A National Survey of Rett Syndrome: Age, Clinical Characteristics, Current Abilities and Health

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Abstract

As part of a wider study to investigate the behavioral phenotype of a national sample of girls and women with Rett syndrome (RTT) in comparison to a well-chosen contrast group and its relationship to parental well-being, the development, clinical severity, current abilities and health of 91 participants were analyzed in relation to diagnostic, clinical and genetic mutation categories. Early truncating mutations or large deletions were associated with greater severity. Early regression was also associated with greater severity. All three were associated with lower current abilities. Epilepsy and weight, gastrointestinal and bowel problems were common co-morbidities. Participants with classic RTT had greater health problems than those with atypical RTT. A substantial minority of respondents reported fairly frequent signs of possible pain being experienced by their relative with RTT. Overall, the study provides new data on the current abilities and general health of people with RTT and adds to the evidence that the severity of the condition and variation of subsequent disability, albeit generally within the profound range, may be related to gene mutation. The presence of certain co-morbidities represents a substantial ongoing need for better health. The experience of pain requires further investigation.

*Key words*: Intellectual disabilities, Rett syndrome, *MECP2*, clinical characteristics, health

**INTRODUCTION**

Rett syndrome (RTT) is a genetic disorder that causes severe cognitive and physical impairments. In its classic form, it appears to affect almost exclusively females, with an incidence of up to one in every 10,000 live female births. Its cause is most often a mutation in the methyl-CpG binding protein-2 (*MECP2*) gene, located on the X chromosome at *Xq28* [Amir et al., 1999]. However, although a *MECP2* mutation is found in most instances of the classic form, RTT remains a clinical rather than a molecular diagnosis. *MECP2* mutations have not been found in all individuals with RTT and the mutation has been found in individuals who do not meet the clinical diagnostic criteria for classic or variant RTT [Hagberg, 2002].

Neul et al. [2010] described revised diagnostic criteria for RTT. Classic RTT requires apparently normal psychomotor development in the first 6 months of life followed by a period of regression, which is not due to brain injury secondary to trauma, neurometabolic disease, or severe infection, and involves partial or complete loss of acquired purposeful hand skills and language, gait abnormalities and the development of stereotypic hand movements, followed by stabilization or even some degree of recovery. An important aspect of the regression is a period of social withdrawal or impaired communication. Atypical RTT requires a similar period of regression and subsequent stabilization/ recovery, at least two of the above four behavioral manifestations and the presence of at least five, out of 11, supportive criteria. Other variant forms have also been described [Neul et al., 2010].

Supportive criteria include clinical characteristics often found in RTT. These include breathing abnormalities, teeth grinding, impaired sleep pattern, abnormal muscle tone, small and cold hands and feet, scoliosis/kyphosis, growth retardation and spells of inappropriate laughing and/or screaming [see, Cass et al., 2003; Reilly and Cass, 2001; Young et al., 2007]. Feeding difficulties have also been described [Oddy et al., 2007]. These researchers found that body mass index z scores for a RTT sample were lower than age group comparisons and decreased steadily with age. Twenty percent had enteral nutrition support and this was more common in the older age group. Those with low mobility had lower mean body mass index z scores than those with higher mobility. Increased frequencies of breath-holding and hyperventilation were associated with lower body mass index z scores.

The majority of people with RTT have epilepsy, with reported rates of 60-80% [Cardoza et al., 2011; Glaze et al., 2010; Jian et al., 2007]. Rates vary across mutation types, although findings are not entirely consistent. At least two of the three studies above reported lower rates for C-terminal mutations and p.R255X and p.R294X mutations, and higher rates for p.T158M and p.R270X mutations. Rett ‘episodes’, which consist of a non-epileptic behavior often misidentified as a possible seizure in which the eye gaze is not fixed, the person appears not to be breathing, with absence of hand movements and motor activities, were reported in 74% of a UK sample [Cardoza et al., 2011] with rates varying between mutation types from 50% to 100%.

As the above illustrates, the literature on typical clinical characteristics, particularly on those that underpin the diagnostic criteria, is well-established. However, studies on the health of people with RTT are scarce. A Medline search pairing the key terms, ‘Rett syndrome’ and ‘health’ produced a zero return. General health was assessed in a longitudinal study of ageing among 53 at T1 Dutch women with RTT [Halbach et al., 2013]. These researchers found that general health was usually rated as good. During the previous 5 years, 10 of the 53 women had been hospitalized for reasons of pneumonia, respiratory distress, status epilepticus, rectal bleeding, PEG probe, bladder inspection, decline in walking and refusal to eat and/or drink. Three women had had orthopedic surgery for contractures, and two dental surgery for extraction of wisdom teeth.

The purpose of our research was to gain a UK national RTT sample mainly to investigate the associated behavioral phenotype in comparison to a well-chosen contrast group and its relationship to parental well-being. This paper focuses on abilities and health in relation to diagnostic, clinical and genetic mutation categories.

**MATERIALS AND METHODS**

Survey sample

Before commencing the study, ethical approval was received by the Research Ethics Committee for Wales: Application number: 09/MRE09/50.

