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Clinical presentation of Rett syndrome in relation to quality of life and family functioning

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Abstract

Objective: Rett syndrome (RTT) is a chronic condition that manifest in young children, with concomitant comorbidities such as respiratory problems, scoliosis, epilepsy, and malnutrition, which may affect children's quality of life (QoL) and family functioning. The objective of this cross-sectional descriptive correlation study was to understand the clinical presentation of RTT in relation to QoL and family functioning.

Methods: We included 23 parents of children with RTT. In this study, we used the PedsQL™ Family Impact Module, the Pediatric Quality of Life Inventory 4.0 generic core scales (PedsQL™ 4.0), and an author-designed questionnaire to assess QoL and family functioning.

Results: A significant relationship was observed between PedsQL™ 4.0 score and child's age in the physical functioning dimension. Children aged 8 to 12 years demonstrated significantly higher scores than those in the other age groups. Malnutrition in the child significantly affected functioning of the family in the family relationships dimension. Children receiving 5 hours of rehabilitation treatment a week had significantly higher QoL in the school functioning dimension.

Conclusions: QOL in children with RTT, as perceived by their parents, is reduced. RTT has a significant negative correlation with family functioning.

Keywords

Quality of life, rare disease, Rett syndrome, family functioning, comorbidity, rehabilitation

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Introduction

Rett syndrome (RTT; OMIM #312750) was first observed and studied in 1966 when Andreas Rett, an Austrian neurodevelopmental pediatrician in Vienna, described specific symptoms of the disorder in several girls.[1] The same year, Bengt Hagberg, a Swedish pediatric neurologist, described the condition again without knowing that someone else had already observed the same behaviors in girls characteristic of a neurological disorder that would later be called Rett syndrome.[2] RTT is a genetic neurological disorder caused by a mutation of the gene encoding methyl-CpG-binding protein 2 (*MECP2*) located on the X chromosome, near the end of its long arm at Xq28.[3,4] Rett mutation is sex-linked and develops almost exclusively in girls.[5,6] Its prevalence is estimated to be 1 per 10,000 girls,[7] but there have also been reports of RTT in boys.[8] Survival in girls is owing to having one chromosome from the mother and one from the father. As a result, girls have cells with an active chromosome containing a damaged or a functional copy of the gene. If the chromosome with the mutated gene is inactivated, the girl will not develop the disorder but she might eventually give birth to a child with RTT.[9]

The clinical picture associated with typical RTT is characterized by a brief period of normal development followed by a partial or complete loss of acquired purposeful hand skills and spoken language as well as gait abnormalities, postnatal deceleration of head growth, hand stereotypies, breathing disturbances when awake, and seizures.[10] Loss of acquired language is based on best acquired spoken language skills, not strictly on the acquisition of distinct words or higher language skills. The onset of behavioral regression can be sudden; most children are born with a normal pregnancy and delivery.[11] After the period of regression, a stage of stabilization and potential improvement ensues, with some individuals partially regaining skills. The clinical diagnosis is based on certain key criteria of classic or typical RTT. Additionally, some individuals present many of the clinical features of RTT, such as regression, but do not have all features of the disorder; these cases are termed "atypical".[12]

MECP2 mutations can now be identified in some individuals prior to any clear evidence of regression. The diagnosis of "possible" RTT is given to those individuals under 3 years of age who have not lost any skills but have clinical features suggestive of RTT. These individuals should be reassessed every 6 to 12 months for evidence of regression. If regression manifests, the diagnosis is changed to definite RTT.

The experience of living with RTT is vastly more complex than its medical features. Factors beyond physical manifestations of the disease, such as psychological well-being, coping, and illness perceptions, influence quality of life (QoL) and may serve as potent targets for intervention.[13]

Previous research into RTT has focused primarily on phenotypic impairment and treatment of the disorder. Our study is one of the few in which the parents of children with RTT have been interviewed. By 2021, we identified only six articles describing QoL in children with RTT. Some of those studies used standardized QoL questionnaires, among which one[14] was condition-specific, to investigate the effect of the child's chronic pathology of RTT. All past studies have revealed that RTT has a considerable impact on both the child's development and on the family. Advancing our understanding of QoL in RTT, including of the contributing factors at different ages, is of great importance for clinical practice and emerging drug trials. The aim of this paper was to investigate the influence of RTT on the QoL of affected children and the impact of the child's state of health on family functioning.

