

# Sleep Quality in Children and Adults with Rett Syndrome

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## Abstract

**Background** Over 80% of individuals suffering from Rett syndrome (RTT) are affected over their life period by sleeping disorders. Little is known about the impact of those on the quality of life and a clinical approach to the treatment of sleep disturbances is lacking.

**Aims** Primary aim was to assess sleep quality in children and adults. Secondary aim was to assess behavioral disorders and their relationship to sleep quality. The medication taken by the subjects was also included.

**Methods** Sleep quality and medication were assessed using the sleeping questionnaire for children with neurological and other complex diseases (SNAKE). Behavioral disorders were assessed by the Rett Syndrome Behavior Questionnaire (RSBQ). Questionnaires were sent to the 700 members of the *Elternhilfe für Kinder mit Rett Syndrom in Deutschland e.V.* (Rett Aid) of which 287 were included. Questionnaires were filled out by the primary caregivers.

**Results** Sleep quality was rated as very good to good by over 60% of caregivers in contrast to data available in the literature. Behavioral disorders related to regression such as loss of acquired hand skills ( $p = 0.046$ ) and isolation ( $p = 0.002$ ) were found to be associated with sleep quality. Melatonin showed a significant association ( $p = 0.007$ ) with sleep quality.

**Conclusion** Our study showed sleep dysfunction to be less prevalent in RTT-affected individuals than evidence from past studies has suggested. Nevertheless, this remains a subjective assessment of sleep quality and therefore the need to find objective, disorder-specific parameters that measure sleep quality in RTT patients persists.

## Keywords

- ▶ Rett syndrome
- ▶ quality of life
- ▶ sleep quality
- ▶ SNAKE
- ▶ RSBQ
- ▶ MECP2

## Introduction

Rett syndrome (RTT) affects 1 in 10 000 females and is a neurodevelopmental disorder caused by a de novo mutation in the methyl-CpG-binding protein 2 gene (*MECP2*) located on the X chromosome.

The clinical presentation and severity of RTT can be variable due to the degree of X inactivation and differing occurrence of *MECP2* in different populations of cells.<sup>1</sup>

Following a period of nearly normal postnatal development, symptoms start after 6 to 18 months. RTT can be divided into four stages correlating to the patients' age. The first phase (6–18 months) is characterized by stagnation of development. The second phase (1–4 years) is marked by regression as children experience a loss of already acquired abilities and commonly develop autistic-like behavior.<sup>2</sup> Epileptic seizures occur during the third stage (2–10 years) and the fourth stage (>10 years) is defined by late motor deterioration and

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scoliosis. Even though, RTT is the second most common cause of intellectual disability in females after Down syndrome, its diagnosis remains challenging owing to its complex phenotype and the limited awareness of RTT.<sup>3</sup>

Although research on sleeping disorders in RTT is scarce, it is estimated that over 80% of individuals affected by RTT suffer from sleep disturbances.<sup>4</sup> Angriman et al suggest that sleep disorders are linked to an endogenous dysfunction in hormone and neurotransmitter release or to altered perception of the zeitgebers. Sleep dysfunction in RTT often presents as irregular sleep/wake patterns, excessive daytime naps, and problematic nighttime behavior such as nocturnal laughter, bruxism, screaming and inconsolable crying, nocturnal seizures, sleep terrors, and talking.<sup>5</sup> Sleep disorders severely impact on family stress levels as they have detrimental effects on daytime behavior, cognition, growth, and overall development of the child.

McDougall et al state that poor sleep affects mood, energy levels, and general performance of both child and parents. It also impacts on social activities and relationships. Therefore, there is an urgent need for a therapeutic approach.<sup>6</sup>