Families were recruited through the British Isle Rett Syndrome Survey (BIRSS). The BIRSS was established in 1982 by Dr Alison Kerr at Glasgow University and developed by her over more than 20 years. On her retirement in 2005, the BIRRS database was transferred to Cardiff University, where it is maintained by Professor Angus Clarke. In September 2010, the database held data on 933 people with RTT: 807 living and 126 deceased. Invitation letters were sent by the BIRSS and details of potential participants were not known to the researchers in this study until the families provided them.

As the study began before the new diagnostic criteria for RTT were established, participants were selected on the basis of fulfilling the Hagberg et al. [2002] diagnostic criteria. Participants to be included were to be of all ages living in the family home and have a clinical diagnosis of either classic RTT or classic RTT incomplete, usually when head circumference at birth was unknown, regardless of *MECP2* mutation test result, or atypical RTT but with a positive *MECP2* mutation test result. Initially, a random sample of 150 individuals and families was selected from a sample of 364 who met the inclusion criteria for the study and had given consent to be contacted further. The sample was stratified by age into four groups: 5-11 years, 12-17 years, 18-25 years and 26 years or over. There were 40, 67, 111 and 146 people respectively in each age group, who met the inclusion criteria in the BIRSS database, of whom 16, 28, 46 and 60 were respectively randomly selected for inclusion in the study.

An invitation letter, containing an information leaflet, consent and assent forms, prepaid envelope and prepaid card that families could return if they did not wish to participate in the study was sent to all but 16 of the families of the 150 identified individuals. Sixteen families were omitted as the BIRSS did not have established contact with them*.* However, following a low response rate in which only 56 families (41.8%) returned a consent form, invitation letters were then sent to the families of the remaining 174 individuals who met the inclusion criteria and were contactable. In total, 308 invitation letters were sent out. A follow-up letter was sent to families who did not return the consent form or the card, two months after being sent the first invitation letter, repeating the invitation to take part and including second copies of all enclosures. This letter explained that they would not be contacted again.

A total of 126 families (40.9% of the original 308 contactable families) returned a consent form. Questionnaire packs with prepaid return envelopes were then distributed and families were contacted first by telephone and then by letter if they had not returned the questionnaires within two months of them being sent. Thirteen families indicated that they did not wish to fill in the questionnaires and wanted to be removed from the list of participants. In a further 2 cases, invitation letters were returned because of an incorrect address. Ninety-three families returned completed questionnaires (30.2% of the original 308). Ninety-two participants with RTT were female and 1 male. The male participant was excluded from the final analysis. One participant passed away during the study and was also not included in the analysis.

Measurement

Families were asked to complete two questionnaire packs, one relating to the person with RTT, covering their early development, current skills, health and behavioral characteristics and the other relating to various aspects of family experience. It is some of the first set of measures that are of concern here. After parents returned the completed questionnaire packs, the Vineland Adaptive Behavior Scale – Survey Form [Sparrow et al., 1984 - see below] was carried out as a telephone interview with one of the parents.

*Demographic information.* Information was requested about date of birth, age of diagnosis, who diagnosed the condition and whether or not a genetic cause of RTT had been identified.

*RTT development.* Information was requested about development and current abilities based on the diagnostic criteria for RTT [Hagberg et al., 2002], pregnancy, delivery, early development, head growth, regression and current abilities, height and weight.

*Simplified Severity Score* [Smeets et al., 2009].Information was requested about six features of RTT: sitting, walking, hand use, speech, epilepsy and spine deformation. Each domain is scored from 0 to 3, where 0 indicates a normal situation, 1 indicates impaired ability to sit and walk, reduced hand use, some words, epilepsy is controlled with medication and scoliosis is mild; 2 indicates that the abilities to sit, walk, use hands and speak are lost, epilepsy is uncontrolled and scoliosis is severe; 3 indicates that the individual never acquired the abilities to sit, walk, use hands and speak, status epilepticus occurs and scoliosis has been operated upon. The score, which has a maximum of 18, evaluates the overall severity of the syndrome and indicates domains that are considered to influence evolution and severity in the long term. Scores of 9 or less are considered mild or less severe. Internal consistency of the data in this study was good, alpha = 0.73.

*Health Questionnaire* [Hall et al., 2008].Information was requested about 15 possible medical problems in relation to two time periods: ever in their life and during the last month. Each problem is rated from 0=never to 3=severe. An Overall Health Score is obtained by summing the total for both time periods. Inter-rater reliability scores of 0.72 for health problems occurring in the person’s life and 0.76 for the health problems occurring during the last month have been reported [Hall et al., 2008]. Internal consistency of the data in this study was good, alpha = 0.77 for the overall health score.

