Aging in People With Specific Genetic Syndromes: Rett Syndrome

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The aging process of people with intellectual disabilities has been a topic of interest in recent years. Good knowledge of the specific healthcare problems in adults with intellectual disabilities and anticipating on these problems are important issues in providing support and healthcare for these persons. Nevertheless little is known about the aging process of people with specific syndromes, like Rett syndrome. In association with the Dutch Rett syndrome parent association, 70 postal questionnaires were sent to the contact persons of the females aged at least 16 years with a clinical diagnosis of Rett syndrome. The questionnaire consisted of general questions, questions about living conditions, skills, physical and psychiatric morbidity. The response rate was 76% (n = 53). In general adults with Rett syndrome seemed to be reasonably healthy, whereas neurological, respiratory and behavioral morbidity appeared to be of great influence. High care dependency was confirmed. In contrast with underweight, overweight showed to be an under-ascertained feature. The general disorder profile was confirmed, considering the increase with age regarding kyphosis and the better communication and autonomic dysfunction in the oldest age group compared to the younger age groups. Features of autonomic dysfunction deserve more medical attention, especially the interrelation between quality of sleep, respiration and behavior in Rett syndrome. Longitudinal studies including genotype–phenotype analyses are needed for insight in individual changes in support needs and health.

Key words: Rett syndrome; aging; morbidity; intellectual disabilities


INTRODUCTION

Thanks to better life circumstances and major advances in medical care and technology, the life expectancy of persons with childhood onset diseases and/or genetic syndromes has increased [Patja et al., 2000; Donckerwolcke and van Zeben-van der Aa, 2002; Maaskant et al., 2002; Fisher and Kettl, 2005]. Consequently, the number of adults with intellectual disabilities (ID) has increased substantially during the last decades and will continue to increase in the next years [Janicki and Breitenbrach, 2000; Bernard et al., 2002]. Compared to persons without ID, age specific conditions occur more often and earlier in life [Maaskant et al., 1996; van Schrojenstein Lantman-de Valk et al., 1997]. Nevertheless little is known about aging in people with specific syndromes, except for Down syndrome [Roeden and Zitman, 1995; Torr and Davis, 2007; Jervis and Prinsloo, 2008]. In this study we focus on Rett syndrome (RTT), a neurodevelopmental disorder affecting almost exclusively females. The prevalence is 1:10,000 girls at 11 years and therefore a common genetic cause of severe ID in females [Hagberg et al., 1983; Smeets and Schrander-Stumpel, 2005; Williamson and Christodoulou, 2006]. In spite of the molecular confirmation of a MECP2 mutation, diagnosis of RTT remains...
mainly clinically based on internationally accepted criteria [Amir et al., 1999; Hagberg et al., 2002]. RTT manifests particular symptoms at certain ages, including a wide variability in clinical evolution and severity [Smeets et al., 2003; Williamson and Chris-todoulou, 2006]. Hagberg and Witt-Engerström [1986] devised a staging system that divides the natural history of RTT into four stages: early stagnation, rapid regression, pseudo stabilization and late motor deterioration. The general RTT profile is that of a slowly continuing deterioration of gross motor performance over the years in contrast with a relatively better preserved cognitive ability to communicate, mainly with the eyes. An inactive, small and thin woman with trophic skin changes is the general long-term clinical disorder profile, suggesting a kind of “pre-aging” in RTT [Hagberg, 2002; Cass et al., 2003]. The aim of the present study is to gain insight into age-related features in RTT. The research question is: what physical, behavioral and psychiatric conditions are present in adults with RTT and which of these conditions are age-related?

**MATERIALS AND METHODS**

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

**Subjects**

Subjects were recruited through the Dutch RTT parent association. Questionnaires were developed and sent to 70 contact persons (mainly parents), of which 76% were returned. In total, data were derived from 53 Dutch females aged 16 years and older with a clinical diagnosis of RTT, confirmed by experienced clinicians. The parents answered in 47 cases, parents together with a professional career in 3 cases, a professional career in 1 case and a physician in 1 case. Those who completed the questionnaires are further referred to as “parents.”

