

Case Report: Retracing Atypical Development: A Preserved Speech Variant of Rett Syndrome

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Abstract The subject of the present study is the development of a girl with the preserved speech variant of Rett disorder. Our data are based on detailed retrospective and prospective video analyses. Despite achieving developmental milestones, movement quality was already abnormal during the girl's first half year of life. In addition, early hand stereotypies, idiosyncratic vocalizations, asymmetric eye opening, and abnormal facial expressions are early signs proving that this variant of the Rett complex, too, manifests itself within the first months of life.

Keywords Autism spectrum · Development · Genetic disorder · General movements · Language · MECP2 · Stereotypies

A Rett variant shares with the classical Rett syndrome the same staging and a number of symptoms including hand stereotypies. Girls with the Preserved Speech Variant (PSV) preserve or recover speech and language abilities to a certain

extent and can potentially improve their purposeful hand movements (Zappella 1992; Hagberg and Skjeldal 1994; Zappella et al. 1998; Renieri et al. 2008). The majority of patients carries either missense mutations, especially the p.R133 change, late truncating mutations in the *MECP2* gene but also at least in one case an early truncating mutation (Renieri et al. 2008). As the diagnosis of Rett syndrome and its variants is tentative until at least toddler age, there is little comprehensive knowledge of pre-diagnostic development. The only objective evaluation of possible behavioral abnormalities before regression consists in a close analysis of family videos from the first 2 years of life. We provide a unique case report of a girl with a PSV, having observed her neurological and socio-communicative development longitudinally over a period of 10 years.

Subject

At the age of three, a girl born in Germany in 1998 was clinically diagnosed with Rett syndrome. Genetic testing at 3 years and 9 months of age revealed a large intragenic deletion (c.378-43_964delinsGA). This mutation most probably causes a complete loss of function of MeCP2. The patient meets, however, the inclusion criteria for Rett variants (Hagberg and Skjeldal 1994) and is now classified as PSV (Zappella et al. 1998). The girl was a singleton birth at 40 weeks of gestation; birth weight 2,970 g; length 53 cm; occipitofrontal circumference 34 cm; Apgar scores 9 (1 min) and 10 (5 min).

Methods

The focus of this report lies on longitudinal observations of age-specific motor and postural patterns as well as the

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child's behavior, documented by videotapes. We retrospectively analyzed family videos, parental diaries and the medical history of the first years of life. Prospectively, the following assessments were applied: the Austrian Rett survey; behavioral observations in the girl's natural surroundings; the Austrian Communicative Development Inventories (Marschik et al. 2007); spontaneous speech samples; various language development tests. Observational data were obtained by means of the Observer program (Noldus Information Technology, The Netherlands). Two independent scorers (CE, PBM) achieved a high interscorer agreement (Cohen's Kappa = 0.91).

General Motor Performance

At 6 months of age the girl could roll from supine to prone and back; she had a good anticipatory shift of the center of gravity before reaching sideward or upward while sitting; she crawled at 9 months and stood free at 11 months; she walked independently at 14 months. At 17 months she performed coordinated belly dancing. Despite achieving the gross motor milestones, she showed abnormal movements during her first months of life. The body movements that are most common at this early stage are so-called general movements with a strictly age-specific appearance (review: Einspieler and Prechtel 2005). Our test subject showed fidgety general movements that were abnormal and slow in comparison with normal fidgety movements (i.e. continual small movements of moderate speed with a variable acceleration of neck, trunk and limbs in all directions) (Prechtel et al. 1997).

Although the girl developed coordinated crawling, she exhibited excessive rolling between 8 and 10 months of age. At 2 years and 4 months of age her gait became instable and the gait width was broad, invariable and maladjusted.

Hand and Finger Movements

Aged 3 months, the girl reached for objects; at 8 months she demonstrated good pincer grasping; at 10 months she started using gestures to express needs, including index finger pointing; at 14 months she could feed herself and drink from a cup. However, when she started pincer grasping she also touched objects with undifferentiated movements with her fingers mainly extended. Stereotypical hand movements for the first time occurred at the age of 6.5 months in terms of repetitive uni- or bilateral hand pronation with simultaneous wrist dorsiflexion and finger spreading. These stereotypical hand movements co-occurred but were not synchronized with repetitive opening and

closing of the mouth. Aged 16 months, she occasionally exhibited wiping hand movements; at the age of two, we observed the first excessive hand rubbing after the girl got frustrated.

Facial Expressions

Every now and then, blinks were rare. At 7 months of age the girl even showed a prolonged phase of staring. In addition, eye opening after a blink was sometimes performed asymmetrically. At 2 years and 4 months of age, the first awkward mouth movements and bizarre grimaces were observed. At the age of 6 months, repetitive unmodulated vocalizations were present. At the same age the girl showed bursts of abnormal facial expressions consisting of several repetitions of the following sequence: head in midline with neutral facial expression (second 1); head turned sideward with a crying expression often combined with atypical inspiratory vocalization (second 2); head in midline with neutral facial expression (second 3); etc.

Early Communication

Normal babbling was interspersed with atypical episodes of forceful and/or inspiratory vocalizations often associated with grimaces of effort. Intentional gestures were limited and partly used in an inappropriate manner. The girl uttered her first words around her first birthday but was unable to combine words before the regression period.

