Original article

Abnormal general movements in girls with Rett disorder:
The first four months of life

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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 14 infants with Rett disorder were carefully assessed for their spontaneous movements, in particular general movements (GMs), during the first 4 months of life. A detailed analysis clearly demonstrated that none of the infants had normal GMs. However, a specific abnormal GM pattern could not be detected for Rett disorder. The abnormal GMs described here, and their individual developmental trajectories are different from the abnormal GMs described in infants with acquired brain lesion. Our study is the first to apply specific standardised measures of early spontaneous movements to infants with Rett syndrome, proving conclusively that the disorder is manifest within the first weeks of life.

Keywords: Fidgety movements; Generalised movements; infant; Spontaneous movements; Video analysis

1. Introduction

In the observation of young infants the focus of interest has changed from the analysis of the infant’s capacity to respond to a range of sensory stimulations to the observation of the un-stimulated infant. Naturalistic observation led to the conclusion of the dominance of spontaneous behaviour—i.e. behaviours endogenously generated by the young nervous system and not generated by sensory stimulation (for a review see [1]). Spontaneous movements have a long prenatal history; they occur in distinct motor patterns from 8 weeks postmenstrual age onwards [2–4]. The first movement to occur is sideward bending of the head. At 9–10 weeks postmenstrual age, complex and generalized movements occur. These are the so-called general movements (GMs) [5] and startles. Both include the whole body, but the general movements are slower and have a complex sequence of involved body parts, while the startle is a quick, phasic movement of all limbs, trunk and neck [4]. The majority of foetal movement patterns develop during the first half of pregnancy and continue not only until term but also after birth. Amazingly, there are hardly any changes in the form and pattern of the spontaneous movements immediately after birth, despite the profound changes in the environmental condition. During the first 2 months postterm the human neonate demonstrates a continuum of neural functions from prenatal to postnatal life. GMs occur with a writhing character with large amplitude ellipsoid components, particularly in the arms. Around the third month a major neurological transformation occurs [6,7]. The infant’s head is no longer positioned to the side but is now held centred in the midline; muscle power is rapidly increasing and can more easily overcome the force of gravity, including proper head control; GMs gradually lose the writhing character and a new pattern of GMs, the fidgety movements, emerges [8]. The neural mechanisms of GMs involve central pattern generators in the brainstem. Separate generators are assumed to be responsible for both GMs of writhing and of fidgety character, as both patterns may be seen simultaneously during a period of overlap [9,10].
After the change in paradigm from reflex to spontaneous motor activity was achieved, the way was paved for the discovery of the importance of the quality of GMs in assessment of the integrity of the young nervous system [1,11]. Infants with brain damage move differently from those with intact brains [1,10–15]. From studies on foetuses and infants with brain malformation [16,17] it became clear that malformations of the forebrain and the diencephalon dramatically alter the expression of GMs to a chaotic movement pattern. Thus, an intact brain is a prerequisite for the normal quality of GMs. Consequently, the question was posed whether genetic brain disorders might have an impact on GM quality.

An apparently normal prenatal and perinatal period followed by an apparently normal psychomotor development during the first 6 months of life, were considered as criteria for classical Rett syndrome [18,19]. However, careful retrospective analyses suggested that subtle behavioural disturbances might be present shortly after birth [20–23]. Lack of response to the environment, autistic features and hypotonia were found in medical reports of the first months of life [21,24,25]. Retrospective parental inquiries revealed that the babies had been particularly placid, had an empty gaze, had slept too well, and had to be woken for feeds [21,24–27]. Based on family film analyses, some investigators had, however, failed to identify abnormal signs between birth and 12–18 months [28,29]. By contrast, other video analyses clearly demonstrated that already the young infant with Rett disorder had abnormal repetitive limb and trunk movements [20,25,26].

In order systematically to study the early motor repertoire of infants with Rett disorder, we first carried out a pilot study on 17 daily life video clips taken by parents. We observed six normal infants and eight infants who later turned out to have Rett disorder during their first 6 months of life, and we were able correctly to identify all cases. This encouraging result led to a detailed video analysis of 22 girls with Rett disorder, which clearly demonstrated that all infants had abnormal signs during their first months of life. In addition to abnormal GMs, postural stiffness, and tremor, the first stereotypies of hand and body movements were described. The analysis of the face revealed asymmetrical eye opening and closing, bursts of abnormal facial expressions, tongue protrusion, and bizarre smile [30]. The most striking result was that none of the infants with Rett disorder had a history of normal GMs. We, therefore, felt the need to report on the GM assessment of these infants in more details. Specific questions we asked were:

- Do infants with Rett disorder have a specific pattern of abnormal GMs?
- What are their individual developmental GM trajectories?
- What are the characteristics of other age-specific motor patterns?