**Questionnaire**

The questionnaire consisted of four major subdivisions. The first part included questions about demographic characteristics, including height, weight and abdominal circumference. The second part comprised questions about living conditions and use of care facilities. In the third part the Observational Questionnaire Elderly Residents with Intellectual Disabilities (Observatielijst Ouderwondene Bewoners, OOB) was inserted. The OOB is an instrument that assesses functioning, behavior and care dependency; it has to be completed by a care-provider familiar with the client. The OOB has four subscales: (1) activities of daily living (ADL), (2) psychological functioning, (3) (inappropriate) reactions, and (4) physical functions and care dependence. The questionnaire was supplemented with questions addressing RTT specific features. 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 demonstrated to be satisfactory to good [Hoefnagel, 1989]. Questions on the medical history, medication use, genetic diagnosis, physical and psychiatric morbidity were inserted in the fourth part of the questionnaire. Ultimately, the view of parents regarding significant changes in skills and morbidity from the age of 10 years was rated on a 3-points scale (no change, improvement, or decline). All data were processed anonymously.

**Response**

Table I shows the characteristics of the respondents. The mean age was 26.9 years. Among the 53

| TABLE I. Characteristics of the Respondents According to Age, Genotype and BMI |
|--------------------------|---|---|
| **Age**                  | N | % |
| 16–20 years              | 11 | 21 |
| 20–30 years              | 24 | 45 |
| 30+ years                | 18 | 34 |
| Mean age: 26.9 years, range 16–53, s.d. 7.85 |
| **Genotype**             |   |   |
| Mutation analyses performed | 37 | 70 |
| MECP2 positive           | 31 | 58 |
| MECP2 negative           | 4  | 8 |
| Results unknown          | 2  | 4 |
| Mutation analyses not performed | 12 | 23 |
| Unknown                  | 4  | 11 |
| **BMI category**         |   |   |
| <18.5 (underweight)      | 22 | 42 |
| 18.5–25 (normal weight)  | 18 | 34 |
| >25 (overweight)         | 5  | 9 |
| Unknown                  | 8  | 15 |
| Mean BMI: 20.0, range 13.0–38.1, s.d. 4.51 |
persons with clinical RTT, mutation analyses were performed in 70%, of which 89% were molecularly confirmed. Forty percent of the RTT persons had a normal weight, 49% were underweight and 11% were overweight. Seventeen contact persons did not return the questionnaire. The mean ages of non-respondents and respondents were 25.7 and 26.9 years, respectively ($P = 0.17$). There are no indications that the non-response was selective and affected the results.

Data Analyses

Questionnaires were reviewed before data were correlated; in case of two answers the best answer was consistently chosen. SPSS version 14.0 was used for analyzing the data. Three age groups (16–20, 20–30, 30+) were to analyze possible age-related conditions. Prevalence rates were calculated for morbidity and mean scores were calculated for BMI and perceived health. Concerning skills and behavior, frequencies and mean scores were calculated. The following statistical tests were performed: Chi-square (for nominal and ordinal data) and Kendall’s tau-b (for ordinal data), independent tests (means of two groups) or ANOVA (means of more than two groups).

RESULTS

Living Conditions and Use of Care Facilities

Approximately one third (36%) of the RTT persons lived full-time or part-time with their parents. About two thirds (71%) lived in residential facilities, of whom 13% still spent some (weekend) days a week with their parents. Three RTT persons (6%) lived in apartments with 24 h daily support. Significantly more young adults lived with their parents and older adults lived in residential facilities (Kendall’s tau b: $P < 0.01$ respectively $P < 0.05$). Analyses regarding age at entering residential facilities showed an ordinal relation with age (Kendall’s tau b: $P < 0.01$).

Most RTT persons (67%) spent their days in day care facilities. Respite care facilities were used by 12%, specifically and non-specifically for persons with ID (10% respectively 2%).

