Is the Early Development of Girls with Rett Disorder Really Normal?

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ABSTRACT

An apparently normal early development was one of the initial criteria for classical Rett syndrome. However, several investigators considered Rett syndrome to be a developmental disorder manifesting very soon after birth. Videos of 22 Rett cases were assessed carefully for movements, posture, and behavior during the first 6 mo of life. All signs that deviated from the normal standard were recorded meticulously. Special attention was paid to the face, the hands, and body movements. A detailed analysis clearly demonstrated an abnormal quality of general movements (100%), tongue protrusion (62%), postural stiffness (58%), asymmetric eye opening and closing (56%), abnormal finger movements (52%), hand stereotypies (42%),

bursts of abnormal facial expressions (42%), bizarre smile (32%), tremor (28%), and stereotyped body movements (15%). Our study is the first to apply specific standardized measures of early spontaneous movements to Rett infants, proving conclusively that the disorder is manifested within the first months of life. Although not necessarily specific, the signs that we have observed will be of value in alerting clinicians to the possibility of the diagnosis at an early stage, when intervention is likely to be most effective. (*Pediatr Res* 57: 696–700, 2005)

Abbreviation

MECP2, methyl-CpG-binding protein 2 gene

Rett disorder is a neurodevelopmental condition resulting from mutations in the gene for methyl-CpG-binding protein 2 (*MECP2*) (1). This protein binds to methylated DNA and may function as a transcriptional repressor by associating with the DNA chromatin-remodeling complexes. Gestation and birth of the classic Rett infant is usually uneventful (2) despite pathologic evidence pointing to subtle anomalies arising already *in utero* (3,4). After unexceptional early development during the first months of life, children with Rett disorder enter a period of rapid regression during which speech and purposeful hand use diminish and cranial growth slows. They become withdrawn, develop breathing irregularity, and show gait disturbances. Repetitive hand movements (wringing, clapping, or other stereotyped motions) are characteristic of the disorder (2,5).

An apparently normal psychomotor development during the first 6 mo of life was considered as one of the criteria for classical Rett syndrome (2). However, retrospective analyses

suggested that subtle disturbances of muscle tone and feeding difficulties might be present shortly after birth (3,6). Lack of response to the environment, autistic features, and hypotonia were found in medical reports of the first months of life (3,7,8). Retrospective inquiries revealed that ~50% of the parents believed that their child's development or behavior during the first 6 mo had been unusual. The most common comments were that the infants had been particularly placid, had an empty gaze, had slept too well, and had to be woken for feeds (3,7–10). However, recall might have biased these reports.

The only objective evaluation of behavioral abnormalities is the analysis of films. On the basis of family film analyses, Carmagnat-Dubois *et al.* (11) and Holm (12) failed to identify any abnormal signs between birth and 12 to 18 mo. By contrast, in other studies of family videos, the infant with Rett disorder was observed displaying excessive bilateral hand movements (8,9), excessive hand patting, repetitive limb and trunk movements, repeated opening of the hand with which the child sought to grasp, twisting movements of wrists or arms, and repeated small twitching movements of the eyes and mouth (6,9). We considered that a careful video analysis of the early behavior of the Rett child might indicate distinct clinical features so that an early diagnosis could be considered and the infant could be tested for *MECP2* mutations.

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METHODS

Videos (including film-to-video conversions) of 22 girls who had classical Rett syndrome and were born between 1964 and 1997 were donated by British families (informed consent and ethics committee approval) for the purpose of this study and thus were available for the assessment of movements, posture, and behavior during the first 6 mo of life. This material was recorded by the families as part of their family archive without the knowledge that the child had Rett syndrome. Fifteen cases have now been mutation tested, 12 proving positive: three with the common mutation R168X, two with T158M, and the others each different (Table 1). In three girls, no mutation was found.