Methods

Setting and participants

We conducted a cross-sectional study among parents of children with RTT from January 2018 to February 2019. Parents of children with RTT were included if they met the following inclusion criteria: the child has a diagnosis of RTT made by a pediatrician and/or neurologist in accordance with clinical criteria and confirmed in molecular testing, and being the biological parent of the child. An author-designed questionnaire (ADQ), the Pediatric Quality of Life Inventory 4.0 generic core scales (PedsQL™ 4.0), and the PedsQL™ Family Impact Module (PedsQL™-FIM) were administered to families whose children were patients of the Polish Rett Syndrome Association.

The Bioethics Committee of Wroclaw Medical University, Wroclaw, Poland (no. KB–511/2019) approved this research protocol. All participants gave their written informed consent after receiving a thorough explanation of the procedures involved. The study was carried out in accordance with guidelines of the Declaration of Helsinki and Good Clinical Practice.

Measures

Data collection and measurement tools used in this study included the following survey instruments: an ADQ as well as two standardized questionnaires: the PedsQL™-FIM, and PedsQL™ 4.0 were used to collect medical and sociodemographic background data. Eligible parents were contacted and mailed traditional pencil-and-paper questionnaires together with a stamped, self-addressed envelope in which they were to return the completed survey to the research team. The invitation to participate in the study included a letter and an information packet explaining the study and the questionnaires to complete. Participant anonymity was ensured by marking each questionnaire package with a different random number rather than with the participant's name.

PedsQL™ 4.0

PedsQL™ 4.0[15–18] is a 23-item instrument evaluating perception of pediatric health-related QOL. There are four scales: physical functioning, emotional functioning, social functioning, and school functioning. Mean scores are calculated on a 5-point Likert response scale. Items are reverse-scored and linearly transformed to a 0 to 100 scale ($0 = 100$, $1 = 75$, $2 = 50$, $3 = 25$, $4 = 0$), with higher scores indicating better QoL.

PedsQL™-FIM

PedsQL™-FIM[19] assesses family functioning and is designed to measure the impact of chronic pediatric health conditions on the parents and family. The instrument consists of 36 items measuring parents' self-reported functioning on six subscales: physical functioning (6 items), emotional functioning (5 items), social functioning (4 items), cognitive functioning (5 items), communication (3 items), and worry (5 items); two additional subscales measure parent-reported family functioning: daily activities (3 items) and family relationships (5 items). Each item is scored using a 5-point Likert scale from 0 (never a problem) to 4 (always a problem), which is then transformed to a 0 to 100 scale ($0 = 100$, $1 = 75$, $2 = 50$, $3 = 25$, $4 = 0$), with higher scores indicating better functioning.

Author-designed questionnaire (ADQ)

Along with family demographic and medical questions, an ADQ was completed by parents. The ADQ included questions about age, residence, child's medical problems, average age at diagnosis, age at

regression of acquired skills, and rehabilitation activities.

Statistical analysis

The analysis of original variables was performed by calculating the mean, standard deviation, median, minimum, and maximum. We adopted a significance level $p<0.05$. The statistical analysis was carried out using SPSS for Windows 17.0 (SPSS Inc., Chicago, IL, USA), with the Mann–Whitney U test and chi-squared test.

Results

The parents of 23 children with RTT were included in this study. The children's ages ranged from 2 to 12 years and the mean age was 7.22 years (standard deviation [SD] = 3.57). Table 1 presents information of participants, including age, residence, respiratory problems, bruxism, apraxia, scoliosis, and seizures. Among respondents, 83% indicated that there were no abnormalities during prenatal development of the child. The average age at diagnosis for children with RTT was 3.5±3.1 years, and the average age when symptoms were first noticed was 1.2±1.1 years. Seventeen children (75%) age 1 to 2 years experienced a significant regression in acquired skills, with developmental deterioration, severe dementia with loss of speech, autistic features, and stereotypies.

Table 1. Characteristics of 23 children with Rett syndrome.

Age, years	Number (%)
2–4	5 (22)
5–6	4 (17)
7–12	13 (57)
13–18	1 (4)
Residence	
Urban	13 (57)
Rural	10 (43)
Respiratory problems	20 (87)
Seizure	10 (43)
Scoliosis	3 (13)
Bruxism	5 (22)
Apraxia	19 (83)

Only 14 children (60%) were able to move unassisted, with 9 (40%) requiring assistance to move. Malnutrition was observed in 18 children (78%), 10 children (43%) were diagnosed with epilepsy, and 3 children (13%) had scoliosis. Respiratory problems occurred in 20 children (87%), the most common being apnea (n = 10, 43%), rapid breathing (n = 7, 30%), and hyperventilation (n = 5, 22%). Onset of breathing irregularities usually occurred during early childhood.

