Original Article

Aging in Rett syndrome: a longitudinal study


Little is known about the aging process of people with specific syndromes, like Rett syndrome (RTT). Recognition of the clinical and behavioral characteristics of the adult RTT is needed in order to improve future management of the RTT girl and counseling of parents. In association with the Dutch RTT parent association, a 5-year longitudinal study was carried out. The study population consisted of 53 adult women with a clinical diagnosis of RTT. Postal questionnaires were sent, including demographic features, skills, physical and psychiatric morbidity. At the time of the second measurement seven women had died. In 2012, 80% of the questionnaires (37/46) were returned. Mean age of the women was 31.4 years. Molecular confirmation was possible for 83% of the women for whom analyses were carried out. The adult RTT woman has a more or less stable condition. The general disorder profile is that of a slow on-going deterioration of gross motor functioning in contrast to a better preserved cognitive functioning, less autonomic and epileptic features and good general health. This is the first longitudinal cohort study about aging in RTT. Continuing longitudinal studies are needed to gain more insight into the aging process in RTT.

Owing to advances in medical care and technology, persons with childhood onset diseases and/or genetic syndromes are now living to advanced ages (1–5). Expectations are that their life expectancy will even continue to increase in the next years (4, 6, 7). Therefore, clinicians are increasingly challenged by the care for adults with specific genetic syndromes (4, 8, 9). Still little is known about the aging process of people with specific syndromes, like Rett syndrome.

Rett syndrome (RTT, OMIM 312750) is one of the most common causes of severe intellectual disabilities in girls, with a prevalence of 1:10,000 to 1:15,000 (10–13). In spite of the molecular confirmation of a MECP2 mutation, RTT remains a clinical diagnosis based on internationally accepted criteria (14, 15). RTT is characterized by early neurological regression affecting motor, cognitive and communication skills, along with autonomic dysfunction and the development of stereotypic hand movements (10, 13, 16). The natural history of RTT is divided into four stages: early stagnation, rapid regression, pseudostabilization and late motor deterioration (17).

Studies on aging in RTT are scarce, counting a few cross-sectional studies and some longitudinal follow-up case studies (9, 18–23). The clinical condition of RTT women tends to stabilize over time, and prolonged survival has recently been showed (24, 25). A longitudinal study was designed in order to gain better understanding of the aging process and mortality in RTT. Recognition of the clinical and behavioral characteristics of the adults with RTT is needed, in order to improve future management and follow-up of the RTT girl and counseling of parents regarding prognosis, natural course of the disease, and life expectancy.
Materials and methods

Prior to the start of this study, ethical approval was obtained from the Medical Ethical Committee at the Maastricht University Medical Center.

Subjects

In association with the Dutch RTT parent association, a 5-year longitudinal study was carried out including two measurements (2007–2012). The initial study population consisted of 53 women above 16 years of age with a clinical diagnosis of RTT, confirmed by experienced clinicians. Results of the first measurement have already been published (22).

Since 2007, seven of these 53 RTT women, aged between 21 and 43 years (mean age: 26.7 years), had died. Exact cause of death was known for two women: pneumonia and status epilepticus. For the remaining five women cause of death was not registered, the possibility of sudden death was sometimes mentioned. Postal questionnaires were sent to the remaining 46 contact persons.

Questionnaire

The questionnaire consisted of four major subdivisions (22). The first two parts included demographic features including living conditions (living at home or in residential facilities) and use of care facilities (day care or respite care facilities). In the third part the Observational Questionnaire Elderly Residents with Intellectual Disabilities (OOB) was inserted. This instrument assesses functioning, behavior and care dependency. It has four subscales: (i) activities of daily living (ADL), (ii) psychological functioning, (iii) (inappropriate) reactions, and (iv) physical functions and care dependence. The range for the scale is 0 or 1–4: the higher the score, the better the functioning. The reliability and validity of the OOB has been showed to be satisfactory to good (26). Questions on the medical history (hospital admission and surgery), medication use (type and dose of medication including duration of use), genetic diagnosis (presence and specific type of MECP2 mutation), physical (e.g. epilepsy, scoliosis, breathing problems and osteoporosis) and psychiatric morbidity (e.g. mood changes, screaming spells and abnormal agitation) were inserted in the fourth part of the questionnaire. Finally, the view of parents regarding significant changes in skills and morbidity from the age of 10 years was recorded on a 3-point scale (no change, improvement or decline). The age of 10 years was selected because by this age most affected girls, even the atypical ones, have emerged from the regression stage (stage 2). Parents were asked to evaluate changes in each of the RTT features. Parents’ responses that had been provided in 2007 were compared with those provided in 2012, allowing changes over these 5 years to be appreciated. All data were processed anonymously.

