Rett Syndrome

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Clinical Vignette

A.J. is a 4-year-old female with Rett syndrome (MECP2 mutation T158M) who presents to the sleep clinic for difficulty falling asleep and staying asleep. During the night, she wakes up laughing and oftentimes moves her arms in the air while trying to go back to sleep. Her parents are concerned as this behavior prevents A.J. from going back to sleep and disrupts sleep for other family members. During the day, A.J. is sleepy and not able to participate in activities with her siblings or in her physical and occupational therapy. A.J. sleeps only 4–5 h during the night and then 2–4 h during the day, for a total of 6–9 h of sleep per 24-h period. Her family is requesting recommendations.

Introduction

Rett syndrome (RTT) is a severe neurodevelopmental disorder that affects 1/10,000 females and is rarely diagnosed in males. There are more than 250 known genetic MECP2 mutations that are associated with RTT [1]. A mutation in the MECP2 gene, located on the X chromosome (Xq28), is identified in 95% of individuals with typical RTT. MECP2 encodes for the methyl-CpG-binding protein 2 (MECP2) and is expressed in all organs. However, it is predominantly expressed in the central nervous system (CNS), thus supporting the early clinical symptoms of neurologic regression described below [2].

Following an initial period of apparent normal development, there is a period of neurologic regression between 6 and 18 months. During this time, there is loss of verbal communication skills and purposeful hand motor skills. The development of repetitive stereotypic hand movements occurs, and an abnormal apraxic/ataxic gait is common. Autistic features may be seen in some individuals with RTT during this time. Following this period of regression, the girls appear to plateau. They have better eye contact and social interactions; however, the core features do not improve to any significant degree. Ninety percent or more of individuals with RTT experience epilepsy, growth failure, gastrointestinal problems such as gastroesophageal reflux and chronic constipation, and autonomic dysfunction including breathing abnormalities and motor dysfunction. The incidence of sudden unexpected death is increased in individuals with RTT over the general population. However, in over 70% of individuals with RTT, the prognosis for life expectancy is good, with survival into the fifth decade. There is no approved or proven treatment for RTT, and at this time, management is symptomatic.

Sleep and Rett Syndrome

Sleep is a normal, active physiologic process that is vital for adequate growth and development. In the general population, sleep disorders affect approximately 25% of all children at some point during childhood [3]. A recent study of individuals with neurodevelopmental disorders, such as RTT, autism, Angelman syndrome, etc., identified a significant prevalence of sleep problems [4]. Sleep problems have been identified in 80–94% of individuals with RTT [5, 6]. Despite the length of time elapsed since the first report of RTT in 1966 by Andreas Rett, the exact mechanism, genetic predisposition, and phenotype of its associated sleep disorders are still unknown. Sleep problems may develop before or at the time of regression. More than one primary sleep

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disorder, such as sleep-disordered breathing or periodic limb movement disorder, as well as medical problems including epilepsy, gastroesophageal reflux, or constipation, may occur simultaneously or in succession and contribute to fragmented sleep.

Poor quality of sleep as a result of sleep problems promotes poor cognition, behavioral problems, mood disturbances including irritability, and overall decreased quality of life during the day. Oftentimes, hyperactivity and inattentiveness may occur as a result of insufficient sleep or poor quality of sleep. Sleep problems in individuals with RTT can also be disruptive and/or frightening to a girl's family, resulting in increased stress and poorer overall quality of life for all family members.

Sleep Characteristics

Several studies have identified that individuals with RTT have sleep disturbances in the form of multiple nighttime awakenings along with behaviors such as nocturnal laughter or screaming. A large Australian study using the Australian Rett Syndrome Database (ARSD) and various sleep questionnaires identified sleep problems in over 80% of individuals with RTT. The most commonly reported sleep problems included nocturnal laughing, teeth grinding, and nocturnal seizures [5]. Other nocturnal behaviors seen in this population included non-rapid eye movement (NREM)-related parasomnias such as confusional arousals and night terrors. NREM-related parasomnias typically occur during the first third of the major sleep period. These episodes result in incomplete awakening from sleep and typically the individual does not respond to efforts to awaken her by a family member. There is also partial or complete amnesia of the episode. For episodes of confusional arousals, the individual may continue to appear confused and disoriented for several minutes or longer following the episode. Night terrors are characterized by episodes of abrupt terror, typically beginning with an alarming scream. There are autonomic signs associated with night terrors such as mydriasis, tachycardia, tachypnea, and diaphoresis. Similar to confusional arousals, the individual is not able to remember the event afterward. In general, NREM-related parasomnias increase in frequency and severity during periods of insufficient sleep as well as when the individual is abruptly awoken during the episode.