On the PedsQL™ 4.0, the total QoL score obtained by the parents of included children was 45.43 (SD = 13.87), with the highest scores in the emotional functioning dimension (total score: 58.26; SD: 18.38), and the lowest in the physical functioning dimension (total score: 30.43; SD: 24.08). We observed a statistically significant correlation between the PedsQL™ 4.0 score and the child's age in the physical functioning dimension ($p = 0.047$). Children aged 8 to 12 years demonstrated significantly higher scores than those in the other age groups. The values are presented in Table 2.

There was no statistically significant correlation between residence, education, and individual PedsQL™ 4.0 generic core dimensions.

The total QoL score obtained by parents whose children experienced respiratory problems was 45.80 (SD: 12.74), with the highest scores in the social functioning dimension (total score: 60; SD: 20.64) and emotional functioning dimension (total score: 59; SD: 18.17) and the lowest in the physical functioning dimension (total score: 29.84; SD: 24.32).

The total QoL score obtained by the parents of children with epilepsy was 43.48 (SD: 12.45), with the highest scores in the social functioning dimension (total score: 60; SD: 20.95) and emotional

Table 2. Children's age and quality of life score in the PedsQL™ 4.0.

PedsQL™ 4.0 dimension	2–4 years (N = 6)	5–7 years (N = 6)	8–12 years (N = 11)	p
Physical dimension				
SD	17.5 ± 22.13	49.31 ± 20.8	55.68 ± 26.76	0.047 *
m	4.17	56.25	66.67	
Emotional dimension				
SD	24 ± 20.43	57.5 ± 34.89	54.55 ± 26.31	0.107
m	30	55	50	
Social dimension				
SD	30 ± 16.18	48.96 ± 27.5	57.95 ± 34.92	0.322
m	37.5	56.25	56.25	

*Denotes a significant difference.
PedsQL™ 4.0, Pediatric Quality of Life 4.0 generic core scales; m, median; SD, standard deviation.

functioning dimension (total score: 58.5; SD: 20.69) and the lowest in the physical functioning dimension (total score: 24.38; SD: 26.95).

The total QoL score obtained by the parents of children with scoliosis was 49.64 (SD: 24.12), with the highest scores in the physical functioning dimension (total score: 56; SD: 44.3) and emotional functioning dimension (total score: 51; SD: 15.28) and the lowest in the social functioning dimension (total score: 43.33; SD: 31.75).

The total QoL score obtained by the parents of children with malnutrition was 46.28 (SD: 12.63), with the highest scores in the social functioning dimension (total score: 60.83; SD: 20.31) and emotional functioning dimension (total score: 58.61; SD: 18.77) and the lowest scores in the physical functioning dimension (total score: 30.73; SD: 24.19).

There were no statistically significant correlations between comorbidities in RTT (respiratory problems, epilepsy, scoliosis, malnutrition) and the PedsQL™ 4.0 generic core dimensions.

The mean family functioning summary score measured using the PedsQL™-FIM was 50.94 (SD: 19.31), with the highest scores in the family relationships dimension (total score: 69.78; SD: 23.10) and cognitive functioning dimension (total score: 66.30; SD: 24.64) and the lowest in the daily activities (total score: 34.06; SD: 27.17) and worry (total score: 37.39; SD: 22.91) dimensions. The data are presented in Table 3.

The analysis did not reveal significant correlations between the PedsQL™-FIM dimensions and the age of children. In the case of children aged 2 to 4 years, low scores were observed in the daily activities (total score: 20; SD: 19.18) and worry (total score: 28.00; SD: 14.4) dimensions.

Interestingly, malnutrition in the child was observed to significantly ($p = 0.041$) affect family functioning in the family relationships dimension. Epilepsy and scoliosis did not have a significant impact on the functioning of families in the dimensions measured with the PedsQL™-FIM.

The study findings demonstrated that 10 children (43%) were involved for up to 10 hours a week in rehabilitation activities, 5 (22%) to 5 hours, and 5 (22%) to 15 hours. Ten respondents (43%) engaged in rehabilitation treatments in a specialist facility once a year. Such facilities were attended twice a year by only 1 respondent (4%). The study findings showed that 74% of parents were not satisfied with the effects of rehabilitation. Interestingly, children who spent more than 10 hours a week in rehabilitation programs had significantly higher ($p = 0.044$) QoL in the physical functioning dimension than

Table 3. Average scores in the PedsQL™-FIM.