Response

Eighty percent of the questionnaires sent were returned (n = 37). The parents answered in 30 cases, parents together with a professional carer/physician in six cases and a professional carer in one case. Those who completed the questionnaires are further referred to as ‘parents’. Reasons for non-responding were mainly unknown address and lack of time of parents and/or professional carer, despite two reminders.

Table 1 shows the characteristics of the respondents in 2007 and 2012. The mean age in 2012 was 31.4 years (range: 21–46 years, SD = 7.37). Eighty-three percent of the women in whom mutation analyses were performed, diagnosis was molecularly confirmed. In four women mutation analyses were not performed, and in four women it was unknown whether analyses were performed. Forty-six percent of the RTT women in 2012 had a normal weight, 35% were underweight, 9% were overweight and in 11% BMI status was unknown.

Those who died and those for whom the questionnaire was not completed did not differ significantly from the rest of the cohort, concerning age, general health, skills, physical and psychiatric morbidity.

Data analyses

SPSS version 18 was used for analyzing the data.

The main aim was to compare data of 2007 and 2012 regarding several variables for the whole group (n = 37). The variables were: demographic features including living conditions and use of care facilities, data on functioning via OOB (total, subscales and individual item scores), physical and psychiatric morbidity and view of parents regarding changes in skills and morbidity. For ordinal data χ² tests were used. In case data were on ratio level and normally distributed, the t-test for related groups was used. However, in case these data were not normally distributed, Wilcoxon signed-rank test (nonparametric tests for related groups) was used.

For each age group (16–19 years, 20–29 years and 30+ years), the scores for 2007 and 2012 were compared. On the basis of the number of respondents per age-groups, the nonparametric Kruskall–Wallis test (nonparametric tests for more than two unrelated groups) rather than a parametric test was used for analyzing the data.

For all tests, a p-value of 0.05 or less was used for statistical significance.

Results

The ages given in this section are those of 2007.

Living conditions and use of care facilities

Approximately one-third (n = 12) of the RTT women lived full time or part time with their parents. Eighty-two percent lived in residential facilities, of whom 14% still spent some (weekend) days a week with their
parents. Two RTT women lived in apartments with 24 h daily support. Compared to 2007, eight RTT women now spent less time living with their parents and four women spent more time with their parents. More young women lived in residential facilities, in contrast to the oldest age group with no changes in living conditions (p = 0.005). In the oldest age group only one woman still lived at home.

Sixty percent of the RTT women spent their days in day care facilities. The use of these facilities increased in four women, of whom three were between 16 and 20 years of age. Despite care facilities were used by three RTT women.

Health

General health of the individuals was assessed on a 5-point scale ranging from very good (1) to very bad (5). In general, the respondents reported the health of RTT women as good (mean: 2.24, range: 1–4, and SD = 0.86). Health had improved the most in the oldest age group (p = 0.007). Concerning physical complaints a significant improvement was shown in the total RTT population (p = 0.03).

During the last 5 years 10 women were hospitalized. Main reason was pneumonia (three women), followed by different seven indications: respiratory distress, status epilepticus, rectal bleeding, PEG probe, bladder inspection, decline in walking and refusal to eat and/or drink. Surgery was performed in five women; three women had an orthopedic surgery because of contractures, and two women had a dental surgery for extraction of wisdom teeth.

