

Early development and regression in Rett syndrome

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CONFLICT OF INTEREST

Each of the authors has no conflict of interest to report.

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Keywords

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Abstract

This study utilised developmental profiling to examine symptom presentation in 14 girls with genetically confirmed Rett Syndrome and whose family was participating in the Australian Rett Syndrome or InterRett database. Regression was mostly characterised by loss of hand and/or communication skills (13/14) except one girl demonstrated slowing of skill development. Social withdrawal and inconsolable crying often developed simultaneously (9/14) with social withdrawal of shorter duration than inconsolable crying. Previously acquired gross motor skills declined in just over half of the sample (8/14), mostly observed as a loss of balance. Early abnormalities such as vomiting and strabismus were also seen. Our findings provide additional insight into the early clinical profile of Rett syndrome.

Introduction

Rett syndrome is a rare neurodevelopmental disorder with a prevalence of approximately 1 per 9,000 live-born females in Australia (1). Established clinical criteria include developmental regression (2) and diagnosis is usually confirmed by testing of the *MECP2* gene. Developmental deviations prior to regression, have been described in a population-based study (3) and observed in infant videos (4). Developmental regression occurred at a mean age of 19.3 months in a sample of US and Australian cases (n=299) born since 1999 (5). Those with earlier regression were less likely to learn to walk or talk whereas those with later regression were more likely to do so. Relationships between the early clinical features of Rett syndrome and specific *MECP2* mutations were also confirmed (5). Regression is usually followed by a period of stability when the child re-engages with the environment and learning is again possible (6).

Despite established clinical criteria and genetic testing, there is a lack of clinical knowledge about the regression period especially when early presentation can be variable. Previous studies lacked genetic information (7, 8) or included cases that were adults at time of data collection (7). The current study therefore sought to describe developmental pathways of the pre-regression and regression period in depth in a small genetically characterised sample of young girls with Rett syndrome.

Materials and Methods

Ethics approval was obtained from Curtin University. Interviews were conducted with 14 mothers who were participating in the Australian Rett Syndrome Database (ARSD)(9) (n=3) or InterRett database (10) (n=11). Median age at interview of cases was four years (range 2-5 years). All had a clinical diagnosis of Rett syndrome and a pathogenic *MECP2* mutation: four p.R255X; three p.R133C; two each with p.R270X and p.T158M; and one each with a C-terminal deletion, p.R106W or p.R294X mutation. Median age of

diagnosis was 24 months (range 19-42 months) (Table 1). Previous diagnoses included global developmental delay (n=3), autism (n=2) or pervasive developmental disorder not otherwise specified (n=2). Abnormal EEG activity had been recorded for five girls and three mothers reported active seizures that were currently managed by anti-epileptic medications.

The interview schedule included questions about initial concerns; gross motor (e.g., sitting, crawling, walking), fine motor (e.g., hand function, stereotypies) and communication (e.g., speech, non-verbal communication) skills; symptoms of Rett syndrome (e.g., inconsolable crying, night laughing) and personal-social (e.g., autistic symptoms) aspects. Prior to interview, mothers reviewed infant records to facilitate better recall of events. Pre-existing information (e.g., genetic mutation, age of diagnosis) was obtained from the ARSD and InterRett databases. Interviews were conducted by telephone and recorded. Mothers were requested to submit home videos or photos to assist with validation and seven provided materials. All photos and videos, some of which were serial, validated the findings. Interview recordings were transcribed and nine mothers completed the member-checking portion of the study. All data was used to construct the final developmental profiles as a timeline summarising the age of onset and duration of symptoms.

Results

The following observations are presented in broad chronological order and the themes and age of onset for each girl are shown in Table 1.