2. Patients and method

Videos of 26 girls with classical Rett syndrome, born between 1964 and 1997, were donated by British families (informed consent and ethics committee approval) for the purpose of a detailed behavioural analysis. Fourteen girls were recorded during their first 4 months of life and were thus available for the assessment of GMs. The recordings were performed by the families as part of their family archive without the knowledge that the child had Rett disorder. All but one was born at term. Case 20 was born at 31 weeks postmenstrual age; for the assessment her age was corrected for preterm birth. Twelve cases have now been mutation tested, all proving positive; three with the common mutation R168X, the others each different (Table 1). Cases 7 and 16 are not mutation tested but clinically classical cases.

For the assessment of GMs, video sequences with a median duration of 3 min (range 1–22 min) with the infant lying in supine or semi-upright in a relaxing chair could be used. The duration of the video clip and the infant’s position were in accordance with the guidelines for the GM assessment [31]. GMs are age-specific with a writhing character until the end of the second month postterm, and a fidgety character from 3 to 6 months [15]. Writhe GMs involve the whole body in a variable sequence of arm, leg, neck and trunk movements. They wax and wane in intensity, force and speed, and they have a gradual begin and end. Rotations along the axis of limbs and slight changes in the direction of movements make them fluent and elegant and create the impression of complexity and variability [11,15]. Fidgety movements are continual small movements of moderate speed, and variable acceleration of neck, trunk, and limbs in all directions [14]. They may be seen as early as 6 weeks but usually occur around 9 weeks and are present until 20 weeks or even a few weeks longer. At that time intentional and antigravity movements occur and start to dominate [8,15]. The quality of GMs was assessed according to the protocol of Prechtl’s method of GM assessment [15,31].

In addition, we recorded the occurrence and quality of other motor patterns concurrently present with GMs such as wiggling-oscillating arms movements, swipes, kicking, movements towards the midline (hand–hand-contact, uni- or bilateral hand–mouth-contact, foot–foot-contact), and antigravity movements (legs lift with or without hand–knee contact) [8,15].

The videos were analysed by the two observers (CE and HFRP) separately with an interscorer agreement for the detailed scoring of 96% and once again discussed together. In addition, the first author re-analysed all recordings after an interval of 18 months and again found 96% agreement with the first analysis.

3. Results

The quality of writhing movements could be reliably assessed in nine cases. All but two infants had abnormal
wringing GMs (Table 1). The abnormalities consisted of a poor repertoire of GMs, 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 GMs [13,31]. Four infants had predominantly jerky and fast movements (Cases 1, 7, 16, and 17, Table 1); two others moved in abnormally slow motion and seemed almost to get stuck in their movement sequence (Cases 13 and 14, Table 1). Case 18 had cramped-synchronised GMs during the first 4 weeks of life. These abnormal movements appear rigid and lack the normal smooth and fluent character; all limb and trunk muscles contract and relax almost simultaneously [13,31].

Only one case (Case 7, Table 1) was not recorded after the 6th week of age. All other 13 infants had the head centred in the midline and a symmetrical posture in supine position by the third month. However, none of them ever showed normal fidgety GMs. Fidgety movements were

Table 1
The quality of GMs of 14 girls with Rett disorder during their first 4 months postterm age (* born preterm, corrected age)

<table>
<thead>
<tr>
<th>Case</th>
<th>Mutation</th>
<th>Birth until 2 weeks</th>
<th>3 and 4 weeks</th>
<th>5 and 6 weeks</th>
<th>7 and 8 weeks</th>
<th>9 and 10 weeks</th>
<th>11 and 12 weeks</th>
<th>13 and 14 weeks</th>
<th>15 and 16 weeks</th>
</tr>
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<tbody>
<tr>
<td>5 CR</td>
<td>R185X</td>
<td>N</td>
<td></td>
<td></td>
<td>AF jerk, abrupt, disorganised</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>3 CR</td>
<td>del. ex</td>
<td>N</td>
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<td></td>
<td>F-</td>
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<td></td>
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</tr>
<tr>
<td>14 CR</td>
<td>PR TR</td>
<td>PR TR</td>
<td></td>
<td>AF jerk, slow</td>
<td>AF jerk, slow</td>
<td>AF jerk, slow</td>
<td>AF jerk, slow</td>
<td>AF jerk, slow</td>
<td></td>
</tr>
<tr>
<td>16 CR</td>
<td>PR</td>
<td></td>
<td>AF jerk, abrupt, disorganised</td>
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<td>1 CR</td>
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<td>F-</td>
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</tbody>
</table>

Case Mutation | Birth until 2 weeks | 3 and 4 weeks | 5 and 6 weeks | 7 and 8 weeks | 9 and 10 weeks | 11 and 12 weeks | 13 and 14 weeks | 15 and 16 weeks |
|-------------|---------------------|---------------|---------------|---------------|---------------|----------------|----------------|----------------|
16 CR        | Q244X               | CS TR         | CS TR         |   |   | AF jerk, slow       |
13 CR        | P182R               | PR TR         |   |   | AF jerk, slow       |
17 CR        | T158M               | PR            |   |   | AF jerk, slow       |
7 CR         | not tested          | PR            |   |   | AF jerk, slow       |
23 CR        | R255X               | F-            |   |   |   |                           |

(continued on next page)
either absent (four cases) or abnormal, i.e. jerky and too slow (six cases) or jerky, abrupt and disorganised (three cases; Table 1).