Health

Health of the individuals was assessed on a 5-point scale ranging from very good (1) to very bad (5). In general, the respondents valued the health of the RTT persons as good (mean 2.15, range 1–4). Perceived health was not related to age (Kendall’s tau b: $P = 0.86$) with mean scores in the different age groups of 2.0, 2.2, and 2.1. Further analyses showed a significant relation between health and apnea (Kendall’s tau b: $P < 0.01$), breath holding spells (Kendall’s tau b: $P < 0.05$), mood changes (Kendall’s tau b: $P < 0.01$), spasticity (Kendall’s tau b: $P < 0.01$) and joint deformities (Kendall’s tau b: $P < 0.001$). Care dependence and physical complaints had a negative relation with health (Kendall’s tau b: $P < 0.01$ and $P < 0.001$).

Weight Status and Eating Behavior

Discarding the missing values in some respondents, prevalence of underweight RTT persons was 49%; 40% had a normal weight and 11% were overweight. Comparing BMI and eating behavior a positive relation was shown (Kendall’s tau b: $P < 0.01$). No relation between BMI and perceived health or age was found (ANOVA: $P = 0.95$ respectively $P = 0.78$).

Communication

Only one third of the RTT persons were at least sometimes able to express themselves by spoken language and/or signals, of which 13% through eye pinpointing behavior. Concerning this group, the communication was considerably better in the older age groups (Kendall’s tau b: $P = 0.10$). Changes in communication skills were experienced by parents: 10 parents considered improvement in their children’s communication from the age of 10 years, whereas 3 parents experienced a decline (Chi-square: $P = 0.01$).

Morbidity

Table II shows the morbidity and behavioral problems of RTT persons per age group. Arranged by subject, explanatory remarks are made below.

Skin problems, sleep abnormalities, respiratory problems and behavioral problems are considered as manifestations of autonomic dysfunction. To investigate potential relations between the different items further analyses were performed.

Autonomic Manifestations

Skin problems. Cold feet were notified in 96% of the RTT persons, 50% with blue discoloration, and 50% without. Pressure sores and vesicles occurred in 46%. The prevalence of trophic skin and nail changes was 30%, whereas the occurrence was significantly lower in the oldest age group (18%, Chi-square: $P = 0.05$). According to the parents, in 7 of their children’s a decline in skin problems was observed from the age of 10 years.

Sleep abnormalities. Half of the RTT persons sometimes had nightly unrest, whereas 20% had nightly unrest at least once a week up to daily. The prevalence of nightly unrest was higher in the two older age groups, although these differences were
not statistically significant (64% to 79% to 83%, Kendall's tau, b: P = 0.16). Prolonged wakefulness and/or early morning awakening was more or less pronounced in 51%. Daytime sleeping was reported in 85%, ranging from sometimes in 50% to constantly in 89%. No statistically significant relationships with age were found (Kendall's tau, b: P > 0.16).

**Respiratory problems.** Apnea was reported in 38% of the RTT persons, ranging from 16% once a month up to 14% daily. The prevalence was significantly lower in the oldest age group (23%, Chi-square: P = 0.01). Thirty-nine percent of the RTT persons had apnea once or twice a week. Prolonged wakefulness and daytime sleeping was reported in 80%, a significance level of P < 0.01. Whereas the occurrence was significantly higher in the younger age group (P = 0.001–0.01), and respiratory problems and sleep abnormalities (Kendall’s tau, b: P < 0.01–0.019), and respiratory problems and sleep abnormalities (Kendall’s tau, b: P < 0.001–0.03).

**Musculoskeletal.** The prevalence of scoliosis in our study was 90%, whereas the occurrence was significantly higher in the older age groups (0% to 24% to 19% respectively, Kendall's tau, b: P = 0.05). Analyses regarding osteoporosis and kyphosis showed 25% occurrence of osteoporosis in the kyphosis group in contrast to 0% occurrence in the remaining group (Chi-square: P < 0.01). Hereby, the occurrence of osteoporosis was unknown with 50% of the kyphosis group and 70% of the remaining group. Ambulation and mobility were very limited in all age-groups, and no relationship with age was found (Kendall's tau, b: P > 0.01). Anticonvulsiv treatment was used by 100% of the osteoporosis group, 75% of the kyphosis group and 70% of the remaining group (Chi-square: P = 0.66). Since our statistical power to investigate explicit anticonvulsiv treatment was limited, we were not able to perform these analyses.

