HISTORICAL ARTICLE

Methodological note: Video analysis of the early development of Rett syndrome—one method for many disciplines

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Rett syndrome is a profoundly disabling X-linked neurodevelopmental disorder that predominantly, but not exclusively, occurs in females. It is mainly caused by mutations in the gene MECP2 for methyl-CpG-binding protein 2 (Xq28 [1]); recently, CDKL5 and FOXG1 have also been described to correspond with the early-seizure onset variant and the congenital variant of Rett syndrome [2, 3]. MECP2 is primarily expressed in neurons, when they become functionally mature, and before synaptogenesis [4]. Hence, Rett syndrome should be understood as a genetic interference with normal brain development rather than the result of tissue loss or destruction.

Mutations in the gene MECP2 can be found in 95–97% of girls with classic Rett, but only in 50–70% of its variants [5, 6]. There are, however, girls who show the clinical criteria for Rett but no MECP2 mutation, asymptomatic female carriers and boys with MECP2 mutations who exhibit severe post-natal encephalopathy and die early. Furthermore, individuals with a MECP2 mutation but different neurodevelopmental disorders like autism, Angelman syndrome or intellectual disabilities not otherwise specified have been described. Hence, MECP2 mutations are neither necessary nor sufficient for the diagnosis of Rett syndrome. Consequently, the diagnosis is clinical and is based on consensus clinical criteria that were recently re-defined [5]. The presence of a regression period that goes along with the following four main criteria constitutes the basis for the diagnosis of Rett syndrome [5]: (1) partial or complete loss of acquired purposeful hand skills; (2) partial or complete loss of acquired spoken language; (3) gait abnormalities; and (4) stereotypic hand movements (e.g. wringing, washing, mouthing). Furthermore, two exclusion criteria for typical Rett and 11 supportive criteria for atypical Rett were defined. Rett syndrome has been reported to typically manifest in a four-stage trajectory: an apparently inconspicuous early development is followed by a stagnation (pre-regression period, Stage I) and furthermore by the loss of certain abilities (regression period, Stage II). Regression of various functions such as communication, fine motor abilities and gross motor abilities sets in at individual points in time (8–18 months) [5, 7, 8]. At Stage III a certain improvement of behaviour may be noticed. Stage IV, the late deterioration stage, is characterized by severe cognitive and motor impairment.

Focusing on the early development (i.e. before the onset of regression) a number of researchers, clinicians and parents have assumed that the early development of girls with Rett is not asymptomatic, as had been previously believed [9–15]. Admittedly, the subtlety of peculiarities and the intermittent character of typical and atypical age-specific behavioural patterns make it difficult to detect the disorder before the onset of profound regression [5, 11, 14, 15]. One methodological approach to get around this issue to a certain extent and yet assess the early behavioural characteristics comprehensively is the retrospective video analysis. This method is based on family videos recorded at a time when parents were not aware of the...
neurodevelopmental disorder of their child (the diagnosis is often unclear until toddler age). It enables one to focus on behavioural peculiarities before diagnosis and to identify early developmental abnormalities, thus providing new insights and a better understanding of the early development of Rett syndrome and Autism Spectrum Disorders in general [11, 16–18]. It has, thus, proved to be a valuable and practical instrument for the identification of physiological, behavioural and cognitive functional features and details that are hard to capture otherwise. Even more importantly, it has become a substantial tool for a thorough description of developmental trajectories and the improvement or regression of functions.

Nonetheless, the retrospective video analysis has certain limitations as a tool for the interdisciplinary analysis of a particular genetic disorder. One of its most prominent insufficiencies is the absence of certain features in a given data set: if a particular behavioural pattern like babbling is missing, for instance, this does not necessarily mean that the pattern in question is missing in the socio-communicative repertoire of the participant [15, 17]. Video analysis allows one to describe observable phenomena and point out peculiarities, but one must never conclude that the absence of a sign or typical feature is definite. This potential for incomplete or biased information is accompanied by the difficulty to obtain standardized material that allows an objective comparison of inter-individual differences [16, 17, 19]. Furthermore, the application of the method needs extensive observer training and detailed coding protocols, in order to obtain high inter-observer reliability.

The strength of video analysis lies in the description of observable behaviour which, in the case of Rett syndrome, clearly deviates from the typical age-specific developmental patterns [11, 13, 20]. Here, the video-based general movement assessment as a means to functionally assess the nervous system at an early stage has proved to be a valuable tool in detecting excellent markers and predictors for cerebral impairment and dysfunctions [12]. Numerous studies have shown that the age-specific general movements between the third and fifth months of life [11, 13, 20]. The deviation of the mentioned early motor behaviour is not specific to Rett syndrome, as it has also been found, e.g., in infants with retinopathy of prematurity [21]. Interestingly enough, in the case of Rett syndrome, abnormal general movements co-occur with simultaneous or subsequent subtle signs such as asymmetric blinking, long-lasting or repetitive tongue protrusion, hand stereotypies, bizarre smiling and atypical vocalizations as early as during the first 6 months of life [11, 13, 15]. It remains to be clarified, however, whether the co-occurrence of these signs constitutes a symptom constellation typical of Rett disorder. Further detailed developmental analyses are needed in order to deduce general developmental trends and gain a better neurobiological understanding of this specific developmental trait. It requires a profound interdisciplinary approach across various methods of research—video analysis being one of them—so as to document the inter-relation between a number of developmental domains and to piece together the jigsaw of neurodevelopmental disorders with a late (noticeable) clinical onset.

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References