*Non-communicating Children’s Pain Checklist* [NCCPC-R, Breau et al., 2002].The NCCPC-R was designed to be used for children, aged 3 to 18 years, who are unable to speak because of cognitive or intellectual impairments, by parents or carers, without training. It has 30 questions arranged in seven sections: Vocal, Social, Facial, Activity, Body and Limbs, Physiological, Eating and Sleeping. It was designed as an observational assessment to cover a two-hour period. Psychometric properties and threshold scores are given in Breau et al. [2002]. This study follows the example of others designed to measure ‘typical’ pain experienced by individuals with neurodevelopmental disabilities [e.g., Eden et al., 2014; Symons et al., 2009] by using a modified form of the NCCP-R. Respondents were asked to rate the occurrence of items over the previous week rather than two hours. The published cut-off scores do not apply. Moreover, items in two sections, Activity and Physiology, have not been included in the analysis because they contain items, such as ‘Not moving, less active, quiet’ and ‘Breath holding’, that are characteristic of RTT. The information within the other five sections is presented descriptively.

*Gastro-oesophageal Distress Questionnaire* [GDQ, Oliver and Wilkie, 2005].The GDQ is a 17 item informant-based questionnaire designed to assess the frequency of behaviors in the previous two weeks that are indicative of pain in the oesophagus and stomach. Twelve items are rated on a five point scale where 0 = Not occurred, 1 = Once a week, 2 = Once a day, 3 = Once an hour and 4 = More than once an hour. Two items are dichotomous (Yes/no) and three are rated on a four point scale where 0 = Not occurred, 1 = Once a week, and the wording of the more frequent two values depend on the item in question. Data on its psychometric properties have not been published. Hence the data are also treated purely descriptively, with only the item on perceived pain being reported.

*Vineland Adaptive Behavior Scale – Survey Form* [VABS, Sparrow et al., 1984].The VABS Survey Form is a well established scale to assess adaptive behavior in people with and without intellectual disabilities. It contains 297 items. The scale is divided into four domains: Communication, Daily Living, Socialization and Motor Skills. Standard scores (mean = 100; SD= 15) and age equivalent scores can be combined to derive an Adaptive Behavior Composite. Internal consistency (median Communication 0.89, Daily Living Skills 0.90, Socialization 0.86, Motor Skills 0.83, Adaptive Behavior Composite 0.94), test re-test reliability (Communication 0.86, Daily Living Skills 0.85, Socialization 0.81, Motor Skills 0.81, Adaptive Behavior Composite 0.88) and inter rater reliability (Communication 0.75, Daily Living Skills 0.72, Socialization 0.62, Motor Skills 0.78, Adaptive Behavior Composite 0.74) have been reported [Sparrow et al., 1984].

Data analysis

Analysis investigated severity score, current abilities and health in relation to, first, whether a mutation in the *MECP2* gene had been identified and, if so, the nature of the mutation and, second, diagnostic classification: classic, atypical and *MECP2* related disorder. Non-categoric measures were tested for normality using the Kolmogorov-Smirnov test and a critical region of p< .05. Results from such testing and examination of skewness and kurtosis found that severity and adaptive behavior scores were non-normal. Non-parametric tests were therefore used to explore differences between groups.

**RESULTS**

Age and diagnosis

Thesample were 91 girls and women with a diagnosis of RTT, of whom 80 (87.9%) lived at home and 11 (12.1%) lived in out-of-family placements. Although the survey sought to include only individuals living with their parents, the information on the BIRSS database was not up-to-date and a minority did not do so. Their ages ranged from 4 to 47 years with a mean of 20.5 years. In terms of the Neul et al. [2010] criteria: 69 had classic RTT (75.8%), 19 atypical RTT (20.9%) and three a *MECP2*-related disorder (4.3%). Seventy-one were known to be *MECP2* positive (78.0%): 52 in the classic group and 16 in the atypical group in addition to the three with *MECP2*-related disorder. Only one person classified as having classic RTT was known not to have a *MECP2* mutation, the remainder without a known mutation had been diagnosed prior to testing becoming routine clinical practice. Not all participants in the more up-to-date atypical category had a known *MECP2* mutation as this group now contained individuals previously classified by the Hagberg et al. [2002] criteria as having classic RTT incomplete.

Mutations found in two or more cases were C-terminal (N = 13), p.R168X, p.R270X and p.R306C (all N = 6), p.R255X and p.R294X (both N = 5), p.T158M and p.P152R (both N=4), p.R306H (N = 3). Diagnosis of RTT was made by a pediatrician in 42.9% of cases, a clinical geneticist in 26.4%, by both a pediatrician and clinical geneticist in 3.3% and by another professional in 25.3%. This information was missing for the remaining 2.2%. Median age of diagnosis was 3.0 years (range, 1-39 years). Diagnosis occurred most commonly between 2 and 4 years of age.

Although data on the *MECP2* mutation were available, six broad categories were created to avoid subgroups being too small: missense (n=23, 25.3%), early truncating (n=26, 28.6%), late truncating (n=7, 7.7%), C-terminal (n=13, 14.3%), large deletion (n=2, 2.2%) and no known mutation (n=20, 22.0%). Disregarding the last category, these were then combined into two broader mutation groups: (a) early truncating and large deletion, and (b) missense, late truncating and C-terminal, in line with the findings of Neul et al. [2008].