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**TABLE II. Prevalence of Morbidity in RTT Persons Per Age-Group and Significance Level**

<table>
<thead>
<tr>
<th>Morbidity by age group</th>
<th>16–20 (n = 11) (%)</th>
<th>20–30 (n = 24) (%)</th>
<th>30+ (n = 18) (%)</th>
<th>Total (n = 53) (%)</th>
<th>Kendall's Tau b</th>
<th>Chi-square</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin problems</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cold feet</td>
<td>100</td>
<td>96</td>
<td>94</td>
<td>96</td>
<td>P = 0.41</td>
<td>P = 0.56</td>
</tr>
<tr>
<td>Pressure sores and vesicles</td>
<td>40</td>
<td>54</td>
<td>39</td>
<td>46</td>
<td>P = 0.73</td>
<td>P = 0.56</td>
</tr>
<tr>
<td>Trophic skin and nail changes</td>
<td>33</td>
<td>39</td>
<td>18</td>
<td>30</td>
<td>P = 0.16</td>
<td>P = 0.05*</td>
</tr>
<tr>
<td>Sleep abnormalities</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Nightly unrest</td>
<td>64</td>
<td>79</td>
<td>83</td>
<td>77</td>
<td>P = 0.16</td>
<td>P = 0.16</td>
</tr>
<tr>
<td>Prolonged wakefulness and/or early morning awakening</td>
<td>36</td>
<td>58</td>
<td>50</td>
<td>51</td>
<td>P = 0.54</td>
<td>P = 0.66</td>
</tr>
<tr>
<td>Sleepy during the day</td>
<td>80</td>
<td>83</td>
<td>89</td>
<td>85</td>
<td>P = 0.59</td>
<td>P = 0.59</td>
</tr>
<tr>
<td>Respiratory problems</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Apnea</td>
<td>44</td>
<td>46</td>
<td>23</td>
<td>38</td>
<td>P = 0.13</td>
<td>P = 0.01*</td>
</tr>
<tr>
<td>Hyperventilation</td>
<td>30</td>
<td>42</td>
<td>39</td>
<td>39</td>
<td>P = 0.05</td>
<td>P = 0.76</td>
</tr>
<tr>
<td>Breath holding spells</td>
<td>80</td>
<td>83</td>
<td>56</td>
<td>73</td>
<td>P = 0.24</td>
<td>P = 0.30</td>
</tr>
<tr>
<td>Air swallowing</td>
<td>40</td>
<td>44</td>
<td>39</td>
<td>41</td>
<td>P = 0.83</td>
<td>P = 0.96</td>
</tr>
<tr>
<td>Behavioral problems</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nightly screaming</td>
<td>33</td>
<td>46</td>
<td>33</td>
<td>39</td>
<td>P = 0.56</td>
<td>P = 0.96</td>
</tr>
<tr>
<td>Mood changes</td>
<td>67</td>
<td>61</td>
<td>72</td>
<td>66</td>
<td>P = 0.32</td>
<td>P = 0.82</td>
</tr>
<tr>
<td>Agitation</td>
<td>22</td>
<td>65</td>
<td>56</td>
<td>54</td>
<td>P = 0.27</td>
<td>P = 0.25</td>
</tr>
<tr>
<td>Anxious impression</td>
<td>50</td>
<td>79</td>
<td>62</td>
<td>68</td>
<td>P = 0.89</td>
<td>P = 0.49</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scoliosis</td>
<td>90</td>
<td>88</td>
<td>94</td>
<td>90</td>
<td>P = 0.43</td>
<td>P = 0.41</td>
</tr>
<tr>
<td>Kyphosis</td>
<td>0</td>
<td>24</td>
<td>19</td>
<td>16</td>
<td>P = 0.21</td>
<td>P = 0.05</td>
</tr>
<tr>
<td>Spasticity</td>
<td>60</td>
<td>41</td>
<td>61</td>
<td>52</td>
<td>P = 0.51</td>
<td>P = 0.37</td>
</tr>
<tr>
<td>Joint deformities</td>
<td>44</td>
<td>65</td>
<td>61</td>
<td>60</td>
<td>P = 0.77</td>
<td>P = 0.70</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>82</td>
<td>62</td>
<td>83</td>
<td>74</td>
<td>P = 0.93</td>
<td>P = 0.51</td>
</tr>
</tbody>
</table>

*P < 0.05.
The prevalence of spasticity was 52%, mainly affecting the arms and legs. Sixty percent of the RTT persons had joint deformities, mainly affecting the feet.