Data analysis. We aimed to record all motor and behavioral milestones during the first 6 mo of life. In addition, all signs that deviated from the normal standard were noted meticulously. We paid special attention to the infant's face, to hand and finger movements, and to body movements. The most frequently occurring body movements during early infancy are the so-called general movements (for a recent review, see 13). Involving the body in a variable sequence of arm, leg, neck, and trunk movements, they wax and wane in intensity, force, and speed. General movements are age specific with a writhing character until the end of the second month and a fidgety character from 3 to 6 mo, when intentional and antigravity movements gradually begin to dominate (14). An impairment of the nervous system has been previously shown to affect the quality of general movements (13–15). Special attention was paid to muscle tone despite the impossibility of evaluating active muscle power or resistance against passive movements from video. Thus, we concentrated on sequences in which postural stiffness or a slumped posture were present. Hand and finger movements were noted when they were performed abnormally or were stereotyped. In addition, any conspicuous sign was recorded regarding the face, particularly the eyes and the mouth.

The video sequences that were suitable for analysis (median duration: 11 min; range: 5 to 73 min) included the following: the infant in supine and prone

position, semi-upright held by the caregiver or in a relaxing chair, sitting with support or free, feeding and bathing situations, and short crying and sleeping episodes. The videos were analyzed by the two observers (C.E. and H.F.R.P.) separately with an interscorer agreement for the detailed scoring of 94% and once again discussed together. In addition, C.E. re-analyzed all recordings after an interval of 18 mo and found 92% agreement with the first analysis. The funding source had no involvement in the analysis and interpretation of the data.

RESULTS

A series of abnormal signs was observed throughout the first 6 mo of life. Naturally, the longer the recording, the more signs were found (Spearman rank order correlation, $p < 0.01$). Cases 11 and 12 did not demonstrate abnormal signs, but their recordings did not allow a full assessment, including the quality of general movements (Table 1).

General motor performance. Some infants demonstrated normal rooting, a proper Moro reaction, normal vestibulo-ocular responses, and an age-adequate asymmetric tonic neck response. By the third month, all infants had the head centered in the midline and a symmetrical posture in supine position. Almost all infants were able to roll over when they had reached the end of their first 6 mo. The majority of the infants had a good anticipatory shift of the center of gravity before reaching

Table 1. The absence (○) or presence (●) of various abnormal signs within the first 6 mo of life of 22 girls with Rett disorder

Case	Mutation	General motor performance				The hand			The face		
		Abnormal general movements	Postural stiffness or slumped posture	Tremor	Body stereotypies	Abnormal finger movements	Hand stereotypies	Asymmetric eye opening and closing	Tongue protrusion	Bizarre smile	Bursts of abnormal facial expression
		100% (N = 16)	68% (N = 19)	28% (N = 18)	15% (N = 13)	52% (N = 21)	42% (N = 19)	56% (N = 18)	62% (N = 21)	32% (N = 19)	42% (N = 19)
11	Not tested	*	○	*	*	○	○	*	○	○	○
12	T158M	*	○	○	○	○	○	○	○	○	○
6	Not tested	*	*	*	*	○	*	*	●	*	*
7	Not tested	●	*	*	*	*	*	*	*	○	*
8	R255X	●	*	*	*	○	*	*	○	*	*
2	806delG	*	●	○	○	○	○	○	○	*	●
5	R168X	●	●	○	*	○	○	○	○	○	○
10	Q2444X	*	○	○	○	●	○	○	○	●	○
13	P152R	●	○	●	*	○	○	○	●	○	○
21	R168X	●	●	○	*	○	○	○	●	○	○
4	Truncating deletion 1116–1201	●	●	○	○	●	○	○	○	○	●
16	Not tested	●	●	○	○	○	○	●	●	○	○
3	Negative	●	●	○	*	●	○	●	●	○	○
20	Substitution at 401†	●	●	○	*	●	●	○	○	○	●
22	Negative	●	●	●	○	○	○	●	●	○	○
17	T158M	●	○	○	○	●	●	●	●	●	○
9	Not tested	●	○	○	○	●	●	●	●	●	●
15	Not tested	*	●	○	●	●	●	●	●	○	●
19	Negative	●	●	○	○	●	●	●	●	○	●
18	Q244X	●	●	●	○	●	●	●	●	●	○
1	Not tested	●	●	●	○	●	●	●	●	●	●
14	R168X	●	●	●	●	●	●	●	●	●	●

The number of infants (N) for whom a particular sign could be reliably assessed is given. The cases are ranked according to an increasing number of abnormal signs.

* The recording did not allow a proper assessment.