The frequency of specific sleep problems is associated with age. Young children (0–7 years of age) with RTT are more likely to have more nighttime awakenings than older children with Rett syndrome. Daytime napping and nighttime seizures increase with age, while nocturnal laughter, teeth grinding, and nighttime screaming decrease with age.

Individuals with RTT have irregular sleep onset times as well as total daytime sleep that is longer when compared to typically developing individuals [7]. The age-related decrease in total and daytime sleep expected in typically developing children is not present in individuals with RTT. It is suspected that this is most likely related to the arrested brain development that is expected in individuals with RTT [7, 8].

A 2001 cohort study using validated sleep diaries reported that individuals with RTT showed an irregular sleep-wake pattern, prolonged sleep latency, multiple awakenings during the night several times per week, as well as poor sleep quality [8]. In addition, this study identified that individuals with seizures had significantly more daytime sleep and a higher percentage of total sleep time occurring during the day than those without seizures. Individuals with RTT who were ambulatory had a higher sleep efficiency and less daytime sleep than those who were not ambulatory [8]. This suggests that daytime function, as well as comorbid conditions such as seizures, contributes to the overall sleep characteristics found in individuals with RTT.

Genotype/phenotype correlations regarding the severity and frequency of sleep problems in individuals with RTT have been reported. Young et al. found that the frequency and type of sleep problems varied according to the mutation type. Sleep problems were most reported in individuals with large genetic deletions, as well as with either p.R294X or p.R306C mutations. Nighttime laughter was most common in those with large genetic deletions, p.R168X, and more recently with p.R106W [5, 6]. Daytime napping was most reported in those individuals with p.R270X, p.R255X, and p.T158M mutations. There was no relationship between a specific genetic mutation and nocturnal screaming or with nocturnal seizures [5]. These findings suggest that different mechanisms contribute to the phenotypic expression of sleep problems in individuals with RTT.

PSG Findings

Normal development of the sleep/wake cycle begins in the newborn period. In the 1st month, the sleep/wake cycle revolves around feeding times. Gradually, the cycle begins to adjust to light exposure to follow a day-night cycle. Major sleep periods begin to occur during the night, with less sleep time during the day. The sleep periods during the day decrease to daytime naps with the major sleep period at night. Around age 4–5 years, the naps begin to phase out, resulting in only one major sleep period at night.

Normally body movements occur throughout sleep, which help individualize the different stages of sleep. Larger gross motor movements occur in lighter stages of sleep. As the sleep cycle progresses, these movements evolve into twitches. The twitching movements gradually increase during rapid eye movement (REM) sleep, as well

as in the latter parts of the night. As the brain develops, the unique characteristics of the different sleep stages mature. The gold standard for objectively identifying sleep architecture is the polysomnogram (PSG). During scoring of a PSG, wakefulness, NREM sleep, and REM sleep are identified. Clinically, individuals with RTT exhibit a normal development of sleep from the newborn period until the time of neurologic regression.

Total sleep time is similar in younger children with RTT in comparison to typically normal developing children, whereas older children with RTT have decreased total sleep time [9]. Individuals with RTT also gradually sleep more during the day; thus, the total sleep time in a 24 h period is increased compared to typically developing individuals [10].

NREM 1 and NREM 2 sleep is decreased in younger children with RTT, which may be due to a decreased sleep latency period [9]. In older individuals, NREM 1 and NREM 2 sleep occurred in similar proportions to typically developing individuals [9]. The characteristic findings of NREM 2 sleep of K complexes and spindles eventually were not distinguishable in older children due to the neurologic dysfunction. However, in adult women with RTT, K complexes may reappear.

Slow-wave sleep (particularly NREM 3 sleep) in individuals with RTT is generally similar to typically normal developing individuals. It occurs in higher amounts during the first part of the night. However, in older individuals with RTT, slow-wave sleep occurs during the latter part of the night [11–13]. There is also an increase in slow-wave sleep, a trajectory opposite to the typical pattern, in which the amount of slow-wave sleep decreases as age increases toward adulthood. In regard to REM sleep, studies have shown that there is a decrease in the percentage of REM sleep and that REM sleep latency is longer in individuals with RTT compared with controls [9].

