Published in final edited form as:
J Dev Phys Disabil. 2014 April ; 26(2): 171–182. doi:10.1007/s10882-013-9351-3.

Monozygotic twins with Rett syndrome: Phenotyping the first two years of life

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Abstract

The first two years of life for children with Rett syndrome (RTT) have previously been viewed as relatively asymptomatic. However, it is possible that subtle symptoms may be present in early development. To identify possible early indicators of RTT, we analysed videotapes of two twin girls with RTT. The videotapes were analysed to (a) describe the motor and communicative development of this twin pair with RTT; and to (b) explore whether early abnormalities and their age of onset differed between the twins and were related to their later clinical phenotypes. The results indicated several neurodevelopmental abnormalities present before the children exhibited any obvious signs of regression. Abnormalities were evident in the motor, speech-language and communicative domains. These data support an emerging evidence base showing the presence of developmental abnormalities in children with RTT during the first year of life. The results have implications for early screening and clinical assessment.

Keywords

Rett syndrome; Early symptoms; Retrospective video analysis

Introduction

Rett syndrome (RTT) is a severe progressive neurodevelopmental disorder mainly caused by mutations in the X-linked gene encoding methyl-CpG-binding protein 2 (MeCP2) (Neul et al. 2010). The majority of cases (99%) are sporadic (Mittal et al. 2011b), though in rare instances germ-line mosaicism can lead to familial cases (Comings 1986; Evans et al. 2006, Zhang et al. 2012). In fact, it was the rarely occurring familial cases that ultimately held the

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Declaration of Interests
The authors report no conflict of interests. The authors alone are solely responsible for the content and writing of this paper.

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key to understanding RTT's genetic basis (Pini et al. 1996; Schanen et al. 1997), before the causal role of the *MECP2* gene was discovered (Amir et al. 1999). Studies incorporating family data subsequently hypothesized that genetic or epigenetic factors, besides *MECP2* mutations, may account for the large variability in developmental profiles observed in RTT siblings (Ishii et al. 2001; Scala et al. 2007). Scala et al. (2007), for instance, described two sisters with an identical intragenic *MECP2* deletion who developed discordant phenotypes. One of the girls happened to develop typical RTT, while the other exhibited the preserved speech variant of RTT, which is a relatively milder phenotype.

Symptoms of RTT have been observed in family members of various relationships to one another: Specifically; aunt and niece (Schanen et al. 1997), sisters (Hanefeld 1985; Comings 1986; Killian 1986; Haenggeli et al. 1990; Miyamoto et al. 1997; Leonard et al. 1999; Wan et al. 1999; Cheadle et al. 2000; Ishii et al. 2001; Evans et al. 2006; Scala et al. 2007; Rosser et al. 2008), brothers with a severe early onset encephalopathy (Lundvall et al. 2006), and even in a brother-sister pair (Mittal et al. 2011a). Furthermore, 15 twin pairs with RTT have been reported in the literature (Coleman et al. 1987; Partington 1988; Tariverdian 1990; Bruck et al. 1991; Migeon et al. 1995; Ogawa et al. 1997; Krepischi et al. 1998; Ishii et al. 2001; Carter et al. 2008; Mittal et al. 2011b; Zhang et al. 2012). Migeon et al. (1995) and Tariverdian and colleagues (Tariverdian et al. 1987; Tariverdian 1990) described concordant phenotypes in a few twin pairs with RTT, while others have reported on monozygotic twin females with RTT with noticeable differences in their development (Bruck et al. 1991; Mittal et al. 2011b). Ishii et al. (2001) speculated that variable clinical phenotypes in monozygotic twins might be explained by differences in X-inactivation patterns between each sibling.