A study from 2016 conducted by Blackmer and Feinstein reviews the management of sleep disturbances in children with neurodevelopmental disorders. Blackmer states that evidence on pharmacological treatment of sleeping disorders in children with RTT or neurodevelopmental disabilities in general is lacking. Treatment algorithms are nonexistent, and the choice of therapy is typically determined on a case-by-case basis. Several medications to treat sleep disturbances were tested but the only drug that demonstrated efficacy in RTT was melatonin. It improved family stress scales and was even more effective in combination with cognitive behavioral therapy. Nevertheless, sleep hygiene is regarded as first-line therapy.<sup>4</sup> An international study by Boban et al showed that high sleep hygiene scores were not only associated with lower "Disorders of Initiating and Maintaining Sleep" (DIMS) subscale scores but also with a lower odds of moderate/major impact on the family.<sup>7</sup> Sleep disorders constitute a universal symptom that many RTT patients struggle with over a lifetime. Due to their high impact on family functioning and stress scales, they are listed as a quality of life (QoL) domain in several studies.<sup>3,5,8</sup> It is critical to further characterize the influence of sleep disorders on QoL and to identify factors impacting on the quality of sleep. There is only little evidence available on sleep quality in RTT; this study, therefore, aims to contribute to existing literature and provide insight into this important topic for future research.

## Methods

### Participants

The conducted study is a prospective pilot study that evaluates the quality of sleep in RTT patients whose parents are members of the *Elternhilfe für Kinder mit Rett-Syndrom in Deutschland e.V.* (Rett Aid). The Rett Aid is Germany's largest society supporting families in need of medical, financial, legal, or social advice with children affected by RTT. Therefore, addressing their

members allowed us to obtain the largest possible, representative sample. Letters were sent to the 700 members containing the Sleeping Questionnaire for Children with Neurological and other Complex Diseases (SNAKE), the Rett Syndrome Behavior Questionnaire (RSBQ), the patient information sheet, the declaration of consent for data protection, and the patient consent form. The data were analyzed in four groups, group 1 comprised patients aged from 0 to 6 years ( $n=55$ ), group 2 comprised patients aged from 7 to 12 years ( $n=54$ ), group 3 comprised patients aged from 13 to 18 years ( $n=51$ ), and group 4 comprised patients over 18 years old ( $n=127$ ). Inclusion criteria encompassed children and adults who were diagnosed with RTT before data collection and whose parents' consent was obtained. Patients had to be excluded if they had incomplete documents or another diagnosis (such as FOXP1 syndrome/CDKL5 mutation) not attributable to RTT. The questionnaires were filled out by the primary caregivers, often the parents, of the affected individual. Both are further referred to as "parents." The response rate of 48% exceeded the expected response rate of 40%. Data was collected from September to December 2017 with 336 respondents in total from which 287 could be included. Forty-nine respondents were excluded due to incomplete documents ( $n=11$ ), atypical RTT or another diagnosis ( $n=22$ ), and suspected RTT ( $n=16$ ).

### Variables

The SNAKE was chosen as it is the first questionnaire that addresses sleep disturbances in children with developmental disabilities. It is based on the International Classification of Sleep Disorder, Second edition classification for sleep problems and takes the patient's impaired perception, intellectual ability, limited behavioral repertoire, and motor impairment into account and serves both as a valuable scientific and a clinical screening tool. The SNAKE was developed by conducting a comprehensive literature review, interviews with three pediatric experts on sleep and sleep disorders and interviews with twenty parents with children suffering from severe psychomotor impairment and sleep disturbances. It assesses symptoms and consequences of sleep disturbances along with conditions that are known to have direct or indirect impact on sleep in children with severe psychomotor impairment. It consists of two parts that ask parents to assess their child's sleep in the last 4 weeks. The first part refers to the sleeping habits and the second part refers to the daytime activity. Components of the SNAKE include items on sleep conditions (locality, sleep disturbing factors of underlying disease or environment, medication), sleep onset latency (SOL), duration of sleep, sleep efficiency, sleep quality and symptoms, and consequences of sleep deficiency (disturbances going to sleep and remaining asleep, arousal and breathing disorders, daytime sleepiness, and daytime behavior disorders).<sup>9</sup>

The RSBQ was developed by Mount et al by testing the specificity of behavioral features of RTT compared to individuals with severe intellectual disability. It asks the parents to only assess the characteristics their child currently shows. Individuals with RTT suffer from severe cognitive as well as physical impairment, both of which are related to

behavioral and emotional disturbance. The RSBQ includes both items that describe behavioral features as well as physical ability ratings including hand function, ability to sit unaided, and ability to walk. Other items that are assessed include sleeping problems, breathing difficulties, mood disturbances, self-injury, social contact, and repetitive movements unrelated to the hands. To date, the RSBQ is the only available tool to measure behavioral features in RTT.<sup>10</sup>

### Analysis

Chi-squared, Cramers-V, and Fisher's exact test were applied to test categorical data. Ordinal logistic regression was further used to analyze categorical data and continuous variables in regard to sleep quality. A *p*-value of < 0.05 was regarded significant.