Maternal pregnancy, early development and regression features.

Eight-five (93.4%) of mothers reported experiencing a normal pregnancy and 74 (81.3%) a normal delivery. The majority reported normal development in the first few months of life (85.7%) with no apparent problems (73.6%). Regression was reported in 87 (95.6% of the sample). In one case (1.1%), the mother was not sure if the child had had a regression and, in 3 others (3.3%), all with *MECP2*-related disorder, they reported that the child did not have a regression. Mean age of regression was 18.9 months (range, 6-84 months; SD 11.75). The most common month for regression onset was 18 months (18.7% of cases). Overall, 15 (16.5%) had a regression before 12 months, 49 (53.8%) between 12 and 18 months, 18 (19.0%) between 19 and 36 months and 5 (5.5%) after 36 months. Loss of hand use was reported in 92.3% of the sample, loss of communication skills in 83.7%, loss of mobility in 70.3% and loss of social contact in 53.8%. In one case, the parent reported that the child had never gained any skills in communication, mobility, functional hand use and sociability. There were no significant differences in age of regression or reported loss of previously acquired skills either between the classic and atypical group or between the two mutation groups.

Characteristic features

Loss of functional hand skills, followed by the appearance of hand stereotypies such as hand wringing, clapping and tapping, was reported in all but one case (98.9%). Breath holding (76.9%), hyperventilation (58.2%), teeth grinding (57.1%) and sleep disturbances (61.5%) were also commonly reported. Rett ‘episodes’ were also frequent (72.6%). Individuals with classic RTT were more likely to present with breath holding than those with atypical RTT (χ²(2)=8.38,p< .05).

Clinical Severity

Total Severity Scores ranged from 3 to 15 (mean 8.6, SD 3.16). Fifty-five (60.4%) presented with a mild phenotype (severity score ≤ 9) and the remaining 36 (39.6%) with a more severe phenotype (score >9). The severity scores of mutation groups significantly differed (χ²5= 11.62, p< .05, see Table I). Those with an early truncating or large deletion mutation had greater severity scores in total and in relation to walking and hand use than those with missense, late truncating and C-terminal mutations (U= 377.5, 324.5 and 445.0; p<.01, .01 and .05 respectively). In addition, age of regression was significantly inversely associated with severity score (rs = -0.31, p<.01).

Current abilities

According to parental report, 14 individuals (15.4%) had retained some speech, although only 3 (3.3%) of the sample had 30 or more words. About two-thirds (65.9%) could communicate with gesture or sound, predominantly with eye contact or eye pointing, and 67.0% could make a choice between two items. Although hand use was lost during regression, minorities could still feed with fingers and/or use a spoon or fork (36.9% and 17.6%, respectively). The ability to reach for an object was retained or regained in 52.7% and to hold an object in 35.2%. Although the ability to walk was impaired, 52.7% of the sample could walk with support and 37.4% could walk independently.

According to the VABS (N = 84), 71 (84.5%) scored below 20 on the Adaptive Behavior Composite and the remaining 13 (15.5%) between 20 and 34. Descriptive analysis indicated that those with an Adaptive Behavior Composite above 20 were children aged 4 -11 years. Mean age equivalent scores were 10.5 months (SD 3.15, range 4 – 23) for the Adaptive Behavior Composite, 9.9 months (SD 4.67, range 1 – 34) for the Communication domain, 12.7 months (SD 3.91, range 1 – 23) for the Daily Living Skills domain, 9.0 months (SD 4.53, range 1 – 23) for the Socialization domain and 5.5 months (SD 5.52, range 1 – 23) for the Motor Skills domain. Level of developmental delay was thus assessed as profound in 77 (91.7%) and severe in seven (8.3%). There were significant negative associations between the simplified severity score and all VABS domains except for socialization skills (-0.75<rs<-0.32, all p<.01.) Older age of regression was significantly associated with higher Daily Living Skills (rs = 0.32, p<.005) and Motor Skills (rs = 0.33, p<.005). In addition, individuals with an early truncating mutation or a large deletion had significantly lower Adaptive Behavior Composite, Communication domain, and Socialization domain scores (U= 564.5, 619.0 and 537.5; p<.01, .05 and .01 respectively).

Health

About two-thirds of the 91 participants was reported to have seizures (n=63, 69.2%) and to be currently on anti-epilepsy medication (n=59, 64.8%). However, about half (n=44, 48.4%) had not experienced seizures for at least a year. In contrast, 7 of the sample (7.7%) was reported to have seizures daily and 18 (19.8%) weekly. Although an apparently higher proportion of people with classic RTT were reported to experience daily or weekly seizures (32.4%) compared to those with atypical RTT (10.3%), this difference failed to reach statistical significance (χ²(1)=3.54,p= .060). Similarly, although an apparently higher proportion of people with early truncating or large deletion mutations were reported to experience daily or weekly seizures (44.4%) compared to those with missense, late truncating and C-terminal mutations (23.3%), this difference also failed to reach statistical significance (χ²(1)=3.46,p= .063).