Early concerns

The median age of initial symptom presentation was 12 months (range 2 -34). The classic criteria of loss of hand or speech skills were the first identifiable sign of abnormality in four girls and the development of hand stereotypies in two. For two girls, the first identifiable sign of abnormality was the development of strabismus or crossed eyes occurring

between 12 and 14 months. Two mothers reported severe vomiting as the first sign of abnormality. For both cases, the vomiting occurred prior to 6 months of age and remained severe (e.g., occurring daily) until approximately three years of age. For one of the girls, it was associated with severe reflux and for the other no diagnosis was made although one course of anti-reflux medication was trialled. The first symptoms for three girls were inconsolable crying and poor sleep and for one girl a persistent crick in the neck in combination with sudden left hand dominance and a mild strabismus. These were accompanied by early general concerns including the girls being placid in infancy (7/14), poor head control (4/14), and early developmental delay (7/14). See Table 2 for the initial concerns, ages of onset, and illustrative quotes.

Regression

The median age at onset of regression was 18 months (range 9-34) with the regression being ‘rapid’ or ‘sudden’ in eight and occurring ‘slowly over time’ in five girls. Seven experienced regression prior to or at 18 months of age: two with the mutation p.R255X, two p.T158M, one p.R106W, and two p.R270X. Of these, one walked independently. Six girls experienced regression later than 18 months of age: two with the mutation p.R255X, three with the mutation p.R133C and one p.R294X. Five of these were independently mobile. The 14th case (C-terminal deletion) had learned to walk and although regression of hand and speech skills had not been observed, developmental progress in these domains was slower.

Ten girls lost previously acquired speech or language at a median age of 16 months (range 9-36). Some girls were described as going ‘quiet’, and, irrespective of their level of speech, were described as being ‘less vocal’. Following regression, the majority did not use words although four used words inconsistently (i.e. occasionally and in isolation). In contrast, four girls did not experience a loss of speech: for three ‘babble’ was the highest speech level achieved while one girl had delayed speech acquisition but still retained over 50 words.

At a median age of 18 months (range 10 to 36) 13 girls lost hand function skills such as the pincer grip, self-feeding skills, holding their bottle, pushing buttons, and picking up or carrying toys. Hand function was retained in one case with delayed development rather than regression of skills (C-terminal deletion).

Nine girls lost both speech and hand function skills and of those, six (66.7%) lost speech skills prior to losing hand function skills.

Hand stereotypies

Hand stereotypies developed in all cases with onset at a median age of 15 months (range 9-33) and were often frequent and intense. Hand stereotypies developed prior to a loss of hand function in eight girls, after loss of hand function in three, and simultaneously in the remaining three.

Social withdrawal, diminished eye contact and inconsolable crying

Eleven girls developed autistic type symptoms of social withdrawal and diminished eye contact at a median age of onset of 15 months (range 9-36). In eight, symptoms were noticed contemporaneously with loss of speech and hand skills. At interview, ten of the 11 no longer displayed these symptoms, their median duration having been 5 months (range 3-23).

Eleven also experienced inconsolable crying, both during the day (8/14) and at night (9/14). The median age of onset was also 15 months (range 9-47) and median duration 25 months. Three girls were still experiencing inconsolable crying episodes at interview. Inconsolable crying developed simultaneous to loss of speech or hand function in 7/14 and with social withdrawal in 9/14. Only one girl (C-terminal deletion) had not presented with autistic type symptoms.

Balance and walking

Over the early developmental period, six learned to walk independently, two were able to take supported steps, and three were able to stand with support. At interview these skills remained and one additional girl was able to stand with support. Of those able to walk independently, three had a p.R133C mutation, one p.R270X, one p.R294X, and one had a C-terminal deletion. None of those with a p.R255X mutation was independently mobile.

Half of the girls experienced altered gross motor skills following regression, often a deterioration of balance and sometimes accompanied by an abnormal gait. Balance problems were observed not only in girls who were able to walk (5/6), but also those who were only able to take supported steps (1/2), stand with support (1/3), or sit independently (1/3). The median age of onset of gait and balance problems was 36 months (range 18-42), and was observed in two each with the mutations p.R270X, p.R255X and p.R133C and in the one with a C-Terminal deletion. Loss of gross motor skills was subtle, developing slowly over time.