The SNAKE generated categorical as well as continuous data. The first part of the SNAKE asked parents to rate their child's sleeping habits by choosing one of the following four frequency responses: "never, less than once a week, once to twice a week and three times a week or more." The second part of the SNAKE asked parents to rate their child's daily activities by choosing one of the following four frequency responses: "never, seldom, sometimes and often." These parts constitute the categorical, ordinal data.

Continuous variables such as the following sleep parameters defined by the SNAKE were also evaluated:

- Wake time after sleep onset (WASO)
- Sleep onset latency (SOL)
- Total sleep time (TST)
- Time asleep during the day (TAD)
- Time restless during the day (TRD)

Measuring WASO, SOL, TST, TAD, and TRD along with the four categories of sleep quality (very good, good, satisfying, and bad) enables an estimation of the child's sleep parameters that includes objective as well as subjective measures reflecting parents' perception rather than a detailed objective record of sleep parameters.<sup>9</sup>

The RSBQ consists of 45 questions that are rated on a three-point Likert scale generating categorical, ordinal data. Parents are asked to rate how accurately a characteristic

describes their child ranging from: 0= not true as far as you know, 1= somewhat or sometimes true, or 2= very true or often true.<sup>10</sup>

Quantitative data was processed using IBM SPSS Version 24. Qualitative data was collected using Microsoft Excel Version 1803. This included free text parts of the SNAKE that were collected and grouped into themes.

Ethical approval of the Landesärztekammer Hessen FF57/2017 and Ethics and Research Governance approval were both obtained.

### Results

The final study cohort included 286 female patients and 1 male patient. ► **Table 1** shows the comparison of macrostructural sleep parameters, daytime sleep, and restlessness between groups 1 to 3 aged <18 years and group 4 aged >18 years. There is no difference between the groups in TRD. On average group 4 has an increased rate of WASO (1.47 vs. 1.31 hours) and TAD (1.5 vs. 1.0 hours). However, group 4 shows a shorter TST (8 vs. 9.5 hours) and decreased SOL (20.0 vs. 22.5 minutes) (see ► **Table 1**).

As ► **Table 2** shows sleep quality was rated as very good to good by over 60% in every group. Comparing the categories between groups, group 1 rates highest in bad sleep quality (14.55%). Group 2 rates highest in satisfying sleep quality (33.33%). Group 3 rates highest in good sleep quality (45.10%). Group 4 rates second highest for bad sleep quality (12.90%). Group 2 (25.93%) and 3 (25.50%) both rate highest in very good sleep quality (► **Fig. 1**).

Logistic regression was conducted to test for an association between age and sleep quality, but a statistically significant association was found neither in the groups 1 to 3 (*p* = 0.465) nor in group 4 (*p* = 0.329). Parents stated that sleep disturbances were variable and that there were phases of good sleep quality followed by phases of worse sleep quality owing to the complex nature of sleep disturbances. As part of the qualitative analysis parents stated that their child generally slept better as she/he got older.

The chi-squared test was conducted to compare behavioral disorders to sleep quality using the data of the RSBQ. In

**Table 1** Comparison of macrostructural sleep parameters and daytime behavior in subjects aged >18 and <18 years

	Groups 1–3 aged <18 ( <i>n</i> = 160)		Group 4 aged >18 ( <i>n</i> = 127)	
	Mean	SD	Mean	SD
Age (y)	9.66	4.94	27.18	6.56
Bedtime (min)	19:42	42	19:57	110
WASO (h)	1.31	1.20	1.48	1.34
	Median	LQ, UQ	Median	LQ, UQ
SOL (min)	22.50	10, 35	20.00	0, 360
TST (h)	9.50	8, 10	8.00	7, 9.5
TAD (h)	1.00	0.68, 2	1.50	0.94, 2
TRD (h)	1.00	0.5, 2.25	1.00	0.5, 2.5

Abbreviations: SD, standard deviation; SOL, sleep onset latency; TAD, time asleep during the day; TRD, time restless during the day; TST, total sleep time; WASO, wake time after sleep onset.