We have conducted several studies into the early development of individuals with RTT using retrospective analysis of family videos made during the first two years of life, during a time when usually the parents were not aware that their daughters had RTT (Marschik & Einspieler, 2011). By meticulous micro-analyses of these videotapes, we were able to delineate apparent motor (Einspieler et al. 2005a, 2005b; Marschik et al. 2009) and communicative abnormalities during the pre-regression stage of RTT (Marschik et al. 2011, 2012a, 2012b, 2012c, 2013a, 2013b). That is our data suggested that abnormalities were already present during the first months of life. In the context of this research we came across a monozygotic female twin pair with RTT, born in São Paulo, Brazil, whose parents provided videotapes for our analysis. The present study involved the analysis of these videotapes to (a) describe the motor and communicative development of this twin pair with RTT; and to (b) explore whether early abnormalities and their age of onset differed between the twins and were related to their later clinical phenotypes.

Method

Participants

We report on one pair of female twins, born after uneventful pregnancy and uneventful spontaneous delivery at 34 weeks' gestation. 46XX monozygosity was confirmed by both blood typing and HLA titers. Family history was negative for cognitive impairments, epilepsies, and consanguinity. Twin 1 had a birth weight of 2250 grams, length of 47 cm,

and a head circumference of 35 cm. Twin 2 had a birth weight of 2310 grams, length of 46 cm, and a head circumference of 33 cm. Apgar Scores (1 minute/5 minutes/10 minutes) were 8/9/9 for both.

At the twins' post-term age of 6:2 (months:weeks) the parents noticed a general developmental delay. Typical RTT was diagnosed at 24 months for both girls. The twins were never genetically tested, but fulfill the following clinical criteria for typical RTT: postnatal deceleration of head growth; a period of regression followed by stabilization; stereotypic hand movements; breathing disturbances and bruxism when awake; EEG abnormalities; impaired sleep patterns; abnormal muscle tone; scoliosis/kyphosis; inappropriate laughing/screaming spells; diminished response to pain; intense eye communication.

At the age of 4 years, both twins had acquired the ability to sit freely, but only Twin 2 was able to walk with support, starting at 8 years of age. Speech-language development did not proceed beyond simple vocalizations (i.e. single consonant- or vowel-like vocalizations). At the present time (March 2013), the twins are adolescents exhibiting different clinical phenotypes (see Table 1). Twin 2 is able to express whether or not she feels well, or where she wants to walk. She also seems to enjoy music as evidenced by the fact that she makes positive vocalizing while listening. Neither twin has purposeful hand use. Their main observable stereotypies are hand-washing and flapping movements (Table 1). With the exception of seizures that are under control, neither has any major health problems.

Procedure

We retrospectively analyzed family videos, parental diaries, and medical history data. Audio-video recordings of sufficient quality standards and a total length of 55 minutes (Twin 1) and 54 minutes (Twin 2) were available for detailed analysis of motor and socio-communicative behaviour. The footage comprised of 38 clips of Twin 1 (9 in supine position, 6 in prone position, 20 in semi-upright position, and 3 clips in which the child was sitting with support) and 36 clips of Twin 2 (12 with the infant in supine position, 3 in prone position, 19 in semi-upright position, and 2 clips with the child sitting with support). Roughly a third of the clips (13 clips of Twin 1; 14 clips of Twin 2) were recorded during interactions with caregivers or the twins' healthy sister, who was 3 years older than the twins. During the remaining clips (25 clips of Twin 1; 22 clips of Twin 2), the girls were not interacting directly with caregivers, but were still often spoken to by the person recording the video. In all recordings, the girls were differently dressed and called by their respective names (89% of the clips) or identified by their parents upon request (11%). The recordings were made at a time when the parents were not aware that their daughters had RTT. First concerns about developmental delays (especially in Twin 1) arose at their post-term age of 6:2 months.

The first recordings were done at the twins' postnatal age of 7 weeks (i.e. 1 week post-term age), while the last recording was performed at 21:3 months (corrected for preterm birth). Both twins were recorded at 0:1, 0:3, and 1:1 months and thereafter several times per month from 8:1 months to 21:3 months (at ages 8:1, 8:2, 9:0, 9:1, 9:2, 10:2, 12:0, 12:2, 13:0, 14:2,

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15:2, 16:0, 16:2, 17:3, 18:2, 21:3). All ages are corrected for the twins' birth at 34 weeks' gestation.