Weight status and eating behavior

Discarding the missing values in some respondents, the prevalence of underweight RTT women was 39%; 52% had a normal weight and 9% were overweight. Compared to 2007 the mean BMI decreased by only 0.21 points (p = 0.70). Concerning the different age groups, BMI only slightly increased in the youngest age group (0.29) and decreased the most in the oldest age group (−0.93; p = 0.44).

The majority of the RTT women are oral feeders needing assistance, only four females used a G-tube.

Communication

Only 22% of the RTT women were at least sometimes able to express themselves by spoken language and/or signals. Since 2007, three women had improved their ability to express themselves and three had shown deterioration in self-expression. Improvement was especially seen in the oldest group (p = 0.16). Parents reported a deterioration in two women and improvement in three women (p = 0.17).

Morbidity

Table 2 shows the morbidity of the total RTT cohort in 2007 (n = 53) and the longitudinal data of 2007 and 2012 (n = 37). Arranged by subject, explanatory remarks are made below. Skin problems, sleep abnormalities, respiratory problems, behavioral problems and drooling are considered as manifestations of autonomic dysfunction.
Table 2. Prevalence of morbidity of total Rett syndrome cohort in 2007 (n = 53), 2007 (n = 37) and 2012 (n = 37)

<table>
<thead>
<tr>
<th>Morbidity</th>
<th>2007* (n = 53)</th>
<th>2007 (n = 37)</th>
<th>2012 (n = 37)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Skin problems</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cold feet</td>
<td>96%</td>
<td>97%</td>
<td>92%</td>
</tr>
<tr>
<td>Trophic skin changes</td>
<td>46%</td>
<td>54%</td>
<td>31%</td>
</tr>
<tr>
<td><strong>Sleep abnormalities</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nightly unrest</td>
<td>77%</td>
<td>81%</td>
<td>78%</td>
</tr>
<tr>
<td>Prolonged wakefulness and/or early morning awakening</td>
<td>51%</td>
<td>56%</td>
<td>54%</td>
</tr>
<tr>
<td><strong>Sleepy during the day</strong></td>
<td>85%</td>
<td>81%</td>
<td>87%</td>
</tr>
<tr>
<td><strong>Respiratory problems</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apnea during daytime</td>
<td>38%</td>
<td>37%</td>
<td>32%</td>
</tr>
<tr>
<td>Apnea during night</td>
<td>41%</td>
<td>40%</td>
<td>30%</td>
</tr>
<tr>
<td>Hyperventilation</td>
<td>39%</td>
<td>40%</td>
<td>26%</td>
</tr>
<tr>
<td>Breath holding spells</td>
<td>73%</td>
<td>72%</td>
<td>60%</td>
</tr>
<tr>
<td>Air swallowing</td>
<td>41%</td>
<td>47%</td>
<td>46%</td>
</tr>
<tr>
<td>Bloating</td>
<td>54%</td>
<td>65%</td>
<td>60%</td>
</tr>
<tr>
<td><strong>Behavioral problems</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Night screaming</td>
<td>39%</td>
<td>43%</td>
<td>35%</td>
</tr>
<tr>
<td>Mood changes</td>
<td>66%</td>
<td>71%</td>
<td>70%</td>
</tr>
<tr>
<td>Abnormal agitation</td>
<td>54%</td>
<td>51%</td>
<td>65%</td>
</tr>
<tr>
<td>Anxiety</td>
<td>68%</td>
<td>72%</td>
<td>65%</td>
</tr>
<tr>
<td>Drooling</td>
<td>80%</td>
<td>83%</td>
<td>65%</td>
</tr>
<tr>
<td><strong>Musculoskeletal</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scoliosis</td>
<td>90%</td>
<td>89%</td>
<td>89%</td>
</tr>
<tr>
<td>Kyphosis</td>
<td>16%</td>
<td>15%</td>
<td>29%</td>
</tr>
<tr>
<td>Spasticity</td>
<td>52%</td>
<td>50%</td>
<td>49%</td>
</tr>
<tr>
<td>Joint deformities</td>
<td>60%</td>
<td>57%</td>
<td>64%</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>74%</td>
<td>68%</td>
<td>76%</td>
</tr>
</tbody>
</table>

<sup>a</sup>Ref. (22).