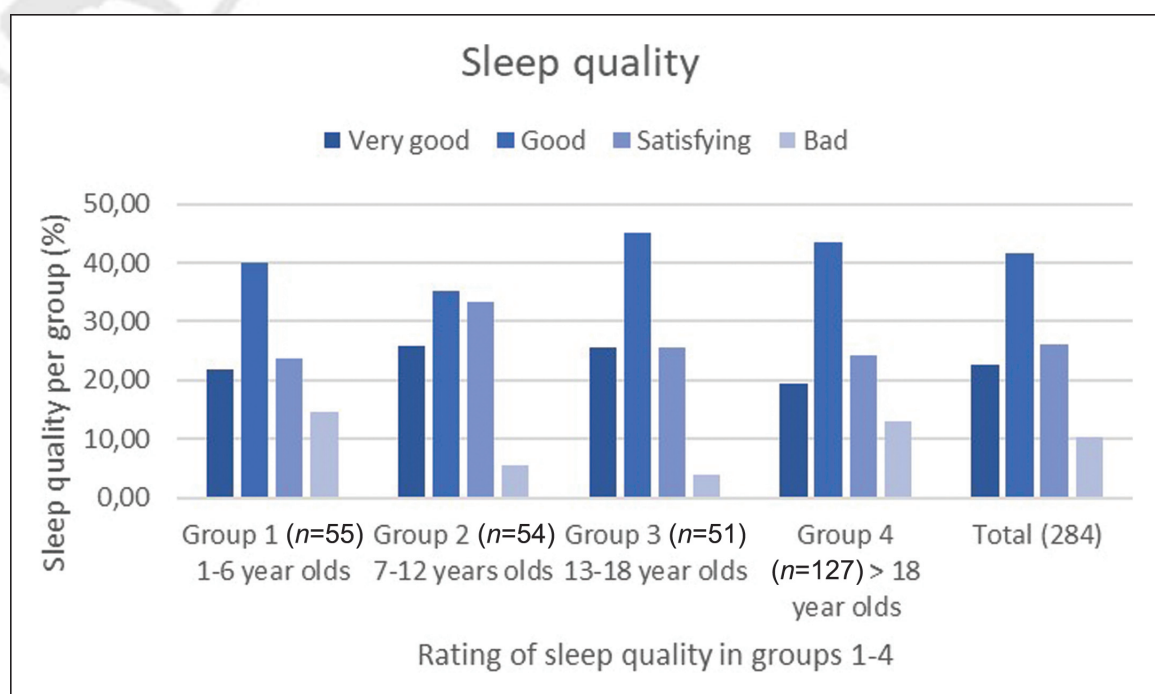
**Table 2** Percentage distribution of sleep quality among groups 1–4

Sleep quality (%)	Group 1 (n = 55)	Group 2 (n = 54)	Group 3 (n = 51)	Group 4 (n = 127)	Total (287)
Very good	21.81	25.93	25.50	19.40	22.60
Good	40.00	35.19	45.10	43.50	41.40
Satisfying	23.64	33.33	25.50	24.20	26.00
Bad	14.55	5.55	3.90	12.90	10.00