The recordings were copied and prepared for analyses by unifying codecs. We analyzed the age-specific quality of gross and fine motor behaviours as well as the quality and rate of occurrence of age-specific vocalizations. Non-speech sounds (sneezing, coughing, etc) were excluded from the analysis. Fixed vocal signals such as crying and laughing were noted if abnormal.

The motor behaviour during the first three months of life was evaluated by means of the Prechtl assessment of general movements (Einspieler and Prechtl 2005; Einspieler et al. 2004). An inter-rater agreement of 89 to 93% and an average Cohen Kappa of 0.88 obtained in 15 studies documented the high objectivity of the assessment of general movements (Einspieler and Prechtl 2005, Fjørtoft et al. 2009). A high inter-individual consistency of movement quality was demonstrated by Kappa-values from 0.90 to 0.96 (Mutlu et al. 2008). The two authors CE and PBM, who were blind to the severity of the RTT phenotype after the second year of life, coded general movements and the concurrent motor repertoire (nominal data) in parallel, with full inter-rater agreement. All further analyses were performed by means of the Noldus Observer-XT (Versions 11, Noldus Information Technology, http://www.noldus.com). One PhD student (TW), who was blind to the background and purpose of the study, and two of the authors (CE and PBM), who were blind to the severity of the RTT phenotype after the second year of life, coded the predefined behaviours (nominal data) in parallel. Fleiss Kappa, a variant of Cohen Kappa for measuring inter-rater reliability, was applied as three scorers assigned categorical scores to a fixed number of items (Fleiss 1971). The inter-rater agreements (Fleiss Kappa) for each behaviour tagged were between 0.84 and 1.00 (Median 0.94). In case of disagreement the behaviour in question was discussed within the team until consensus was achieved.

The study was approved by the Comitê de Ética em Pesquisa da Universidade Federal de São Paulo, Brazil, and the parents gave their informed consent for analyses and publication of the results.

Results

The twins missed most developmental milestones, with the exception of head control and head centred in the midline at 3;0 months (according to the parental diaries). The following series of abnormal signs was observed throughout the first 2 years of life:

Movements and posture

At 0:1, 0:3, and 1:1 months post-term age, both twins displayed a poor repertoire of general movements, i.e. the sequence of the successive movement components was monotonous and of a too slow pace, and movements of limbs, trunk and neck did not occur in the complex way seen in normal general movements (Einspieler et al. 2004). During the first 5 weeks post-term age, we did not observe limb movements to the midline. Only at 9:1 months, both twins demonstrated a few hand-to-mouth contacts with extended fingers. Thumb sucking was observed only once, at 16:0 months in Twin 2. With the exception of one very short-

lasting legs lift by Twin 2 at 9:2 months both individuals showed neither antigravity movements nor any attempt to crawl. At 8:1 months, Twin 1 tried to roll sideways but did not succeed. Twin 2 rolled from supine to side at 13:0 months, and from side to supine at 14:2 months (Table 2). Asymmetric tonic neck responses (ATNR) were observed in both twins during the first 5 weeks after term. Twin 1 also demonstrated this posture from 8:1 to 9:0 months. At 1:1 months, neither twin kept their head centred in the midline, but they eventually did so at 8:1 months. According to the parents, this milestone had been achieved at 3:0 months. Head control was always adequate when the twins lied in prone position. At 9:0 months, Twin 2 was pulled into sitting position twice, but only once was she able to hold her head steadily. From 0:1 to 1:1 months retroflexion of the head and trunk was more pronounced in Twin 2 than in Twin 1 (Table 2). However, thereafter only Twin 1 showed this abnormal posture up to 16:0 months. Until 10:2 months both twins demonstrated postural stiffness; several times one or even both arms were extended, adducted and exorotated. Twice both twins fully extended their arms and legs in supine position (at 8:2 months).