### Autonomic manifestations

#### Skin problems

The prevalence of cold feet was nearly the same as in 2007, occurring in 92% of the RTT women. Trophic skin changes, including sores and vesicles occurred in 31%, whereas improvement was seen in 11 women and deterioration was seen in three women (p = 0.03).

#### Sleep abnormalities

The prevalence of nightly unrest was nearly the same as in 2007, occurring in 78% of the RTT women. Prolonged wakefulness and/or early morning awakening was more or less pronounced in 54%, with a significant improvement in RTT women aged between 16 and 20 years (p = 0.04). Daytime sleeping was reported in 87%, which is in line with previous results in 2007.

#### Respiratory problems

Apnea during daytime was reported in 32% of the RTT women, whereas improvement was mainly seen in women aged between 16 and 20 years (p = 0.08). During night the prevalence was 30%, compared to 40% in 2007. Significant improvements were seen in the total RTT group, but especially in women aged between 20 and 30 years (p = 0.03 and p = 0.04, respectively). Hyperventilation was reported in 26% of the women, significant improvement was seen for the total RTT group (p = 0.02). This is in line with the view of parents, reporting mainly improvement. The prevalence of breath holding spells was 60%, compared to 72% in 2007. Improvement was seen in six women and deterioration in two women (p = 0.03). Air swallowing was present in 46% of the RTT women and bloating in 60%. Both for air swallowing and bloating, no significant changes were seen in the last 5 years.

#### Behavioral problems

Nightly screaming was reported in 35%, whereas improvement was mainly seen in the women aged between 16 and 20 years and deterioration in women aged 30 years and older (p = 0.05). Prevalence of mood changes was 70%, 13 women improved and six women deteriorated (p = 0.19). Abnormal agitation was more or less pronounced in 65%, whereas improvement was mainly seen in the women aged between 20 and 30 years and deterioration in women aged 30 years and older (p = 0.06). Two thirds of the RTT women showed anxiety, whereas improvements were mainly seen in women aged 30 years and older (p = 0.07).

#### Remaining autonomic problems

Drooling was reported in 65% of the women. Nine had improved and two had deteriorated (p = 0.03). Improvement was especially seen in women aged 30 years and older (p = 0.04).

#### Musculoskeletal

The prevalence of scoliosis was 89%, with no changes in the last 5 years. The overall prevalence of kyphosis had increased to 29% (p = 0.06). Three women had deteriorated, all between 16 and 20 years, and one had improved (p = 0.33). Ambulation and mobility were still very limited, whereas mobility mainly deteriorated in the last 5 years (p = 0.08). This is in line with the view of parents, who mainly report deterioration of mobility (p = 0.02). However, some elderly women improved regarding to ambulation and mobility.

The prevalence of rigidity was 49%, whereas improvement was reported in five of the seven women aged 30 years and older (p = 0.008). Joint deformities were seen in 64% of the RTT women, with improvement in three women and deterioration in five women (p = 0.49).

#### Epilepsy

A history of epilepsy was present in 76% of the RTT women, of whom 54% was seizure free for at least 3 months. Anticonvulsive treatment was used by 93% of the RTT females with a history of epilepsy, of whom 64% received combination therapy.
Compared to 2007, improvement was reported in four women mainly aged 30 years and older, deterioration was seen in five women mainly between 16 and 20 years of age (p = 0.17). Parents indicated stabilization and/or improvement of epilepsy in women aged between 20 and 30 years (p = 0.01).

Age related morbidity

Both hypertension and diabetes were not reported in any of the RTT women. Osteoporosis was only reported in two women.

Observational questionnaire elderly residents with intellectual disabilities (ID)

ADL

In general, RTT women scored low on the subscale ‘ADL’ (mean score: 1.14, SD = 0.21), meaning they have limited ADL-skills. In the last 5 years no significant changes were seen in this subscale and/or the individual items.