Reported heights and weights for participants aged below 20 years were entered with their ages into the Center for Disease Control and Prevention body mass index (BMI) calculator for children and teenagers to determine whether they were a healthy weight. Otherwise, for participants aged 20 years or over, a BMI< 18.5 was considered as underweight, a BMI between 18.5 and 24.9 was considered as a healthy weight, a BMI between 25.0 and 29.9 was considered overweight and a BMI of 30 or greater was considered obese. Among the children and teenagers, 19.4% were underweight, 58.3% had healthy weight and 22.2% were overweight. Among adults aged 20 years or over, 44.7% were underweight, 36.8% had healthy weight, 15.8% were overweight and 2.6% were obese. The distribution of weight categories did not differ across diagnostic or mutation groups among the children and teenagers. However, among participants 20 years or over, there was a significant difference between diagnostic categories (χ²(6)=23.19,p=.001). There was a higher proportion of underweight older participants among those with classic RTT than those with atypical RTT or *MECP2*-related disorder and a corresponding lower proportion overweight or obese.

Table II lists the percentage occurrence at some level of a variety of health problems ever in the past and during the last month. The most common was epilepsy (79.1% ever, 51.6% in the last month), followed by gastrointestinal problems, such as reflux or stomach problems, (60.4% ever, 35.1% in the last month), bowel problems, such as constipation or obstruction, (56.0% ever, 41.7% in the last month), dental problems (42.8% ever, 12.1% in the last month) and skin problems (40.6% ever, 29.7% in the last month). The majority of the sample had some degree of scoliosis (59.4%, requiring surgery in 29.7%). Lung or respiratory problems in the last month were also reported by 11.0%. In addition, in response to one of the GDQ questions, 34.1% assessed their daughter as being prone to respiratory tract infections, a tenth of whom reported monthly occurrence, three tenths quarterly occurrence, just over a quarter biannual occurrence and about a third annual occurrence.

Compared to maximum scores possible of 45 in each time period on the Health Questionnaire, mean scores were 3.4 (SD 3.30) in the previous month and 9.5 (SD 5.82) ever during the person’s life. There were no significant differences in the distribution of health problems between diagnostic groups, although there was a difference in the overall health score ever during the person’s life (χ²(2)= 9.97, p< .05). Post-hoc analysis indicated that individuals with classic RTT experienced greater health problems during their lives than individuals with atypical RTT (U = 351.0 z = -3.096, p< .005). Health scores did not differ between mutation groups.

Indications of Pain

Table III gives descriptive information about the five sections of the NCCP-R included in the study. Mean section scores were towards the lower end of their ranges. However, the higher ends of the ranges either equaled or approached the section maximum scores. Moreover, for each of the five sections, only approximately an eighth to a third of the sample had all items rated as not occurring. Similar proportions had at least one item in each section rated as occurring very frequently. Across the five sets of items as a whole, 51.2% of the sample were reported as having experienced at least one item very frequently in the previous week (12.2% had 3 or more very frequently). In addition, in response to one of the GDQ questions, only 33.4% reported that their daughter did not appear to be in pain or discomfort in the previous two weeks. Over a third (37.8%) reported the appearance of pain or discomfort as occurring weekly, 20.0% daily, 4.4% hourly and 3.3% more than hourly.

**DISCUSSION**

In this paper, we presented descriptive, clinical and health data on 91 girls and women with RTT. The sample was drawn from a national database with all families whose child met the criteria invited to participate. It was also a reasonably large sample for a study of RTT. However, it was skewed towards those living in the family home as the main research purpose was to investigate the relationship between child characteristics and parental well-being. The 11 participants in out-of-family placements were, on average, older than those living in the family home (mean, 28.0 yrs vs. 19.5 yrs), albeit that the two groups were similar in age among the adults: almost all of the children lived with their parents. In addition, the two groups were similar in diagnostic distribution (82% classic vs. 75%), mean age of regression (18.5 mnths vs. 19.3) and mean severity score (9.0 vs. 8.5).

The response rate was low and it is not possible to assess the representativeness of the achieved sample. However, the age distribution was similar to a recent all-age, large sample (n=983) study of gastrointestinal and feeding problems [Motil et al., 2012]. In addition, over three-quarters of the sample had a positive mutation in the *MECP2* gene. Not all individuals in the sample had been tested, but in only one case diagnosed with classic RTT was a *MECP2* mutation not found. This is consistent with the literature that a mutation in the *MECP2* gene can be found in over 90% of cases with classic RTT [Neul et al., 2010].

Although there is now evidence of developmental problems in the first months [Burford et al., 2003; Einspieler et al., 2005; Leonard and Bower, 1997; Neul et al., 2014; Witt-Engerstrom, 1987], apparently normal early development was reported by most parents prior to the regression of previously acquired skills. Consistent with other studies, the most common age of onset of regression was between 12 and 18 months. Age of regression tended to predict severity of the condition and subsequent disability. However, clinical severity was also associated with mutation group.