Fisting occurred until 10:2 months. If finger movements occurred, they were sporadic with limited variability. From 8:2 (Twin 2) and 9:2 months (Twin 1) onwards, fingers were usually kept in extension. A few times, both twins briefly touched a toy with extended fingers but did not manipulate it. Twin 1 was batting with her extended fingers on the table at 17:3 months. Long-lasting finger spreading (maximally extended and adducted) occurred in both twins from 9:2 months onwards. Twin 2 demonstrated reaching towards an object at 8:2 and 9:2 months but never thereafter. Twin 1 showed reaching at 16:2 month but did not touch the toy (Table 2). Fingers were extended during every reaching. Hand regard occurred once in Twin 2 at 14:2 months (Table 2); during this behaviour all fingers were extended and motionless. Hand stereotypies could only be detected in three clips, and solely in Twin 2 (Table 2). At 13:0 months repetitive batting with the dorsum of the hand to the mouth was observed. At the same age, and again at 15:2 months, repetitive opening and closing of the right hand with pronation and dorsiflexion of the wrist was observed.

Facial expression

Visual scanning was observed from 8:1 months onwards. From 8:2 to 10:2 months, Twin 1 had strabism (Table 2), which was resolved thereafter. In both twins the mouth was kept widely open until 10:2 months. Both girls frequently displayed either repetitive or long lasting tongue protrusion during all recordings until 15:2 months. In addition, repetitive opening and closing of the mouth (without vocalization) were observed in both twins up to the age of 13:0 months.

Speech-language and communicative behaviour

During most recordings neither twin vocalized. Twin 1 demonstrated a short vocalization sequence without modulation at 1:1 months, and again at 8:1 months. At 9:0 months Twin 1 showed short pressed vocalizations with strained voice quality. The first vocalization heard from Twin 2 occurred at 8:1 months. A second vocalization occurred at 14:2 months. Both were short, cooing-like vocalizations. Pleasure vocalizations were rare. Twin 1 exhibited them around the end of the first year but they were not observed later, whereas Twin 2 only showed one instance of pleasure vocalization, at 18:2 months. Normal cooing and babbling

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were absent in both twins. Neither one was able to speak a word. Communicative gestures were not observed. Social smiling occurred rather frequently in both twins from 8:1 months onwards. It was sometimes interspersed with frozen smiling movements during which eye contact was avoided. Such behaviour was more frequent in Twin 1 (Table 2). Both twins reacted to calling their name. However, whereas Twin 1 reacted to her name at 12:0 months (and thereafter several times), Twin 2 did so only at 21:3 months.

Additional observation

In one instance, at age 8:1 months, Twin 2 was without warning roughly manipulated by her older sister but did not complain or otherwise react.

Discussion

Initially it was believed that the development of individuals with RTT disorder was asymptomatic before regression, but recent research has provided growing evidence of abnormalities in the motor, speech-language and communicative domains already during the first year of life (Kerr 1995; Tams-Little and Holdgrafer 1996; Leonard and Bower 1998; Burford et al. 2003; Burford 2005; Einspieler et al. 2005a, Marschik et al. 2012a, 2012d; 2013a; Lee et al. 2013). Phenotypic characterization of the monozygotic twins in this study contributes to the growing body of evidence suggesting that both subtle and obvious neurodevelopmental abnormalities might be observable in some RTT children before the more obvious signs of regression. Although the parents had concerns about the twins' development at the post-natal age of 8 months (6:2 months when corrected for pre-term birth), detailed video analysis revealed subtle, but non-specific abnormalities in their spontaneous motor repertoire as early as the first weeks of life.

The first video recording at 0:1 months revealed that the main pattern of spontaneous movements, the general movements (GMs), were clearly impaired in both individuals. This finding is in line with previous analyses of GMs in infants with RTT (Einspieler et al. 2005a, 2005b; Marschik et al. 2009), but also in infants with other genetic disorders such as Smith-Magenis syndrome (Einspieler et al. 2012) and infants who develop autism spectrum disorders later in childhood (Phagava et al. 2008; Palchik et al. 2013). We should, however, keep in mind that a poor repertoire of GMs (i.e., GMs lacking the normal variability in sequence, amplitude, speed and intensity) is common in infants born pre-term (de Vries and Bos 2010). In addition, this abnormal movement pattern is not highly predictive of the neurological outcome (Prechtl et al. 1997; Nakajima et al. 2006).