Psychological functioning

Regarding ‘psychological functioning’ the scores were remarkably higher than in 2007 (mean score: 1.85 vs 1.63), which was significant in the elderly RTT women (p = 0.01). On item level three items showed significant differences compared to 2007: memory, alertness and purposeful behavior. Memory improved in women aged 16 to 20 years (p = 0.02). Alertness improved in the whole RTT group, especially women aged 30 years and older (both p = 0.045). Purposeful behavior also improved in the whole RTT group (p = 0.009).

(Inappropriate) reactions

Concerning ‘(inappropriate) reactions’ the RTT women still scored reasonable (mean score: 2.98, SD = 0.59), meaning occasionally appearance of these reactions. Compared to 2007, no significant changes were seen in this subscale, besides the sleep abnormalities as already described in the autonomic section.

Physical functions

Regarding ‘physical functions’ the women scored slightly better compared to 2007 (mean score 2.98 vs 2.87), meaning moderate physical limitations. Improvement was mainly seen in the elderly women (p = 0.15). On item level two items showed significant differences compared to 2007. First, physical complaints, as already described in the health section. Second, constipation improved in the whole RTT group, especially women aged 20 years and older (p = 0.01 and p = 0.009).

Care dependency

Care dependence remained high, with a mean score of 1.86 (SD = 0.35). No significant changes were seen in the last 5 years (p = 0.66).

Aging in Rett syndrome

Genotype–phenotype analyses

Genotype–phenotype analyses have not been performed, as the statistical power to investigate the effect of genotype was limited. Among the 37 women with clinical RTT, mutation analyses were performed in 78%, of which 83% were molecularly confirmed. As a result, 24 RTT women had a confirmed MECP2 mutation and 13 RTT women had a negative or unknown mutation status. Besides, in the past results of mutation analyses were limited to a positive MECP2 mutation, no specific details were given. In this cohort only in seven RTT women a specific MECP2 mutation is known, respectively one p.R133C mutation, one p.D156E mutation, one p.R270X mutation, one p.R306C mutation, two large deletions and one CTS deletion. The mean perceived health of the molecularly confirmed RTT women and those with a negative or unknown mutation status were respectively 2.20 and 2.00 (p = 0.48). There are no indications that the negative or unknown mutation status is due to selection bias and would affect the results.

Discussion

This is the first longitudinal cohort study on aging in RTT. It provides longitudinal data of a 5-year follow-up. A high response rate of 80% resulted in obtained data on 37 Dutch RTT individuals aged 21 years or more, reporting a broad range of clinical symptoms. This is a reasonably large cohort for a relatively recently defined disorder, infrequently diagnosed in adults (18). Molecular confirmation was possible for 83% of the women for whom analyses were carried out. This is reasonable, as not all analyses had access to the Multiplex Ligation-dependent Probe Amplification (MLPA) of MECP2 required for the detection of large deletions (27). Mutation results were not available for eight women. In spite of the molecular confirmation of a MECP2 mutation, RTT remains a clinical diagnosis based on internationally accepted criteria (14, 15). Molecular confirmation is not always necessary or desirable in older people who exhibit the clearly defined clinical characteristics.

Our results indicate improvement in the general health of the adult with RTT, with a reduction in physical complaints. However there remains a high level of care dependency, as a result of many RTT women living in residential facilities. Hospitalization in the adult RTT women is mainly due to pneumonia, also an important cause of death in RTT (24). Therefore, pneumonia should clearly be considered when such a woman is unwell. In this study few operations had been performed, mainly for orthopedic or dental conditions, confirming the overall good health.