Except for kyphosis, the differences between the age-groups and musculoskeletal morbidity were not statistically significant (Kendal’s tau: \( P > 0.43 \)).

**Epilepsy**

A history of epilepsy was present in 74%, of whom 95% used anticonvulsive treatment. The occurrence of epilepsy was significantly higher with combination therapy compared to monotherapy (Kendall’s tau b: \( P < 0.01 \)). The differences in prevalence of epilepsy between the age-groups were not statistically significant (Kendal’s tau: \( P = 0.93 \)).

**Observational Questionnaire Elderly Residents With ID**

In general RTT persons scored low on the subscale "ADL" (mean score: 1.15, s.d. 0.2), meaning they have limited ADL-skills. Regarding “psychological functioning” they also scored low (mean score: 1.63, s.d. 0.6), meaning limited abilities on this subject. Concerning “(inappropriate) reactions” they scored reasonable (mean score 2.9, s.d. 0.7), meaning occasionally appearance of these reactions. Regarding “physical functions” they also scored reasonable (mean score 2.8, s.d. 0.5), meaning moderate physical limitations.

No relationship with age was found (Table III). Further analyses on item-level showed no relation regarding age and ambulation and mobility (Kendall’s tau-b: \( P = 0.72 \) respectively \( P = 0.82 \)), which is in accordance with the view of the parents. In conclusion, care dependence was lower in the older age groups (Kendall’s tau: \( P = 0.08 \)).

**DISCUSSION**

Anticipating on specific health problems in adults with ID is important in providing long-term healthcare for these persons [Schrander-Stumpel et al., 2007]. Concerning RTT, a cross-sectional study was performed. Owing to the high response rate of 76%, we gathered data on 53 Dutch RTT individuals aged 16 years or older with a clinical diagnosis of RTT with a broad range of clinical symptoms. Our data represent almost exclusively the parental view. Since parents are closest to their children in every day life, they have the opportunity to experience their lack or change of development early on. The medical background of parents may limited although.

In general the parents valued the health of the RTT persons as good, irrespective of age, whereas neurological, respiratory and behavioral morbidity appeared to be of great influence. This is important for professionals in considering the significant impact of these features on quality of life of the RTT person and her family.

**Genotype–Phenotype Analyses**

Genotype–phenotype analyses have not been performed, since our statistical power to investigate the effect of genotype was limited.

Among the 53 persons with clinical RTT, mutation analyses was performed in 70%, of which 89% were molecularly confirmed. As a result, we had 31 confirmed MECP2 mutations and 22 RTT persons with a negative or unknown mutation status. The mean ages of the molecularly confirmed RTT persons and those with a negative or unknown mutation status were respectively 27.1 and 26.6 years \( (P = 0.82) \). There are no indications that the negative or unknown mutation status is due to selection bias and would affect the results.
Although care dependency was lower in the older age groups, the required therapeutic services remained high. This is in accordance with the conception of a stable condition with high dependency needs at adult age [Smeets et al., 2003; Williamson and Christodoulou, 2006]. Reported underweight in half of the subjects is in line with previous reports [Williamson and Christodoulou, 2006]. Overweight on the contrary is an underascertained feature in RTT. Some RTT girls will have a tendency to become overweight if they are allowed to eat what they want [Smeets and Schrander-Stumpel, 2005]. A positive relation was shown between eating behavior and BMI. Therefore, nutritional factors and energy expenditure play an important role in weight control and general health at adult age.

Although speech is absent in most RTT persons, in our study non-verbal communication was considerably better in the older age groups. This is in accordance with the view of parents and previous observations that comprehension, contact behavior and non-verbal communication improve with age [Hagberg, 2002; Williamson and Christodoulou, 2006]. Given the importance of mutual understanding life, active management of communication is required in RTT.