Movements to the midline and antigravity movements typically mark the onset of purposeful movements at 3 to 5 months of age (Einspieler et al. 2008). However, the twins were not videotaped during this period and there were no notes in the parental diaries, therefore we assume that these movements did not emerge at the typical age. Analysis of the video recordings revealed that from 8 months onwards, movements to the midline and antigravity movements occurred rarely, which can be interpreted as a precursor to delayed development of sitting or crawling. These observations are in line with a previous study on 14 individuals with RTT, in which four females did not demonstrate movements towards the midline or

antigravity movements; however, this analysis was only carried out until the end of the fourth month after term (Einspieler et al. 2005b).

The twins demonstrated several normal postures, such as centring their heads on the midline, adequate head control during prone position, or ATNR. Postural stiffness, however, was observed within the first year of life in both twins. These postural characteristics were also observed in a previous study, in 11 out of 22 females with typical RTT during their first 6 months of life (Einspieler et al. 2005a)

Witt-Engerström (1987) described RTT syndrome as affecting the voluntary control of arm movements before hand skill is lost. A considerable number of females with RTT have been shown to lack age-appropriate hand movements and, in particular, the ability to manipulate toys during their first 6 months of life (Einspieler et al. 2005a). The twins of the present study showed little ability to manipulate toys, which likely limited their explorative behaviour. We have previously described a female with the preserved speech variant of RTT who, at the end of her first year, demonstrated finger movements alternating between normal pincer grasping and touching objects with undifferentiated movements and fingers mainly extended (Marschik et al. 2009).

Hand stereotypies occurred less frequently, and were only observed in Twin 2 from 13 months onwards. Other studies have also reported that stereotyped hand movements did not occur before 12 months in RTT (Segawa 2001; Huppke et al. 2003; Temudo et al. 2007a). However, hand stereotypies have been observed to emerge during the first months of life in both the typical RTT (Kerr et al. 1987; Kerr 1995; Einspieler et al. 2005a) and preserved speech variant (Marschik et al. 2009; 2012c).

Protrusion of the tongue was shown by both individuals and has been previously described as one of the early signs of RTT (Segawa 2001; Einspieler et al. 2005a; Temudo et al. 2007a, 2007b). Both twins also frequently and repetitively opened and closed their mouth, which has been described in infants with acquired brain lesions (Yang et al. 2012) but not previously in RTT.

The clinical picture associated with typical RTT is not only characterized by a loss of purposeful hand movements, but also a loss of spoken language skills (Hagberg et al. 1983; Neul et al. 2010). Therefore, the analysis of early speech-language development in females with RTT is of special interest. The twins of the present study expressed neither age-appropriate cooing nor canonical babbling. Vocalizations were limited to some consonantand vowel-like vocalizations and a few positive vocalizations, which were observed at the end of the first year in Twin 1, and 6 months later in Twin 2. These observations are in line with a recent study of ten individuals with typical RTT, in which we reported three individuals who never exhibited cooing, and five who never displayed babbling vocalizations (Marschik et al. 2013a). That these early milestones were apparently missed suggest that the trajectory of development was abnormal from the very beginning of life. In other words, these individuals did not exhibit a regression in the speech-language domain.

The twins of our study generally displayed a positive mood and frequently smiled. However, their smiles were sometimes interspersed with frozen, bizarre smiling movements during which eye contact was avoided. Similar observations have been described previously by Nomura and Segawa (1990) and Segawa (2001) in young children with typical RTT, as well as in a 1-year-old child with the preserved speech variant of RTT (Marschik et al. 2009, 2012b).

Neither twin demonstrated communicative gestures. Previous studies described a very limited gestural repertoire in both typical RTT (Tams-Little and Holdgrafer 1996; Dahlgren Sandberg et al. 2000; Marschik et al. 2012d) and the preserved speech variant (Marschik et al. 2012b), and attributed the limited gestural repertoire to a difficulty in focusing their attention to relevant sources of information (Marschik et al. 2012d).