Cheadle et al. [2000] found that individuals with truncating mutations were more severely affected than those with missense mutations, and that the same was true of early truncating mutations compared to late truncating mutations. Neul et al. [2008] reported that individuals with: (a) p.R133C, a missense mutation, were less severely affected than those with large deletion or p.R168X mutation, an early truncating mutation, (b) p.R168X mutation were more severely affected than those with C-terminal mutation or p.R294X mutation, a late truncating mutation, and (c) p.R168X mutation were less likely to walk, retain hand use or use words. Further work based on the large US Natural History study [Cuddapah et al., 2014] has confirmed and extended these observations, in that: (a) individuals with early truncating mutations or either of two specific missense mutations have on average a more severe phenotype than those with late truncating mutations or most other missense mutations, (b) that the phenotype associated with the p.T158M missense mutation is often of intermediate severity; and (c) that severity increases with age at least into the third decade, and that ambulation, hand use and age at onset of stereotypies are strongly linked to overall disease severity. Our results were broadly consistent with these findings. We found that early truncating mutations and large deletions were associated with greater severity overall, poorer retention of walking skills and hand use and less good current skills overall and less good communication and socialization skills in particular.

Health problems most commonly reported included epilepsy, scoliosis, gastrointestinal, bowel and dental problems. Rates of occurrence of epilepsy and ‘Rett episodes’ were broadly consistent with earlier studies [e.g., Cardoza et al., 2011; Halbach et al., 2013]. Poorly controlled epilepsy, that is seizures daily or weekly, appears to be an issue for about a quarter overall, a third with classic RTT and nearly a half of individuals with early truncating or large deletion mutations. Being underweight is also an issue of concern for individuals with classic RTT to the extent that parental report data can be relied upon. The proportion with BMIs indicating underweight found here among children and teenagers (19.4%), although lower than among the older participants, was still considerably greater than that found in the general population [e.g., 0.9% aged 4-5 years and 1.3% aged 10-11 years in the UK, Public Health England, 2014]. The 44.7% found among those 20 years or over was similar to the 39% reported by Halbach et al. [2013]. These findings are consistent with those of Tarquinio et al. [2012] who found that the weight trajectory for classic RTT diverged below the normative pattern at age 6 months and that mean weight was lower than the normative at 13 months. Moreover, the weight of 71% of participants with classic RTT was below the second percentile on the normative reference by the age of 18 years. Leonard et al. [2013] provide recommendations for the clinical management of poor growth and weight gain in RTT derived from evidence review and consensus among an expert panel of clinicians.

In other respects, there were relatively low mean scores on the Health Questionnaire and this appears consistent with the Halbach et al. [2013] study, in which respondents generally reported the health of the RTT women as good. However, in addition to epilepsy, gastrointestinal and bowel problems were a common co-morbidity. Moreover, the fact that the mean score for problems in the last month was over a third as high as the mean score for problems ever during the person’s life would indicate that certain co-morbidity tends to be chronic. Participants diagnosed with classic RTT had higher overall health problem scores than those with atypical RTT.

Scientific evidence about pain among people with RTT is limited and unclear. There is now evidence to suggest that *MECP2* could be implicated in the molecular events required for the initiation of pain and, therefore, alterations in *MECP2* such as those in RTT may affect pain sensitivity [see Downs et al., 2010]. Indeed, Downs et al. [2010] have reported on the prevalence of abnormal pain response in RTT. In their study, the majority of parents (60% of 628) reported reduced pain sensitivity. However, for 15%, pain sensitivity was reported as increased. Moreover, a distinction was made between pain from external causes, such as trauma, accidents, or self-injury, and that from internal causes, such as abdominal pain, flu or headaches. Whereas, sensitivity to pain could be decreased in relation to the former, it could be increased in relation to the latter. There was also preliminary evidence that the precise mutation may play a role in abnormal pain sensitivity. Symons et al. [2013] found that 24% (of 44 parents) reported that their child had experienced pain on 8 or more days in the previous 30 days, a finding which is consistent with a substantial minority of respondents in this survey reporting fairly frequent signs of possible pain being experienced by their relative with RTT. The investigation of pain in RTT deserves further research.

In conclusion, this paper describes a substantial national survey of girls or women with RTT. The representativeness of the sample is not known, but the consistency of findings in some key respects to previous literature is reassuring. The study provides new data on the current abilities and general health of people with RTT and adds to the evidence that the severity of the condition and variation of subsequent disability, albeit generally within the profound range, may be related to the associated gene mutation. Although their general health may be thought to be reasonably good, substantial proportions of females with RTT have poorly controlled epilepsy, are underweight, have gastrointestinal and/or bowel problems and may experience regular pain. The presence of such co-morbidities represent a substantial ongoing need for better health, particularly given the age of participants.

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**REFERENCES**

Amir RE, Veyver IB, Wan M, Tran CQ, Franckle U, Zoghbi HY. 1999. Rett syndrome is caused by mutations in X-linked MECP2, encoding methyl-CpG – binding protein 2. Nat Genet 23: 185-187.

Breau LM, McGrath PJ, Camfield CS, Finley GA. 2002. Psychometric Properties of the Non-communicating Children’s Pain Checklist-Revised. Pain 99: 349-357.