Discussion

Consistent with Hagberg's staging model (6), regression in the current sample comprised a loss of previously acquired hand and speech skills, in addition to the development of hand stereotypies, social withdrawal and inconsolable crying. As in previous large genotype phenotype studies (5), earlier regression was observed in girls with the mutation types p.R255X and p.T158M who also experienced poorer gross motor development and were unable to walk independently. Regression after 18 months of age was observed in girls with the mutation types p.R133C and p.R294X. Hand stereotypies were often frequent and severe, consistent with literature in which the number and intensity of stereotypies were greater during the early years (11).

As with previous research (12), the girl with a C-terminal deletion had a milder clinical profile and no regression in hand or speech skills by time of interview (age 51

months). The most plausible explanation is that this particular mutation is associated with the late regression variant (2, 12, 13) and that earlier symptoms include delay rather than regression of skills.

As expected, social withdrawal and inconsolable crying occurred during regression (6). We found that the period of social withdrawal was short and ability to interact socially was regained quickly whilst inconsolable crying persisted for longer. With social withdrawal and a milder phenotype, some in our study had an earlier diagnosis of autism (14) although there was no evidence to suggest that these autistic symptoms persisted beyond the regression period. This was an extremely challenging time for families and strategies involving less physical contact such as playing a DVD or music were often more effective in calming their distressed child.

The early onset vomiting exhibited by two girls in our study was spontaneous and severe, and clinically confirmed as reflux in one. Gastrointestinal issues can occur early in Rett syndrome (3, 15) and our findings illustrate the potential for gastro-intestinal dysmotility to have early and dramatic effects. Strabismus or crossed eyes could have related to altered muscle tone, with 'unusual behaviour in the eyes' previously reported in the literature as an early symptom (15), and the girl with torticollis had additional neurological signs.

Soon after regression, there was often loss of balance consistent with the development of truncal ataxia and development of impaired gait (6). In another study (n=53), almost half of the girls experienced loss of motor skills during regression (7) although the findings were limited due to possible recall error (age range 2-44 years at time of study). Early gross motor development influences social and emotional development, non-verbal communication skills and spatial abilities (16). Hence, understanding the early gross motor profile may not only provide further insight into the underlying mechanisms of 'abnormal gait' but possibly also other features of Rett syndrome.

The regression period is a difficult time for girls with Rett syndrome and their families, a time when worry, distress and confusion are compounded by lack of a definitive diagnosis. We utilised developmental profiling to explore this period with a comprehensive child development perspective. To minimise recall error, we restricted our sample to girls born after 2007 and requested that mothers review infant records prior to interview. Member checking of the interview transcripts increased the accuracy of the data. We acknowledge that there may be some recall bias in the mother's recollection of early developmental events. To reduce this, we validated our data using existing information in the ARSD and InterRett database and also home videos and photos. Our observations were consistent with previous genotype-phenotype relationships in Rett syndrome but our small sample size precluded statistical analyses of current data. Neurological examination findings would provide additional information in documenting the evolution of gross motor dysfunction.

The early clinical profile of Rett syndrome is complex and other signs often precede the main criteria. We have also illustrated variability in how hand and speech skills may be lost; the temporal relationships between social withdrawal and inconsolable crying; and how previously acquired gross motor skills may decline with loss of balance soon after regression. The clinical profile of RTT should not be characterised by the development of these features in isolation, but more so by how they emerge and interact.

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Table 1: Descriptive details and age of onset (months) for each of the themes of the pre-regression and regression periods for each child