Contrary to the better preserved communication abilities, gross motor performance in RTT slowly but continuously declines over the years [Steffenburg et al., 2001; Hagberg, 2002; Kerr, 2002; Williamson and Christodoulou, 2006]. Nonetheless, we demonstrated no relationship between musculoskeletal problems and age, except for kyphosis. Kyphosis is present in 16% of the respondents and the occurrence was significantly higher in the older age groups. Information about prevalence and age dependency for kyphosis in both RTT and the female Dutch population is extremely limited, making comparison impossible. In this study, analyses showed a significantly high occurrence of osteoporosis in the kyphosis group (25%) compared with the remaining RTT persons (0%). The occurrence of osteoporosis in the female Dutch population at the age of 20–24 years is 0.013% and at the age of 50–54 years 0.74% [Poos and Gijsen, 2003]. Besides, in three quarters of the RTT persons the occurrence of osteoporosis was unknown. Active management and future study regarding diagnostics of osteoporosis and kyphosis is therefore advisable. Scoliosis is seen in 90% of the subjects in our study. This is in accordance with the results of a study in the UK with a prevalence of 87% at the age of 25 years [Kerr et al., 2003]. Scoliosis in RTT is typically noted between 8 and 11 years, whereas the progress usually occurs in early adolescence and close to the growth spurt [Keret et al., 1988; Percy, 2002]. The RTT persons in our study are at least 16 years old; therefore the increase with age has already taken place. In our study scoliosis necessitated surgery in 36%, which is in accordance with approximately 28% in the agegroup 16–20 years [Kerr et al., 2005]. As scoliosis is a major clinical manifestation that has detrimental effects on health and quality of life, medical attention is highly important [Ager et al., 2006].

Regarding epilepsy, we found no relation with age. However, many paroxysmal events diagnosed in RTT as epileptic have been found to be of non-epileptic origin [Glaze et al., 1998; Smeets et al., 2006]. Active management is of great importance, in particular on behalf of the high consumption of antiepileptic drugs reported in our study.

In line with previous reports, we noted a tendency towards improving autonomic dysfunction in adult RTT [Ellaway and Christodoulou, 2001; Julu et al., 2001; Williamson and Christodoulou, 2006]. Trophic skin and nail changes are significantly less prevalent in the older age group, which is in contrast with the view of parents who did not report any improvement. However, this is a cross-sectional study and the view of the parents changes with time. Regarding breathing dysfunction, apnea is significantly less prevalent in the older age group. The prevalence of autonomic dysfunction widely differs in the current literature; making comparisons with our results very difficult [Julu et al., 2001; Mount et al., 2001, 2002]. Another important finding in this study is the positive relation between both behavioral and respiratory problems with sleep abnormalities, which is in line with previous reports. Autonomic dysfunction reflects the immaturity of the brainstem in RTT resulting from the hyperactive sympathetic system with insufficient role in overall health, respiratory and behavioral problems can be seen as the most distressing features in RTT. Therefore, their relationship to quality of sleep is an important target for future study.

Another area that requires more attention in the future is genotype-phenotype analyses. Recent studies show a correlation of disease severity with mutation type and location [Cheadle et al., 2000; Christodoulou and Weaving, 2003; Charman et al., 2005; Archer et al., 2007]. Since our statistical power to investigate the effect of genotype was limited, we unfortunately were not able to perform these analyses. However, there was no indication that this would affect the results.

Finally, since cross-sectional data are used, one has to realize there might be a selection towards survivors, with the most severely affected dying earlier. It is hoped that this information will lead to further longitudinal studies of the natural history of RTT.

CONCLUSION

Although the results in this report relate to cross-sectional data, the adult RTT group has a more or less
stable condition. The general RTT profile is confirmed, considering the increase with age regarding kyphosis and the better communication and autonomic dysfunction in the oldest age group compared to the younger age groups.

Early intervention and preventive management in RTT requires an individualized approach at every age. It is aiming at maintaining or improving motor and communicative skills and trying to find treatment for respiratory health in order to improve the quality of life of the individuals and their families. In order to get a better understanding of the aging process and mortality in RTT, longitudinal studies including genotype-phenotype analyses are of great importance.

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