Burford B, Kerr AM, Macleod HA. 2003. Nurse recognition of early deviation in the development in home videos of infants with Rett disorder. J Intell Disabil Res 47: 588-596.

Cardoza B, Clarke A, Wilcox J, Gibbon F, Smith PEM, Archer H, Hryniewiecka-Jaworska A, Kerr M. 2011. Epilepsy in Rett syndrome: Association between phenotype and genotype, and implications for practice. Seizure 20: 646–649.

Cass H, Reilly S, Owen L, Wisbeach A, Weekes L, Slonims V, Wigram T, Charman T. 2003. Findings from a multidisciplinary clinical case series of females with Rett syndrome. Dev Med Child Neurol 45: 325–337.

Cheadle JP, Gill H, Fleming N, Maynard J, Kerr A, Leonard H, Krawczak M, Cooper DN, Lynch S, Thomas N, Hughes H, Hulten M, Ravine D, Sampson JR, Clarke A. 2000. Long-read sequence analysis of the MECP2 gene in Rett syndrome patients: correlation of disease severity with mutation type and location. Hum Mol Genet 9: 1119-1129.

Cuddapah VA, Pillai RB, Shekar KV, Lane JB, Motil KJ, Skinner SA, Tarquinio DC, Glaze DG, McGwin G, Kaufmann WE, Percy AK, Neul JL, Olsen ML. 2014. *Methyl-CpG-binding protein 2 (MECP2)* mutation type is associated with disease severity in Rett syndrome. J Med Genet 51:152–158.

Downs J, Géranton SM, Bebbington A, Jacoby P, Bahi-Buisson N, Ravine D, Leonard H. 2010. Linking MECP2 and pain sensitivity: The example of Rett syndrome. Am J Med Genet A 152A: 1197–1205.

Eden K, de Vries P J, Moss J, Richards C, Oliver C. 2014. Self injury and aggression in Tuberous Sclerosis Complex; cross syndrome comparison and associated risk markers. J Neurodevelop Disord 6: 1-11.

Einspieler C, Kerr AM, Prechtl HFR. 2005. Is the early development of girls with Rett disorder really normal? Pediatr Res 57: 696-700.

Glaze DG, Percy AK, Skinner S, Motil KJ, Neul JL, Barrish JO, Lane JB, Geerts SP, Annese F, Graham J, Mcnair L, Lee HS. 2010. Epilepsy and the natural history of Rett syndrome. Neurology 74: 909-12.

Hagberg B. 2002. Clinical manifestations and stages of Rett syndrome. Ment Retard Dev D R 8: 61-65.

Hagberg B, Hanefeld F, Percy A, Skjeldal O. 2002. An update on clinically applicable diagnostic criteria in Rett syndrome. Comments to Rett syndrome clinical Criteria Consensus Panel Satellite to European Paediatric Neurology Society Meeting, Baden Baden, Germany, 11 September 2001. Eur Paediatr Neurol 6: 293-297.

Halbach NSJ, Smeets EEJ, Steinbusch C, Maaskant MA, van Waardenburg D, Curfs LMG. 2013. Aging in Rett syndrome: a longitudinal study. Clin Genet 84: 223–229.

Hall SS, Arron K, Sloneem J, Oliver C. 2008. Health and sleep problems in Cornelia de Lange syndrome: a case control study. J Intell Disabil Res 52: 458 – 468.

Jian L, Nagarajan L, de Klerk N, Ravine D, Christodoulou J, Leonard H. 2007. Seizures in Rett syndrome: an overview from a one-year calendar study. European J Paediatr Neurol 11: 310–317.

Leonard H, Bower C. 1998. Is the Rett syndrome normal at birth? Dev Med Child Neurol 40: 115-121.

Leonard H, Ravikumara M, Baikie G, Naseem N, Ellaway C, Percy A, Abraham S, Geerts S, Lane J, Jones M, Bathgate K, Downs J. 2013. Assessment and management of nutrition and growth in Rett syndrome. J Pediatr Gastroenterol Nutr 57: 451-460.

Motil KJ, Caeg E, Barrish JO, Geerts SP, Lane JB, Percy AK, Annese F, McNair L, Skinner SA, Lee H-S, Neul JL, Glaze DG. 2012. Gastrointestinal and nutritional problems occur frequently throughout life in girls and women with Rett syndrome. J Pediatr Gastroenterol Nutr 55: 292–298.

Neul JL, Fang P, Barrish J, Lane J, Caeg EB, Smith EO, Zoghbi H, Percy A, Glaze DG. 2008. Specific mutations in methyl-CpG-binding protein 2 confer different severity in Rett syndrome. Neurology 70: 1313-21.

Neul JL, Kaufmann W, Glaze DG, Christodoulou J, Clarke AJ, Bahi-Buisson N, Leonard H, Bailey MES, Schanen CN, Zappella M, Ranieri A, Huppke P, Percy AK. 2010. Rett syndrome: revised diagnostic criteria and nomenclature. Ann Neurol 68: 944-950.