group 1, sleep quality was associated with mouth grimaces ( $\chi^2 = 16.95$ ,  $df = 6$ ,  $p = 0.009$ , Cramers-V = 0.369) and holding the breath ( $\chi^2 = 14.52$ ,  $df = 6$ ,  $p = 0.024$ , Cramers-V = 0.363). Behavioral disorders such as isolation ( $\chi^2 = 20.81$ ,  $df = 6$ ,  $p = 0.002$ , Cramers-V = 0.435) and loss of acquired hand skills ( $\chi^2 = 12.84$ ,  $df = 6$ ,  $p = 0.046$ , Cramers-V = 0.351), of which the latter is related to the phase of regression, were associated with sleep quality in group 1. In groups 2, 3, and 4, problematic nighttime behavior such as screaming ( $\chi^2 = 15.26$ ,  $df = 6$ ,  $p = 0.018$ , Cramers-V = 0.358,  $\chi^2 = 24.42$ ,  $df = 6$ ,  $p = 0.000$ , Cramers-V = 0.490,  $\chi^2 = 22.97$ ,  $df = 6$ ,  $p = 0.001$ , Cramers-V = 0.307) and laughing ( $\chi^2 = 12.69$ ,  $df = 6$ ,  $p = 0.048$ , Cramers-V = 0.341,  $\chi^2 = 16.96$ ,  $df = 6$ ,  $p = 0.009$ , Cramers-V = 0.420,  $\chi^2 = 15.92$ ,  $df = 6$ ,  $p = 0.022$ , Cramers-V = 0.256) were associated with sleep quality as well. Nighttime laughing was the most frequent feature parents described as part of the qualitative answers in groups 1, 2, and 3. In group 3 and 4, screaming during the day ( $\chi^2 = 14.56$ ,  $df = 6$ ,  $p = 0.032$ , Cramers-V = 0.244;  $\chi^2 = 14.94$ ,  $df = 6$ ,  $p = 0.02$ , Cramers-V = 0.247) and crying during the night ( $\chi^2 = 19.69$ ,  $df = 6$ ,  $p = 0.004$ , Cramers-V = 0.439;  $\chi^2 = 38.47$ ,  $df = 6$ ,  $p = 0.000$ , Cramers-V = 0.397) were also associated with sleep quality. Analyzing the data of all

participants <18, behavioral features associated with autonomic dysfunction such as hyperventilation ( $\chi^2 = 13.47$ ,  $df = 6$ ,  $p = 0.036$ , Cramers-V = 0.206) and holding the breath ( $\chi^2 = 18.28$ ,  $df = 6$ ,  $p = 0.006$ , Cramers-V = 0.239) were associated with sleep quality. Behavioral features that were associated with sleep quality in group 4 were panicking ( $\chi^2 = 19.67$ ,  $df = 6$ ,  $p = 0.004$ , Cramers-V = 0.286), restless phases ( $\chi^2 = 17.69$ ,  $df = 6$ ,  $p = 0.005$ , Cramers-V = 0.269), mood swings ( $\chi^2 = 21.74$ ,  $df = 6$ ,  $p = 0.001$ , Cramers-V = 0.300), bad mood ( $\chi^2 = 26.15$ ,  $df = 6$ ,  $p = 0.000$ , Cramers-V = 0.327), hysteric screaming ( $\chi^2 = 17.94$ ,  $df = 6$ ,  $p = 0.007$ , Cramers-V = 0.272), being irritable without reason ( $\chi^2 = 18.64$ ,  $df = 6$ ,  $p = 0.007$ , Cramers-V = 0.279), crying during the day ( $\chi^2 = 18.92$ ,  $df = 6$ ,  $p = 0.007$ , Cramers-V = 0.278), swallowing air ( $\chi^2 = 15.36$ ,  $df = 6$ ,  $p = 0.022$ , Cramers-V = 0.251) and appearing miserable for no apparent reason ( $\chi^2 = 15.57$ ,  $df = 6$ ,  $p = 0.033$ , Cramers-V = 0.255).

The chi-squared test was also conducted to test for an association between medication and sleep quality. Melatonin ( $p = 0.007$ ) and zolpidem ( $p = 0.01$ ) showed an association with sleep quality in groups 1, 2, and 3. As part of the analysis of qualitative answers parents also stated that treatment with melatonin improved the sleep quality. In



**Fig. 1** Histogram depicting the overall distribution of sleep quality (%) of all participants in their groups. Sleep quality was either rated as 1 = very good, 2 = good, 3 = satisfying, or 4 = bad. Median sleep quality was rated as good.

groups 1 to 3, 25% (40 out of 160) stated that their child did not take any medication and in group 4, 22% (28 out of 127) stated that their child did not take any medication.

Drugs that were taken by patients could be grouped into benzodiazepines, antiepileptics, cannabinoids, antipsychotics, laxatives, glucocorticoids, vitamins, H1 antagonists, selective serotonin reuptake inhibitors, and hypnotics.

The SNAKE questionnaire includes a free text part at the end which enabled parents to add aspects they considered important for their child's sleep quality that were not yet asked. The qualitative analysis of this text part demonstrated that a bedtime routine is essential for good sleep as many parents emphasized the importance of an "evening ritual" before putting their child to bed. A regular daytime routine including going to school and a familiar environment were also critical for a good sleep. Moreover, many parents stated that without taking a midday nap the sleep quality and daytime behavior were worse.