We confirmed the previously reported high mortality in RTT as compared with the general population (28). During the 5-years of follow-up seven women died at a mean age of 27 years. The exact cause of death was not registered in most cases. As previously shown, there was a high incidence of sudden death
in RTT, which makes it difficult to compile the exact causes of death in RTT (28–30). In the initial records we found no significant health differences between those in the cohort who survived and those who later died or for whom the second questionnaire was not returned. In the earlier literature, the clinical picture in adult RTT has been reported to stabilize over time, with a high level of dependency. It is characterized by severe neurological impairment with a decline in motor function. In contrast to the surprisingly well-preserved cognitive functions, reduced seizure activity and improved autonomic function (9, 13, 20–22, 29, 31, 32).

In this study there was only slight deterioration in gross motor function, based mainly on the parental view (9, 20, 21, 32–34). However some elderly women actually improved on these aspects (19–21). Emphasizing that therapy in the adult RTT women is still of great importance, in which the need to be adjusted to the characteristics of RTT (19). Musculoskeletal problems were relatively stable during the 5-year follow-up. However the prevalence of kyphosis increased with age, as previously reported by us, although the data on that change did not reach significance (22). It is note-worthy that kyphosis has not been so far researched in RTT and guidelines for its management are lacking. Our study found less increase in rigidity and contractures as compared to other reports for adults with RTT and we suggest that this observation merits further investigation (9, 13, 20, 21, 29, 31, 32). It is possible that in our study the favorable reports reflected the overall improvement in psychological functioning. Giving a global picture of a more comforting RTT woman, parents could report a decreased level of rigidity.

Improvemnt in psychological functioning was mainly based on an improved memory, alertness and purposeful behavior in the adult RTT women (21, 32). Improved communication was reported in those over 30 but this did not reach statistical significance (9, 13, 20–22, 32, 34–36). Given the importance of mutual understanding, it is clear that active intervention with provision of alternative communication is justified throughout life in RTT (22).

Our study confirmed the previously reported decrease in epilepsy in the older person with RTT (9, 20, 21, 32, 37). Nevertheless, the prescription of anticonvulsant medication remained high, indicating a need for regular review. Also the autonomic problems appeared to improve in the adults (20, 22, 29, 34, 38–40). Arguing the potential survival effect, reported as a possible explanation in our previous study (22). Improvement was seen in several areas of autonomic function: skin problems, sleep disturbances, respiratory irregularities and digestive difficulties. However, night screaming had increased in women aged over 30 years (13, 21, 32).

Age related morbidity appeared uncommon. Hypertension and diabetes were reported to be absent, in contrast to the Dutch age and sex matched prevalence of hypertension of 7.5–15% (www.rivm.nl). Osteoporosis was reported in only two RTT women in our study, contrasting with the reports from other studies (41–43). Under reporting due to absence of screening may be responsible for these unexpectedly low figures. Screening for these age related conditions may be advisable as a routine element in the care for adult RTT women.

In conclusion, many of our findings confirm earlier reports. The general disorder profile of the adult RTT woman in this study is that of a slow on-going deterioration of gross motor functioning in contrast to a better preserved cognitive functioning, less autonomic and epileptic features and overall good general health. Clinical provision should include the maintenance of gross motor skills and communication, awareness of the risk of pneumonia, regular review of anticonvulsant medication and screening for such age related disorders as hypertension, diabetes, osteoporosis and kyphosis. Differences in results with most published RTT studies could be explained by several reasons. First, this study analyzed changes longitudinally rather than in a single cross-sectional review at one time. Comparing results in the same individual excludes the possible survivor effect in cross-sectional studies. However, this longitudinal study has only a follow-up period of 5 years. Extending the follow-up period will probably give better and more reliable results. At last, the data are almost exclusively based on the parental view. Especially in the fourth section of the questionnaire with the vision of parents specifically requested. Our model for investigating the views of parents regarding their aging daughters has not been formally tested. However we consider that, in spite of their lack of medical training, parents are likely to be the first to notice changes in their daughters because they are so close to them in everyday life. The clinical data provided in this study offer insight in the natural course and prognosis of RTT in adults. It holds potential for continuing longitudinal review and the development of guidelines for early intervention and lifelong individualized multidisciplinary provision that can improve the quality of life and health for the RTT woman and her family.

Conflict of interest

The authors declared no conflict of interest.

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