Neul JL, Lane JB, Lee H-S, Geerts S, Barrish JO, Annese F, McNair Baggett L, Barnes K, Skinner SA, Motil KJ, Glaze DG, Kaufmann WE, Percy AK. 2014. Developmental delay in Rett syndrome: data from the natural history study. J Neurodevelop Disord 6:20.

Oddy WH, Webb KG, Baikie G, Thompson SM, Reilly S, Fyfe SD, Young D, Anderson AM, Leonard H. 2007. Feeding Experiences and Growth Status in a Rett Syndrome Population. J Pediatr Gastr Nutr 45: 582–590.

Oliver C, Wilkie L. 2005. Gastro-oesophageal Distress Questionnaire. http://www.birmingham.ac.uk/schools/psychology/centres/cerebra/about/assessments/index.aspx accessed 12 June 2014.

Public Health England 2014. Patterns and trends in child obesity. http://www.noo.org.uk/slide\_sets accessed 4 December 2014.

Reilly S, Cass H. 2001. Growth and nutrition in Rett syndrome. Disabil Rehabil 23: 118-128.

Smeets EEJ, Chenault M, Curfs LMG, Schrander-Stumpel CTRM, Frijns JP. 2009. Rett syndrome and long-term disorder profile. Am J Med Genet A 149A: 199-205.

Sparrow SS, Balla D, Cicchetti DV. 1984. Vineland Adaptive Behavior Scales (Survey Ed.). Circle Pines, MN: American Guidance Service.

Symons FJ, Byiers B, Tervo R, Beisang A. 2013. Parent-reported Pain in Rett Syndrome. Clin J Pain 29: 744–746.

Symons FJ, Harper VN, McGrath PJ, Breau LM, Bodfish JW. 2009. Evidence of increased non-verbal behavioral signs of pain in adults with neurodevelopmental disorders and chronic self-injury. Res Dev Disabil 30: 521-528.

Tarquinio DC, Motil KJ, Hou W, Lee H-S, Glaze DG, Skinner SA, Neul JL, Annese F, McNair L, Barrish JO, Geerts SP, Lane JB, Percy AK. 2012. Growth failure and outcome in Rett syndrome: Specific growth references. Neurol 79: 1653-1661.

Witt-Engerstrom I. 1987. Rett syndrome: A retrospective pilot study on potential early predictive symptomatology. Brain Dev 9: 481-486.

Young D, Nagarajan L, De Klerk N, Jacoby P, Ellaway C, Leonard H. 2007. Sleep problems in Rett syndrome. Brain Dev 29: 609-16.

Table I Mean Total Severity Score (SD, range) in relation to mutation groups

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | No mutation (n=20) | Missense (n=23) | Large Deletion (n=2) | C-Terminal (n=13) | Late Truncating (n=7) | Early Truncating (n=26) |
| Severity Score  (SD, range) | 9.1  (3.34, 4-15) | 8.1  (3.09, 4-15) | 9.5  (2.12, 8-11) | 8.1  (3.20, 3-14) | 5.4  (2.37, 3-10) | 9.7  (2.89, 4-14) |

Table II Health problems during the person’s life and in the last month

|  |  |  |
| --- | --- | --- |
|  | Ever | In the last month |
| Ear problem | 33 (36.3%) | 5 (5.5%) |
| Eye problem | 20 (22.0%) | 8 (8.8%) |
| Dental problem | 39 (42.8%) | 11 (12.1%) |
| Cleft palate | 2 (2.2%) | 1 (1.1%)† |
| Gastrointestinal problem | 55 (60.4%) | 33 (36.3%) |
| Bowel problem | 51 (56.0%) | 38 (41.7%) |
| Heart problem | 9 (9.9%) | 5 (5.5%) |
| Hernia | 4 (4.4%) | 2 (2.2%) |
| Limb abnormalities | 9 (9.9%) | 6 (6.3%) |
| Epilepsy/seizure | 72 (79.1%) | 47 (51.6%) |
| Lung/respiratory | 26 (28.6%) | 10 (11.0%) |
| Liver/kidney | 3 (3.3%) | 2 (2.2%) |
| Diabetes/ thyroid | 1 (1.1%) | 2 (2.2%) |
| Skin problem | 37 (40.6%) | 27 (29.7%) |

† Ongoing: cleft palate not repaired

Table III Indications of Pain in last week

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Mean (SD) | Range | % ‘Not at all’ | % with at least one item ‘Very often’ |
| Vocal (Max=12) (n=88) | 2.6 (2.47) | 0-12 | 23.9 | 12.5 |
| Social (Max=12) (n=91) | 2.9 (2.41) | 0-11 | 19.8 | 16.5 |
| Facial (Max=15) (n=88) | 3.7 (2.67) | 0-10 | 12.5 | 19.3 |
| Body and Limbs (Max=18) (n=88) | 3.2 (2.68) | 0-16 | 17.0 | 27.3 |
| Eating and Sleeping (Max=9) (n=89) | 1.8 (1.88) | 0-8 | 34.8 | 14.6 |