It was possible to assess both, writhing and fidgety GMs in eight of the 14 infants. Normal writhing movements were followed by abnormal or absent fidgety movements (Table 1, Fig. 1). The absence of fidgety movements was preceded by normal or poor repertoire GMs (Fig. 1).

All movement patterns, usually concurrent with GMs, could be observed. Kicking occurred unilateral, alternating or symmetrical. Only Case 20 had abnormal monotonous kicking at the corrected age of 11 weeks. Swiping, saccadic and wiggling-oscillating arm movements could be frequently observed. Hand–hand and hand–face contact was noted from 4 weeks onwards. Foot–foot contact appeared late, usually not before the 12th week, and could never be observed in four girls although their recordings were of sufficient length. Antigravity movements, such as legs lifted with or without hand–leg contact, occurred in the majority of cases but was not present in four infants. Surprisingly, Case 14 had frequent hand–toe contact already at 15 weeks.

Three infants (Table 1) had a small amplitude and high frequency tremor in one or both arms, independent of crying or excitement.

### 4. Discussion

The quality of performance was the crucial part of our video analysis. Already the first reports on viewing some of these videos revealed jerky uncoordinated movements [20].

Our present detailed analysis demonstrated that the main pattern of spontaneous movements, the GMs, were clearly impaired in infants with Rett disorder [30].

During the first 2 weeks postterm age six infants were recorded; two of them had normal GMs (Table 1). These infants (Cases 3 and 5) were not recorded again within the first 2 months postterm age. Therefore, we do not know if and when their writhing movements deteriorated. However, both infants certainly did not have normal fidgety movements. That the quality of GMs deteriorate within a few weeks is also known from infants with brain lesion [15,32].

Poor repertoire GMs were found in six out of nine infants with Rett disorder who were recorded during the first 2 months of life. Despite the sequence of the successive movement components was monotonous in all infants with Rett disorder, the quality of writhing general movements (left) is followed by the quality of fidgety general movements (right). N, normal; PR, poor repertoire of general movements; CS, cramped synchronised general movements; AF, abnormal fidgety movements; F-, absence of fidgety movements.
the movement speed was quite different. Four infants had fast and jerky movements, two moved in abnormally slow motion and almost got stuck in their movement sequence.

Case 18 (Table 1) had cramped-synchronised GMs during the first 4 weeks postterm age. In infants with acquired brain lesion this abnormal GM pattern is highly predictive for the development of spastic cerebral palsy [13,14,33]. Several studies demonstrated that infants with consistent cramped-synchronised GMs will hardly develop fidgety movements at 3–4 months [14,15,33]. Case 18, however, developed fidgety movements but of an abnormal jerky and too slow appearance (Table 1 and Fig. 1).

None of the infants with Rett disorder had normal fidgety movements. This confirms the findings that normal fidgety movements are highly predictive for normal development [14,15]. An absence of fidgety movements has been shown to predict the spastic [14,15,34,35] and dyskinetic [36] forms of cerebral palsy. Abnormal fidgety movements have a low predictive value for the later neurological development [15]. Interestingly, the abnormal quality of fidgety movements in infants with Rett disorder was clearly different to the normal fidgety movements observed in infants with acquired 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 disorganised or in ‘slow motion’.

Although none of the study cases showed normal GMs after the second week of life, a specific abnormal GM pattern could not be detected for Rett disorder. However, the abnormal GMs described here and their individual developmental trajectories are different from the abnormal GMs described in infants with acquired brain lesion.

In a few infants with Rett disorder early tremulous neck movements [25] and tremulous movements of hands and head [24] have been reported previously. The tremulous movements we have observed in four infants occurred mainly in the arms.

Beside the absence of the age-adequate fidgety movements in four infants (Table 1), four more infants lacked other age-adequate motor patterns. Despite sufficiently long recordings, these infants did not show movements towards the midline, particularly foot–foot contact, or antigravity movements such as leg lifting. By contrast, one infant was advanced in her development of hand–toe contact compared to healthy infants [2]. In this context, it should be mentioned, that four infants had fidgety movements (although of abnormal quality) already at 7–8 weeks, which is unusually early for infants born at term [37].

There has long been suspicion that in spite of ‘apparent’ normality and some developmental progress the newborn infant with Rett syndrome displays signs of the disorder [20–25,27,38]. However, our study is the first to apply a specific standardised method to assess early spontaneous movements of these infants, proving conclusively that the disorder is manifest within the first 4 months of life.

The absence of fidgety movements is not specific for Rett disorder, and the abnormal GMs we have described are not homogeneous within the group of Rett infants. However, they indicate problems in the brain stem at this early stage tallying well with neuropathological reports on midbrain and lower brain stem impairment [39,40].

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References