PedsQL™-FIM (n=23)	M	SD	m	Min	Max
Physical functioning	46.01	27.51	50	0	91.67
Emotional functioning	48.7	29.09	45	0	100
Social functioning	50.27	30.41	43.75	0	100
Cognitive functioning	66.3	24.64	70	10	100
Communication	47.83	26.14	41.67	16.67	100
Worry	37.39	22.91	40	0	80
Daily activities	34.06	27.17	33.33	0	100
Family relations	69.78	22.33	70	35	100
Physical functioning	52.61	23.33	50	15	97.5
Emotional functioning	56.39	21.08	59.38	21.88	100
General score	50.94	19.31	46.53	20.83	93.06

PedsQL™-FIM, Pediatric Quality of Life™ Family Impact Module; M, mean; m, median; Min, minimum; Max, maximum; SD, standard deviation.

Table 4. Rehabilitation and PedsQL™ 4.0 scores.

PedsQL™	5 hours/per week (N = 5)	5–10 hours/per week (N = 11)	10 hours/per week (N = 7)	p
Physical functioning				
SD	45 ± 25.25	18.12 ± 14.79	43.75 ± 28.78	0.044
m	50	15.62	40.62	
Emotional functioning				
SD	69 ± 16.36	53.5 ± 20.28	55.83 ± 18.28	0.212
m	65	50	55	
Social functioning				
SD	68 ± 19.56	55 ± 24.38	50 ± 24.9	0.291
m	80	67.5	50	
School functioning				
SD	63.67 ± 25.34	38 ± 19	31.94 ± 13.14	0.032
m	60	35	32.5	
General score				
SD	58.82 ± 10.12	38.18 ± 10.03	45.57 ± 17.03	0.024
m	60.87	41.85	47.83	

PedsQL™ 4.0, the Pediatric Quality of Life 4.0 generic core scales; m, median; SD, standard deviation.

children receiving 5 to 10 hours of rehabilitation treatment a week. Children receiving 5 hours of rehabilitation treatment per week demonstrated a significantly higher QoL ($p = 0.032$) in the school functioning dimension than children involved in rehabilitation activities for more than 10 hours a week (Table 4). Children living in urban areas had significantly better ($p = 0.021$) access to medical professionals than those living in towns and villages. The accessibility to professional medical care significantly ($p<0.05$) depended on the parents' place of residence.

Discussion

Our study demonstrated that access to specialists and rehabilitation centers offering

early RTT diagnostic services was significantly associated ($p = 0.021$) with the residence of respondents. We also determined that the average age of RTT diagnosis was 3.5 years. Individuals living in cities had better access to specialists than those living in rural areas. These findings are in line with those of a study by Daniel et al.,[20] which showed that the age at diagnosis of RTT depended not only on clinical factors but also on demographic, socioeconomic and secular ones. As with autism spectrum disorders[21] and fragile X syndrome,[22] the age at diagnosis was correlated with socioeconomic factors and failure to reach early developmental milestones within the normal range. As diagnosing developmental disorders is an important role of pediatricians, data on the factors related to late diagnosis may help to raise their awareness of the diagnostic criteria for RTT.

Importantly, weight loss may persist in RTT, despite good appetite.[23] Our study indicated that nearly 80% of the children were malnourished, despite having a good appetite. This most likely results from increased energy expenditure as a result of hyperventilation, accelerated heart rate, and increased physical activity related to stereotypies. Moreover, as demonstrated in the literature,[24,25] the most common causes of malnutrition in children with RTT are chewing and swallowing difficulties, gastrointestinal reflux, and frequent vomiting. This was confirmed in a study by Motil et al.,[26] who reported that children found it more difficult to eat solid foods than to drink thick liquids and that uncontrolled grinding of the teeth and involuntary tongue movements increased the length of feeding time. These findings were corroborated in our survey analysis, where apraxia (83%), problems with purposeful movements, stereotypies (70%) and bruxism (20%) may have contributed to low weight gain in the children studied. It is also worth mentioning a study by Killian et al.,[27] which showed that feeding difficulties were associated with lower physical component scores in the children studied. Leonard et al.,[28] in turn, pointed to a positive impact of gastrostomy in girls with RTT. Those authors found that the procedure helped to reverse emaciation and improved the clinical nutritional status of patients. It is interesting to note that our survey analysis showed that feeding difficulties significantly ($p = 0.041$) affected QoL among parents in the family relationships domain. Although QoL in the family relationships domain was rated highly, qualitative data showed that these relationships are based on the division of household responsibilities rather than on helping one another. Family members have to rely on themselves. They appreciate mutual support and trust, rating these quite highly, even though their day-to-day reality involves dealing with their problems and duties on their own. Given the difficulties in coping with everyday problems, parents of children with RTT are at risk of burnout syndrome, which is associated with apathy, distance, and coldness in interpersonal relationships.[29]