Both twins lacked an early normal development, although Twin 2 was less conspicuous in the following respects: (a) although delayed, she demonstrated reaching, hand regard, and rolling sideward (see Table 2); and (b) the durations of abnormal head and trunk retroflexion, and frozen smiles without eye contact, were shorter in Twin 2. On the other hand, Twin 2 did demonstrate certain unique abnormalities. She did not react when called by her name before 21 months, and exhibited hand stereotypies from 13:0 to 15:2 months, abnormalities that were not observed in Twin 1. Nonetheless, in adolescence Twin 2 currently presents with a less severe phenotype than Twin 1 (Table 1). Miyamoto et al. (1997) described two sisters with typical RTT, one of whom was unable to stand or walk alone whereas the older sister had a less severe phenotype demonstrating adequate ambulation. Bruck et al. (1991) reported on the discordant early phenotype of monozygotic twins with typical RTT. One individual was considered abnormal from birth while developmental delay was not suspected in the other twin until she was about 1 year old. At age 4 years, however, the twins were clinically indistinguishable from each other. Others, however, have described twins with typical RTT who were almost concordant in all clinical signs (Tariverdian et al. 1987; Tariverdian 1990).

It is commonly known that retrospective video analysis has certain limitations. The most prominent insufficiency is the potential absence of a certain feature in a given data set: if a particular pattern is missing, it does not necessarily mean that the pattern in question is absent in the repertoire of the participant (Marschik and Einspieler, 2011). Apart from short recording durations, parents might have recorded their child in order to commemorate a special event rather than to capture a representative range of behaviour. On the other hand, video analysis allows us to point observable phenomena and peculiarities, and thus overcome recall biases in retrospective parental reports (Zwaigenbaum et al. 2013).

In conclusion, this study provides more evidence supporting the concept of pre-regression abnormalities in RTT. It furthermore supports the long-held idea that early psychomotor development reveals certain abnormalities (Hagberg et al. 1983; Witt-Engerström 1987; Kerr 1995; Leonard and Bower 1998; Burford 2005; Einspieler et al. 2005a, Marschik et al. 2012a; 2013a, Lee et al. 2013). Only through detailed analyses of retrospective videotapes taken as early as 1 week post-term age were we able to observe these abnormalities, which became more and more prominent in the motor as well as speech-language-communicative

domains. In addition, this study corroborates previous observations of phenotypic diversity (e.g., Colvin et al. 2003) and the variability of clinical severity in monozygotic twins within the diagnostic entity of typical RTT (Bruck et al. 1991; Ishii et al. 2001; Scala et al. 2007; Mittal et al. 2011b). However, more longitudinal studies such as this one are needed to better understand developmental traits across domains, knowledge which could eventually lead tailored treatments for affected children with specific developmental profiles.

Acknowledgements

We are grateful to Ing. Gunter Vogrinec for technical support.

Parts of the study were funded by the Austrian Research Fund, FWF P25241, and the Lanyar Foundation, Project 337.

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Table 1

Clinical Differences Between Monozygotic Female Twins with RTT at Age 14

	Twin 1	Twin 2
Ambulation	Nonambulatory	Walking with support
Scoliosis	Significant	Mild
Stereotypies	Washing movements	Flapping movements
Communication	Few signs of communication	Pre-linguistic communication, sociable, humorous

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Table 2

Behavioural Differences Between Monozygotic Female Twins with RTT During the First 2 Years of Life. Age Range of Occurrence is Given in Months:Weeks and Corrected for Preterm Birth.

		Twin 1	Twin 2
Normal patterns but age-inadequate emergence	Reaching	16:2	8:1 – 9:2
	Hand regard	not observed	14:2
	Rolling sideward	not observed	13:0 – 14:2
	Reaction to name	from 12;0 onwards	21:3
Abnormal patterns	Head and trunk retroflexion in supine position	0:1 – 16:0	0:1 – 1:1
	Strabismus	8:1 – 10:2	not observed
	Frozen smiling movements without eye contact	9:1 – 16:0	12:2
	Hand stereotypies	not observed	13:0 – 15:2