† Not reported in the same format as the other cases but a pathologic mutation.

sideward or upward while sitting with support. Before the end of the sixth month, already three infants were able to sit without support (cases 1, 11, and 16).

Despite reaching this developmental milestone, two of the girls (cases 1 and 16) had an abnormal motor repertoire. This was true for another 16 (86%) of the 21 cases whose general motor performance could be assessed: from birth until the end of the second month, all but two infants had abnormal writhing general movements. The abnormalities consisted of a poor repertoire of general movements, in that the sequence of the successive movement components was monotonous and movements of the different body parts did not occur in the complex way seen in normal general movements (14). Some infants had predominantly jerky and fast movements; others moved in abnormally slow motion and seemed almost to get stuck in their movement sequence. None of the infants ever showed normal fidgety general movements. Fidgety movements (14,15) were either absent (30%) or abnormal, *i.e.* jerky and too slow (35%) or jerky, abrupt, and disorganized (35%). In addition, four infants lacked other age-adequate motor patterns, such as movements toward the midline, particularly foot-foot contact, or antigravity movements such as leg lifting.

Only two infants had a slumped posture with the head and trunk requiring significant support when raised, suggesting hypotonia. Eleven girls demonstrated postural stiffness. At the end of the sixth month, three infants who could sit with support had their legs externally rotated, adducted, and extended, and their feet were in tiptoe position. We noticed that during sleep, in supine position, three other girls had both arms internally rotated, abducted, and extended, which is an unusual sleeping posture.

Four infants (Table 1) had a small amplitude and high-frequency tremor in one or both arms, independent of crying or excitement. Case 14 had a slow tremor of both arms when both shoulders were raised at 4.5 mo.

While sitting with support, two 5-mo-old girls had stereotyped side-to-side body rocking while simultaneously shaking the head. Slight body rocking was present in a few more cases, but this was considered a normal compensatory movement by the infants to keep their balance.

Hand and finger movements. Half of the cases had normal age-adequate finger movements (Table 1). One girl showed excessive finger spreading during the first 2 mo. Two other cases displayed abnormal synchronized opening and closing of all fingers during the whole observation period. Two infants

had consistent fisting from 3 to 4 mo. An additional six cases did not show the age-adequate hand motor patterns (16) at 5 and 6 mo. By contrast, they touched the toys presented to them with extended fingers only and did not manipulate the toys.

Stereotyped hand movements were observed from 3 mo onward (Table 1). They consisted of unilateral or bilateral 1) repetitive pronation of the hand with simultaneous dorsiflexion of the wrist; 2) excessive repetitive opening and closing of both hands, sometimes even with synchronized plantar flexion of all the toes; or 3) repeated bringing of the palmar sides of both hands together (like praying), raising both hands and separating them again.

The face. Almost all infants were visually interested and demonstrated good visual pursuit. Already during the second month, hand regard could be observed. However, nine girls had strabismus. One girl had a sunset sign during the second month, which later disappeared. Another girl hardly ever blinked. More than half of the infants (Table 1) had asymmetric opening of the eyelid after a blink or asymmetric closing of the eyelid during a blink. This sign was most frequently seen at 3 and 4 mo. The asymmetry remained for a few seconds or even a few minutes.

The response to either bottle or spoon-feeding was normal in all infants. However, more than half of the cases (Table 1) displayed frequent repetitive tongue protrusion. Some infants kept their tongue outside for several minutes, with the lips firmly enclosing the tongue. One girl demonstrated repetitive tongue protrusion combined with head nodding.

At 5 and 6 mo, one third of the cases (Table 1) had a frozen, bizarre, and inadequate smile. In two cases, this pattern could be observed also during the first 2 mo, when smiling is not yet socially elicited. One other girl never responded socially at 5 to 6 months despite excessive social stimulation.