An increasing number of studies are being undertaken in Poland and abroad regarding the QoL of people with disabilities and their families. The main purpose of such research is to determine the extent to which an illness affects QoL. Researchers seek to determine which factors may affect QoL and to what extent QoL is influenced by the type and degree of disability. To our knowledge, this is the first study in Poland to focus on the QoL of children with RTT and their families.

Our study revealed that the total QoL score was poor (total score: 45.43). The lowest scores were observed in the physical functioning domain and the highest in the emotional and school functioning domains. Low scores in the physical functioning domain stem from clinical progression of

the disease as well as comorbidities (breathing problems, seizures). The disorder is progressive and disability in a child with RTT becomes more severe over time. Crochon et al.[30] demonstrated that low QoL scores were owing to epilepsy in children. Our analysis did not corroborate this finding. In our study, the parents of children aged 8 to 12 years functioned better than parents of children aged 2 to 4 years in all QoL dimensions. This probably stems from the fact that acceptance of their child's illness grows over the years. This has been confirmed in our study, where the lowest scores were observed in the domains of daily activities and worry of the PedsQL^{TM}-FIM in the group of children aged 2 to 4 years.

Our study did not show a correlation between the level of education and QoL. The higher the education level of the parents, the better their chances of securing a better job and earning a higher income for their family, thereby increasing their socioeconomic status. Educated parents are more likely to understand their child's disease, respond better to their needs, and participate in the therapeutic process more consciously. This contradicts the results of European research, which showed an inverse relationship between the education of parents and mental well-being.[31] That study demonstrated a positive relationship between the education level of a parent and the social acceptance domain. In light of these findings, it seems that analysis of the relationship between education and QoL is more complex than might be expected and that multiple factors must be taken into account to achieve conclusive results.

Numerous authors[32,33] consider that RTT is a progressive neurodegenerative disease, leading to complete disability in the affected child. Our analysis showed that nearly 44% of children with RTT had lost their motor skills and the ability to function independently by the age of 2 years. These data are in line with the results obtained in numerous other studies,[34,35] where in most cases, the regression of previously acquired skills occurred between the ages of 1 and 2 years. Given the loss of skills, QoL assessment makes it possible to adjust treatment to the needs of each patient. The aim of treatment is not only to extend the patient's life but also to improve their well-being and independence in daily activities. Rehabilitation for children with RTT requires consistency and an interdisciplinary approach and should always be carried out in cooperation with the patient's family. Therefore, it is not surprising that children who spent over 10 hours a week in rehabilitation programs presented significantly higher ($p = 0.044$) QoL in the physical functioning dimension than children receiving 5 to 10 hours of rehabilitation treatment per week.

The findings of this study must be considered in light of some limitations. First, the cross-sectional design only revealed correlations between predictors and QoL scores and not casual relationships. Second, the study was conducted using a generic questionnaire; using a disease-specific questionnaire for children with RTT is warranted in subsequent studies. Third, the number of participants included in the study was limited, with only 23 children.

Conclusion

This study offers broader understanding of the QoL in children with RTT. Overall, children with RTT had significantly poorer QoL in all instrument dimensions, with the social well-being dimension of QoL being the poorest. Factors such as epilepsy, respiratory problems, and scoliosis had no significant influence on family functioning. Measurement of QoL indicates areas in which a child and their family are in greatest need of practitioners' help with making appropriate decisions for patient care.

Implications for practice

This study results demonstrated that to improve QoL, it is important to clarify which factors determine the QoL of children with RTT. To provide adequate support to children with RTT and improve their QoL, it is first necessary to identify their needs and expectations. By providing appropriate assistance and targeting individual problems in such children, we can help improve their well-being and QoL. RTT is a disorder that "robs" parents of their healthy child, and parents must face the challenge of watching their child regress rather than develop normally. Undoubtedly, psychological support provided to the caregivers of children with RTT, especially in the early diagnosis stage, is of great importance.

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Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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