## Discussion

### Sleep Quality

This is the first study to address sleep quality in RTT patients in Germany and has a reasonably large sample size of 287 participants, compared with other studies on sleep dysfunction in RTT.<sup>6,11</sup> It has shown that sleep disturbances are not as severe as depicted in the literature and that sleep quality is generally perceived as very good to good by over 60% in every age group. Sleep quality was rated worst in the youngest and oldest age group, as bad sleep quality scored highest (14.55%) in group 1 (0–6 years) followed by group 4 (11.90%) (>18 years old). Previous studies show that sleeping disorders are prevalent in 80% of RTT patients.<sup>4,12,13</sup> In our study, objective parameters such as SOL (groups 1–3: 22.5 minutes, group 4: 20.0 minutes), TST (groups 1–3: 9.5 hours, group 4: 8 hours), and WASO (groups 1–3: 1.31 hours, group 4: 1.48 hours) suggest a normal sleeping behavior. Findings of a case-control study support that there is no difference among TST between RTT patients and healthy subjects.<sup>11</sup> Although this result is rather surprising, a few suggestions can be made. It is likely that there is disagreement between the parental definition and the research criteria for sleep disturbance.<sup>6</sup> It must be considered that this was a subjective assessment of parents who rated their child's sleep quality and that there is no definition of a "norm" for very good, good, satisfying, or bad sleep quality. Parents may further perceive sleep disorders as less severe due to better coping strategies and being able to exchange with other families affected by RTT. To obtain an adequate clinical picture of sleep quality, polysomnography is a useful method to objectively measure a range of respiratory and macrostructural sleep parameters.<sup>11</sup>

There was a trend toward better sleep quality with increasing age as in group 1 the majority rated their sleep quality as bad (14.55%) and in group 3 the majority rated their sleep quality as very good to good (70.60%). Boban et al suggest that even though sleep problems occur across age groups, the prevalence of sleep problems is highest in young

children under seven years.<sup>14</sup> A similar trend was also observed in a study by Wong et al who investigated the influences of age, mutation type, and treatments on sleep problems.<sup>13</sup> However, the result of group 4 contrasts this trend as it rated second highest for bad sleep quality (12.9%). Comparing group 3 to group 4, there is a shift from very good sleep quality (25.50–19.40%) to bad sleep quality (3.90–12.90%). The percentage distribution for good (45.10–43.50%) and satisfying (25.50–24.20%) sleep quality remains very similar to group 3. This could reflect the worsening general health condition in the last stage of RTT caused by scoliosis, late motor deterioration, and even changes in general living conditions. Another aspect that could be accountable for the worse sleep quality in group 4 is the polypharmacy, especially in the oldest group, reflected by 21 different drugs taken by group 4 only (44.7% of all drugs that are taken). This demonstrates the lack of structured, clinical guidelines as treatment is symptom based and not evidence based. In her study on aging in RTT, Halbach et al found that sleep abnormalities improve between 16 and 20 years and deterioration was seen in RTT patients who were 30 years and older.<sup>15</sup> This dynamic development is similar to what we observed as there is an improvement in sleep quality from group 1 to group 3, but a slight deterioration in group 4.

### Behavioral Disorders

Our data suggest that there is a relationship between behavioral disorders and sleep quality that increases with age. Sleep quality was associated with behavioral features that are related to the phase of regression such as loss of acquired hand skills and isolation in group 1. A study by McArthur and Budden found no correlation between stage and sleep quality.<sup>12</sup> As there is little mention of this topic in existent literature, it is suggested to investigate whether sleep disturbances are related to a certain stage of RTT in future studies. In group 4, several behavioral features that relate to mood are associated with sleep quality such as panicking ( $p=0.0004$ ), restless phases ( $p=0.0005$ ), mood swings ( $p=0.0001$ ), bad mood ( $p=0.000$ ), hysteric screaming ( $p=0.0007$ ), being irritable without reason ( $p=0.0007$ ), crying during the day ( $p=0.0007$ ), and appearing miserable for no apparent reason ( $p=0.033$ ).