Only after repeated frame-by-frame analysis did it become clear that eight girls (Table 1) had bursts of abnormal facial expressions. This consisted of several repetitions of the following sequence:

first second: head in midline, neutral expression

second second: head turned sideward with a change in expression (either crying or smiling)

third second: head abruptly turned into midline with neutral expression again

All of these abnormal signs have been observed from the first 2 mo of life onward (Table 2). A comparison of the observed abnormal signs between mutation-positive and mu-

Table 2. First appearance (number of infants per 2-mo epochs) of the various abnormal signs observed in 22 girls with Rett disorder

Age	General motor performance				The hand			The face		
	Abnormal general movements	Postural stiffness or slumped posture	Tremor	Body stereotypies	Abnormal finger movements	Hand stereotypies	Asymmetric eye opening and closing	Tongue protrusion	Bizarre smile	Bursts of abnormal facial expression
Birth until 2 mo	10	8	3	1	3	2	5	8	2	2
3-4 mo	4	3	1	—	2	2	3	2	—	3
5-6 mo	2	2	1	1	6	4	2	3	4	3

tation-negative cases and not-tested cases did not reveal any difference (Kruskal-Wallis test).

DISCUSSION

The quality of performance was the crucial part of our video analysis. Already the very first reports on viewing some of these videos revealed jerky, uncoordinated movements (6). Our present detailed analysis demonstrated that the main pattern of spontaneous movements, the general movements, were clearly impaired. That none of the Rett cases had normal fidgety movements confirms the findings that normal fidgety movements are highly predictive for normal development (15). An absence of fidgety movements has been shown to predict the spastic (15) and dyskinetic (17) forms of cerebral palsy. The abnormal quality of fidgety movements in Rett infants was clearly different from the abnormal fidgety movements observed in infants with brain lesions, whose movements are exaggerated with regard to amplitude, speed, and jerkiness (14,15). The abnormal fidgety movements of infants with Rett disorder were jerky and disorganized or in "slow motion."

In contrast to earlier reports (7–9), only two cases had a slumped posture suggestive of muscle hypotonia. The majority of our postural observations indicated postural stiffness. We also found a high incidence of tremor. In a few cases, early tremulous neck movements (8) and tremulous movements of hands and head (7) have been reported previously.

Witt-Engerström (8) discussed Rett syndrome as affecting the voluntary control of arm movements even before hand skill is lost. One quarter of our cases lacked age-adequate hand movements and, in particular, could not manipulate toys. Hand stereotypies were already present in the first 6 mo of life—in two cases even at the end of the second month—in accordance with Kerr's description (6,9) but in contrast with the results of Segawa (18) and Huppke *et al.* (4), who reported stereotyped hand movements from 12 to 24 mo and not earlier. Rhythmic hand movements, particularly rhythmic opening and closing of all fingers, may be observed in normal infants (19), but in Rett, these movements are more persistent and more stereotyped.

Our observation of a frozen, bizarre, and inadequate smile at an early age agrees with previous reports, although those were made at an older age (7,18). Also, we observed tongue protrusion from the early months onward in more than half of the Rett cases, whereas others reported it only from 21 mo onward (18). Usually we found the protruded tongue firmly enclosed by the lips, but the same infant could also have his or her mouth open with a dropped jaw for a long period of time. Protrusion of the tongue has been reported in young infants with Down syndrome (20), Angelman syndrome (21), Joubert syndrome (22), and congenital hypothyroidism (23).

There has long been suspicion that despite "apparent" normality and some developmental progress, the newborn infant with Rett syndrome displays signs of the disorder (3,4,6–10,18,24). However, our study is the first to apply specific standardized measures of early spontaneous movements to these infants, proving conclusively that the disorder is manifested within the first 6 mo of life, in the majority of cases even within the first weeks (Table 2). It is important to note that not

all signs observed are specific for Rett disorder, such as tongue protrusion or the absence of fidgety movements. In addition, "bursts of abnormal facial expression," which have been detected during frame-by-frame analysis, may not be susceptible to detection during routine clinical observations. It is important to appreciate that all of the early abnormal signs indicate problems in the brain stem at this early stage, rather than the cerebral cortex, tallying well with neuropathologic reports on midbrain and lower brain stem impairment (25,26).

Although not all of them necessarily specific, the signs that we have observed will be of value in alerting clinicians to the possibility of abnormal development at an early stage, when intervention is likely to be most effective. In a clinical routine, it is much easier to detect certain abnormalities if one knows what to look for. Our study provides such hints. From a scientific point of view, the correction of the concept of a late onset of abnormal signs in Rett disorder is evident.

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