] for 7 minutes during active wakefulness. The boy was partly dressed, lying in supine. General movements and the concurrent motor and postural repertoire were assessed in separate runs of the video tape by three observers (MY, CE, PBM) who were unfamiliar with the diagnosis. No phenotypic features could be deduced from the video. Inter-observer agreement revealed a Fleiss’ Kappa from 0.82 (assessment of posture) to 1.00 (assessment of fidgety movements).

The parents gave written informed consent. The study was conducted with the approval of the Ethical Review Board of the Kyoto Prefectural University of Medicine.

Results

The most striking finding was that the motor repertoire was not adequate to the boy’s age: the so-called fidgety movements, which are typical of 3–5-month-old infants, were missing altogether. These age-specific general movements are small movements of the neck, trunk and limbs in all directions and of variable acceleration [15]. Virtually all infants develop normally if such fidgety movements are present and normal, even if their clinical history indicates a disposition to later neurological deficits. Conversely, if fidgety movements are absent between 3–5 months of age, almost all infants develop neurological deficits, even if clinical data do not indicate a significant risk [16, 17].

Apart from some jerky limb movements, the boy made only a few hand movements towards his face. There were no other hand movements towards the midline such as hand-to-hand contact or fiddling with his clothes. Foot-to-foot contacts could be observed but were abnormal: small distal movements were lacking and the legs mainly touched on the tibial side. There were only a few finger movements, with a limited number of finger postures between the movements. The boy could not keep his head in the midline; his arms and legs were predominantly extended. The overall movement character was jerky and monotonous. Based on the
score sheet for the assessment of motor repertoire at 3–5 months ([18], p. 34), the boy's motor optimality score was 10 (the maximum score for an optimal performance = 28).

Discussion
Even though the study by Gropman et al. [5] revealed that nine out of 19 mothers of children with Smith-Magenis syndrome had noticed a decrease of foetal movements, this report is the first to document a behavioural manifestation of the syndrome by as early as 4 months of age.

Various work groups have emphasized the significance of fidgety movements for an early prediction of the neurological outcome at toddler's age or older [15–17]. Fidgety movements are absent in all sub-types of later cerebral palsy, which indicates that it takes intact cortico-spinal fibres and normal outputs from the basal ganglia to generate normal fidgety movements [19]. Fidgety movements are also absent — or at least abnormal — in infants with autism spectrum disorder [20] and Rett syndrome [21, 22], whereby the infants with the most severe phenotypes show no fidgety movements when aged 3–5 months, while otherwise their neurodevelopmental status was found to be more or less normal. In this context, it is of interest that in a recent study on 26 individuals with Smith-Magenis syndrome, the majority of them met criteria for autism spectrum disorder [23].

Although these findings — based on standardized, objective and prospective video analysis — cannot be regarded as specific for Smith-Magenis syndrome, they do contribute to a better understanding of the natural history of this disorder: the lack of age-specific fidgety movements indicates a severe motor impairment at such an early stage of development.

The fact that the boy was unable to keep the head in midline—which would have been appropriate for his age—could indicate low muscle tone, as described by all work groups in young children with Smith-Magenis syndrome [1, 5–8]. However, one should be aware that, on the basis of a video, it is neither possible to evaluate active muscle power nor resistance against passive movements.

Conclusion
The absence of fidgety movements and the presence of certain dysmorphic features, albeit subtle, indicate such a risk of maldevelopment that both genetic testing and early physiotherapeutic intervention are justified. Early intervention can have a positive effect on the child's future functional abilities. Psychological support for parents, maximal functional deployment and early adaptation of the affected child are crucial to improve the developmental outcomes.

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References