### Medication

Overall the spectrum of drugs taken is very wide, but the therapy of sleep disturbances has improved in contrast to the past as melatonin and zolpidem showed a significant association with sleep quality. Other studies demonstrated the efficacy of melatonin in reducing SOL but with limited influence on other parameters such as frequency of nighttime awakenings and TST.<sup>12,16</sup> A randomized, placebo-controlled, double-blind, crossover trial showed that melatonin improved TST and decreased SOL in children with neurodevelopmental disorders.<sup>16</sup> A similar study which tested melatonin in patients with RTT found that it also decreased SOL but the increase in TST was not statistically significant.<sup>12</sup> In general, melatonin was well tolerated as adverse

effects were reported in only one of nine cases in which parents reported “severe mood swings.”<sup>12</sup> In our study as well as in the literature, there is no differentiation between pure melatonin and retarded melatonin. There is lack of information in the literature on the effect of zolpidem on sleep quality in RTT patients; therefore, the efficacy of zolpidem needs to be further investigated. Even though sleep medications may have reduced sleep problems, many individuals using medications to aid sleep, especially combination therapy, remain likely to have more difficulty initiating and maintaining sleep as well as greater impacts from sleep problems.<sup>7</sup> This could be due to a reverse relationship as those requiring sleep medication generally sleep worse than those who are not on any medication. In regard to treatment approaches, this study shows that parents consider a “bedtime routine,” familiar environment, and a regular daytime routine critical for good sleep quality. This reflects the findings of a study by Blackmer and Feinstein that suggest sleep hygiene as first-line therapy.<sup>4</sup> A study by Boban et al also demonstrated that sleep hygiene strategies such as following a bedtime routine, going to bed at the same time each night, and having a dark room were frequently used by RTT patients to aid good sleep.<sup>7</sup> Nevertheless, drug trials need to be designed that further investigate the long-term efficacy and safety of melatonin and retarded melatonin being used as a hypnotic agent RTT patients. The heterogeneity of RTT and the unsatisfactory outcome measures limit the implementation and success of drug trials.<sup>17</sup>

The complex and diverse drug regimen that is taken by patients with RTT reflects the lack of drug-related guidelines as medical treatment is decided due to symptoms and experience.

### Limitations

The significance of this study in regard to the medication was limited by the sample size for the respective drugs as several drugs were taken by less than 10 participants and therefore lack statistical power. Most RTT patients take more than one drug and therefore the influence of a single drug on sleep quality is prone to bias due to polypharmacy and drug interactions. A follow-up would be necessary to measure the long-term efficacy and safety of drugs such as melatonin.<sup>4,5,12</sup>

The SNAKE was chosen to assess the sleep quality, but it was not specifically designed for RTT patients as it is a standardized tool that was developed to investigate sleeping disorders in children with neurodevelopmental disabilities in general.<sup>9</sup> This may lead to an underestimation of sleep disturbances in children with RTT. Furthermore, we acknowledge that instrument administration by mail as well as translation of the RSBQ can have major impact on data quality and integrity as this could lead to difficulties in understanding and interpreting the questionnaire as it was not validated in a German cohort. Validation of questionnaires, interviews, and rating scales is essential because meaning may change in the translated version of the item and sociocultural factors may influence the evaluation of

severity or frequency of a symptom, particularly abnormal behaviors.

### Conclusion

This study showed that sleep quality was overall rated as very good to good in over 60% of RTT patients. We observed a dynamic course of sleep quality that was worse in childhood, improving throughout adolescence, stabilizing in the majority of patients in group 2 and 3 with good and satisfying sleep quality, and deteriorating in a small portion in group 4. Behavioral disorders related to the phase of regression as well as mood swings were associated with sleep quality. Melatonin was significantly associated with sleep quality highlighting its therapeutic efficacy. This study emphasizes the need for a structured multidisciplinary treatment approach for sleep disorders in RTT and the development of drug-related guidelines in the context of clinical care. A disorder-validated questionnaire comprising an objective as well as a subjective assessment of sleep quality in RTT patients is necessary to develop and guide treatment of sleep disturbances. Future research should focus on the development of adequate tools and measurable end points such as objective biomarkers to measure successes or failures in an unbiased way.<sup>18</sup>

### Conflict of interest

All authors reported no conflicts of interest concerning the manuscript.

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# THIEME