Number	Mutation	Birth year	Age at interview (months)	First RTT symptom	Onset of regression	Autistic symptoms	Inconsolable crying	Loss hand function	Hand stereotypies	Loss of speech	Decline in gross motor skills	Age at diagnosis (months)
1	p.R255X	2007	51	14	14	15	15	18	15	14	42	22
2	p.R255X	2007	60	24	24	-	47	24	24	-	-	23
3	p.R255X	2007	53	9	9	9	9	12	12	9	36	29
4	p.R255X	2009	34	18	18	20	18	18	19	19	-	22
5	p.R133C	2007	49	15	34	-	15	34	15	36	36	36
6	p.R133C	2007	49	9	18	10	10	18	9	20	42	19
7	p.R133C	2007	56	12	28	36	36	31	30	28	-	32
8	p.R270X	2007	60	12	18	19	19	24	19	18	18	27
9	p.R270X	2008	44	6	15	15	16	15	15	-	24	25
10	p.T158M	2008	43	14	14	14	-	16	12	14	-	20
11	p.T158M	2009	28	9	10	11	-	12	10	10	-	20
12	C-terminal deletion	2007	51	33	-	-	-	-	33	-	38	42
13	p.R106W	2008	43	6	10	10	11	10	13	10	-	19
14	p.R294X	2008	46	2	36	18	12	36	18	-	-	25

Table 2: Summary of first identifiable concerns and illustrative quote for each child

Number	Mutation	Age of onset (months)	Symptom(s)	Quote
14	p.R294X	2	Vomiting	“She started vomiting daily at almost like every meal, and it was more than just a spit out vomit, it was like projectile vomit. So we would feed her with a bath size towel instead of a burp rag”
13	p.R106W	6	Vomiting	“Her reflux and vomiting became a very serious concern. Which I had to take her to E.R., twice. They dismissed me as well. They thought it was just reflux”
9	p.R270X	6	Night laughing, sleep disturbances	“She might wake up every, once every two, three weeks. She’ll either just be talking, babbling... She’ll sound like she’s in a really good mood. And she wakes up in the middle of the night”
11	p.T158M	6	Crick in neck (hypertonic), predominant left sided hand use and mildly cross-eyed	“She had a crick in her neck with her head always tilted to one side... [and] it was very stiff, like it hurt her for us to try to put it straight”
3	p.R255X	9	Loss speech, social withdrawal, inconsolable crying	“I think the worst of it was between 9 and 12 months...Where babbling ceased altogether and she would look through us and she just cried a lot”
6	p.R133C	9	Hand flapping	“She was doing like a flapping motion with just one hand. But I didn’t think anything of it, because it was almost like she was like playing with her mouth or her, like her, putting her fingers on her lips”
7	p.R133C	12	Cross-eyed	“When she was very little even before she could walk...I started noticing her one eye would go in lot, so she has had that for a while now”
10	p.T158M	14	Cross-eyed	“Her muscles in the eyes are too weak, so she cross the eyes because of that. Before I had pictures of her, with the eyes ok. You know looking straight, but when the regression is started, all the muscles you know, she lost control of all of the muscles including the eyes”
1	p.R255X	14	Loss of speech	“By September of 08, I never really heard any speech, and that was right before October came and everything really happened. I would say September of 08 was the last month that ever heard words”
5	p.R133C	15	Hair pulling,	“At that time there were also several just, inconsolable screaming fits. That there was nothing I

			inconsolable crying, sleep disturbances	could do to appease her. So the hair pulling, the screaming fits, the lack of sleep. Those three things all happened around, like in the spring of 2009”
8	p.R270X	18	Loss of speech, social withdrawal, inconsolable crying and hand stereotypies	“.. she had gotten a lot quieter and sort of wasn’t babbling as much. But it was more her eye contact, she was crying a lot uncontrollably during the night. And yeah, she didn’t really want cuddles, didn’t want to look at you and she was sort of like constantly flicking a book a lot. And carry a hat with her. She always had a hat ... we noticed all that.”
4	p.R255X	18	Inconsolable crying	“I mean there are some days when she would have five or six or more in a day. Even now when she is having a really bad day, sometimes she has four or five, and sometime she doesn’t have any, but I would say most days she has at least a couple”
2	p.R255X	24	Loss hand use	“Before she started school, she was able to grab toys, and like feed herself small finger foods, and then she started to regress... We are still working on trying to get those skills back. So right now, she can’t self feed herself anymore”
12	C- Terminal deletion	33	Hand stereotypies	“She did something where she’d pull on the back of her pants kind of looked like she might need to use the restroom”