Published in final edited form as:

Dev Neurorehabil. 2015 ; 18(4): 280–282. doi:10.3109/17518423.2013.859180.

General Movements in genetic disorders: a first look into Cornelia de Lange syndrome

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Abstract

The assessment of General Movements (GMs), i.e. age-specific motor patterns during the first months of life, has repeatedly proven to be a valuable tool to predict neurodevelopmental outcomes. Abnormal spontaneous GMs were found to be among the most reliable markers for cerebral palsy. To add to the knowledge of the abnormal early motor repertoire we analysed prospectively collected video recordings of a boy clinically diagnosed with Cornelia de Lange syndrome. The observed atypical GMs are a further step to disentangle early motor peculiarities in the light of the genetic impact on the developing brain.

General Movements (GMs) and their assessment were introduced by Heinz Prechtl and colleagues in 1990 [1] and have since then repeatedly proven to be a valuable tool to predict neurodevelopmental outcomes [e.g., 2–6]. GMs are age-specific motor patterns during the first months of life that comprise the entire body and manifest themselves in variable sequences and varying intensity and speed of arm, leg, neck and trunk movements. Frequent variations of the direction of motion and rotations make them look complex and smooth [7]. Monotonous sequences of movement components and the lack of variability in amplitude, speed, and intensity are considered abnormal GMs and classified ‘poor repertoire’ (from birth to 8 weeks postterm age) [e.g., 1,7,8].

The assessment of GMs is based on visual Gestalt perception in preterm infants and term infants aged up to 5 months. Abnormal spontaneous GMs were found to be among the most reliable markers for cerebral palsy [2,7]. Summary estimates of sensitivity and specificity were 98% (95% confidence interval 74–100%; [5]). Apart from acquired brain lesions, abnormal GMs were inter alia described in infants with visual impairment [9], inborn error of metabolism [10,11], but also in infants later diagnosed with autism spectrum disorders

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Declaration of Interest

The authors report no conflict of interest. The authors alone are responsible for the content and writing of the paper.

[12–14] or genetic disorders such as Down syndrome [15], Rett syndrome [16,17], or Smith-Magenis syndrome [18].

To add to the knowledge on the variability of the abnormal early motor repertoire we analysed prospectively collected video recordings of a boy clinically diagnosed with Cornelia de Lange syndrome (CdLS) recorded at 36 weeks of gestation and at 5 weeks postterm age. CdLS is a rare, clinically and genetically heterogeneous disorder diagnosed on the basis of clinical observation. Mutations in the genes NIPBL, SMC1A, SMC3, RAD21 and HDAC8 are known to be causal factors (mutations in NIPBL account for 60%, SMC1A for ~5% and SMC3 for less than 1% of the known cases; <http://www.ncbi.nlm.nih.gov/books/NBK1104/>). Among the clinical characteristics are various facial features, hirsutism, synophrysm, growth retardation, upper limb defects, congenital heart disease, gastrointestinal malformations, microcephaly etc. [19–21]. For the classical as well as the mild forms later neuropsychiatric symptoms that occur frequently are hyperactivity, self-injurious behaviour, aggressive behaviours, autistic like and compulsive behaviours [e.g., 19,22,23].

The infant reported on here was included in a high-risk population study of children born preterm at the Carmel Medical Center, Haifa (Israel). He presented with intra-uterine growth retardation and was born at 34 weeks gestation with a birth weight of 1293g. Classic CdLS was diagnosed immediately after birth as the participant presented with typical morphological features, such as hirsutism, growth retardation, and upper limb defects including oligodactyly. No known genetic conditions were reported to be present in the family. A detailed GM assessment of two comprehensive recordings at preterm and early postterm age revealed the following results: The preterm GMs at 36 weeks were classified as 'poor repertoire' and generally presented at slow pace and small amplitude compared to typical GMs. Apart from very 'poor repertoire GMs' the motor repertoire comprised some isolated leg movements, again of slow pace, and sporadic finger movements that lacked variability if benchmarked against typical development.

The clinical picture did not change until the next video based assessment at 5 weeks postterm age. The age-specific pattern, the so-called 'writhing GMs', were again of slow speed and small amplitude. The movement sequences appeared monotonous, again fulfilling the classification criteria of 'poor repertoire GMs'. Interestingly, we observed some variable rotatory components in the proximal and distal parts of the lower extremities. Several minutes lasting tongue protrusion was among the salient behavioural features.

These observations add to the heterogeneous clinical picture of 'poor repertoire GMs'. Even though of limited predictive validity [24] 'poor repertoire GMs' are an early marker for a non-optimal condition of the developing brain. Interpretations of this abnormal motor pattern have to be drawn on a cautionary note, as its presence does neither precede severe neurodevelopmental impairment nor exclude a normal outcome [2,7,24]. To circumvent this dilemma and to reliably estimate developmental trends a trajectory of GMs, including an assessment of 'fidgety GMs', that are usually present from 9 to 16 weeks post term age, is essential. Even though adding to the knowledge on 'poor repertoire GMs' we consider it a limitation, that we could not re-assess the participant during the period of 'fidgety GMs'.

A further finding in the analysis of the motor repertoire of the case reported here was a restricted repertoire in upper extremities compared to the lower ones. A detailed assessment of GMs clearly revealed less variability in terms of quantity and quality of movements in the upper- vs. lower extremities. We thus observed functional and morphological abnormalities in the upper extremities, the latter of which are seen in about 25% of all cases with CdLS [19]. The frequency of present functional peculiarities in CdLS needs yet to be determined.

An additional parameter, the observed protrusion of the tongue has been reported in young infants with a number of neurodevelopmental disabilities. The simultaneous appearance of abnormal GMs and long lasting or repetitive tongue protrusion has to date been reported for infants with Rett syndrome [25], but a more comprehensive study of this cooccurrence would potentially add to narrow down early markers for severe maldevelopment.

To conclude, even though a case study, these findings are additional proof of the power of Gestalt perception, especially the GMs, to provide valuable information on the integrity of the young nervous system. For the time being, abnormal GMs may be considered a general marker of maldevelopment and a tool to delineate and to some extent predict neurological outcomes in individuals with genetic disorders. In the near future we expect them to be an essential parameter, among others, to account for the identification of specific disorders. Certainly, a more in-depth study including additional cases is needed to generalize findings and perform cross syndrome comparisons. Besides the targeted detailed analysis of GMs in a larger sample of infants with CdLS, recordings during the period of 'fidgety GMs' would bear essential additional information to understand the disorder and provide comparative data to define potential specific signs.

The appearance and implications of atypical GMs in genetic disorders have not yet been intensively studied nor fully understood. Especially when it comes to describing and defining potential syndrome-specific peculiarities we are far from knowing it all. This report is thus a further step to disentangle early motor peculiarities in the light of the genetic impact on the developing brain and hopefully the spark to light a great bonfire.

Acknowledgements

PBM supported by the FWF P25241, Lanyar foundation (P337, 374) and the state of Styria.

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