Apparently Reduced Nociceptive Sensitivity

It was remarkable that the girl did not complain when her excessive rolling locomotion was stopped by bumping into the door frame; when walking barefoot on gravel; when falling down; and even when plunging her head under water.

Regression Period

By the time the girl was aged two her parents were seriously concerned: previously acquired language skills had worsened or entirely disappeared; she withdrew from normal social contact; she would run around aimlessly and in a disquieting manner, often screaming; purposeful hand movements had deteriorated; she gradually lost the ability to feed herself and half a year later stopped using her right hand. Rubbing and washing hand movements as well as

hand-to-mouth and hand-to-tongue contact and manipulations became more frequent. Our video analysis has confirmed the parents' concerns.

At the age of three, Rett syndrome was clinically diagnosed. Her gait had remained instable; her muscle tone was low; reduced nociceptive sensitivity was confirmed. Autistic features became more prominent and her behavior was increasingly dominated by routines, obsessions and ritual actions.

Post-regression Period

Over the next 4 years lost or fragmentarily preserved skills were slowly regained. This period was marked by a slow but steady improvement of gross and fine motor functions, a reduction of autistic behavior; and by a recovery of speech and language. Her phonological and morphosyntactic skills, the lexicon size and composition as well as the complexity of phrasal structures slowly increased, albeit frequently accompanied by idiosyncratic vocalizations, rhythmic prosodic events, and out of context speech.

Current Status

Today, at 10 years of age, the girl has a relatively complex language system with a lexicon size comparable with that of a preschooler. Nevertheless, she has a limited accuracy of articulation and a significant phonological deficiency. There are also morpho-syntactic and socio-pragmatic limitations as well as dysfluency of speech, mostly caused by immediate echolalia or repetitive questioning.

She still shows autistic behavioral characteristics such as finding it hard to recognize borders of intimacy. She needs fixed patterns and shows obsessive behavior (e.g. repetitive checking if there is enough bread). She can be described as hyperkinetic, highly distractible and unable to make decisions. She is hypersensitive to noise and, once excited, can hardly be calmed. She exhibits distinct mood disturbances, unprovoked bursts of anger and seemingly motiveless episodes of sadness or laughter.

She preferably uses her left hand although dyspraxia is noticeable. Hand stereotypies, which are more frequent in her right hand, predominantly consist of hand-to-mouth/tongue contacts. Bilateral hand stereotypies like washing, rubbing, or clapping movements are rare. She has regained the ability to feed herself and even uses forks and knives. Gait and balance are more stable now, but for long distances she uses a wheelchair.

The girl's head circumference is still below the 3rd percentile while weight and height are within the normal range. She shows the following satellite signs typical for

Rett syndrome (Kerr et al. 2001): mild scoliosis; muscle hypotonia; hypersalivation; moderate circulation problems in terms of cold extremities; sleep disturbances; crying spells; aerophagia and hyperventilation during episodes of excitement or anger.

It is worthwhile mentioning that beside her musical aptitude the girl takes riding lessons, does trampolining and likes swimming. Furthermore, she is able to handle a computer mouse when playing drag and drop games.

Discussion

The uniqueness of this case report is twofold: (1) we provide a longitudinal assessment of a girl with PSV based on comprehensive video data; and (2) we focused not only on the achievement of developmental milestones but also on the quality of the performance. Our detailed analysis has revealed that as early as during the first half a year of life the main pattern of motor activity (i.e. the general movements) was clearly impaired. Abnormal, slow fidgety movements, as observed in the reported case, have also been described in girls with classical Rett syndrome (Einspieler et al. 2005a, b). These abnormal movements, which correspond with neuropathological reports on brainstem impairments (Armstrong 2005), indicate deficiencies in the brainstem at this early age. In addition to these abnormal fidgety general movements, the early appearance of hand stereotypies, idiosyncratic vocalizations, prolonged asymmetric eye opening after a blink, and bursts of abnormal facial expression are in accordance with previous studies on girls with classical Rett syndrome (Einspieler et al. 2005a), which proves conclusively that this variant of Rett disorder, too, manifests itself within the first months of life. This contradicts other reports describing a normal development of girls with PSV during their first 6 months of life (Zappella 1992; Zappella et al. 1998). This discrepancy might be explained in terms of different methodological approaches: While the data of other PSV case reports on the pre-regression period are based on parental interviews and medical records, ours is the first study on the early development of a girl with PSV carried out by means of standardized video analysis. It may also be possible, that a subgroup of PSV Rett patients carrying an early truncating mutation (Renieri et al. 2008; this case) may have more likely subtle signs in their first 6 months of life. An investigation by standardized video analysis of a larger cohort of PSV patients carrying "mild" mutations could provide data to the issue of early developmental dysfunctions of those patients.

The comprehensive longitudinal analysis has revealed not only the early onset of conspicuous signs but also that these signs are interspersed with typical patterns of motor

and communicative development. The conspicuity became more and more prominent as the onset of regression was approaching. These findings might potentially help to identify a possible genetic mutation in children at an early age.

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