EEG abnormalities are common in individuals with RTT; however, there is variability in the type of EEG activity. EEG activity is normal before the age of 3 and before clinical symptoms of regression [14–16]. As clinical symptoms of regression begin, the background EEG activity and occipital dominant rhythm gradually begin to slow during wakefulness and during sleep [16, 17]. Subsequently, the background EEG activity consists of irregular slow waves and becomes increasingly disorganized. Expected sleep characteristics such as spindles and K complexes during NREM 2 sleep are lost.

In addition, spikes, polyspikes, and spike and wave discharges gradually become more prominent first during NREM sleep and then during wakefulness, as the disease progresses [15, 18, 19]. Epileptiform abnormalities occur mostly in the central region and gradually involve the temporal region. There are also reports of the involvement of the parasagittal region of the brain [15].

Respiratory Pattern During Sleep

Individuals with RTT have a characteristic breathing pattern that occurs predominantly during periods of wakefulness. Interestingly, this respiratory pattern is not present during the newborn period [20]. The brain stem, which regulates control of breathing, is intact during sleep [17, 20]. The characteristic pattern involves intermittent periods of hyperventilation with decreased partial pressure carbon dioxide (pCO_2) values and periods of breath holding.

The respiratory pattern tends to be disorganized with mild to moderate oxygen desaturations. The events are followed by an increase in respiratory effort, followed by a return to baseline oxygen saturation values [9]. The resulting hypoxemia may be significant enough to provoke a seizure or syncope, but the respiratory abnormalities occurring during wakefulness are independent of seizure activity [9, 21, 22]. There are also episodes of respiratory pauses during which individuals with RTT are calm and indeed, enjoying a particular activity [9, 20]. Stereotypic hand movements are intermittently present during periods of disorganized breathing and also during normal respirations but are not typically present during sleep [9].

During sleep, the respiratory pattern is generally organized and continuous breaths. Oxygen saturation values are typically within normal range. Periodic breathing is minimal during sleep. End-tidal pCO_2 values are in the normal range [9]. Children and adults with RTT may demonstrate upper airway obstruction in the form of snoring and obstructive sleep apneas, as well as central sleep apnea on PSG. Central apneas may be present during the transition from wakefulness to sleep and during REM sleep as a result of the preceding periods of hyperventilation or hyperpnea [12, 23]. As per the American Academy of Sleep Medicine, scorable central apneas in children are characterized by decreased respiratory effort and flow for 20 s or more or at least two breaths in duration but associated with a 3% oxygen desaturation or an arousal. The prevalence of sleep-disordered breathing appears to be higher in individuals with RTT than in typically developing individuals [4, 24].

Evaluation of Sleep Disorders

Evaluation of sleep disorders in individuals with RTT begins with a complete history and physical examination. Initial history from a caregiver can direct the diagnostic evaluation and plan. History of sleep characteristics includes how long it takes for the child to fall asleep and whether she is able to maintain sleep through the night. The number of hours of sleep achieved per sleep period will direct the physician as to whether the child is sleep deprived. Events during sleep will also help guide whether a further evaluation is warranted. For example, snor-

ing, gasping or choking for air, and excessive daytime sleepiness are all suggestive of sleep-disordered breathing. Frequent jerking movements or leg movements may be a sign either of seizures or periodic limb movement disorder.

The child's bedroom environment should also be assessed as part of the sleep history. Some children have televisions, toys, phones, and other siblings in the room with them, any of which may distract them from initiating sleep. In addition, having caregivers outline where and when bedtime starts may provide insight into possible barriers to sleep, such as starting bedtime too early or too late. A comprehensive history should include daytime and nighttime sleep schedule, timing and duration of naps, bedtime routine, and contributing factors such as any caffeine intake. Identifying the overall impact on family dynamics also helps differentiate how aggressive an intervention should be.

A review of medications should be undertaken. This includes medications that have already been tried to help treat the sleep problems as well as medications prescribed to treat other medical conditions such as attention-deficit/hyperactivity disorder or seizures. Oftentimes, such a review will reveal probable medication side effects of insomnia or daytime sleepiness, which can be alleviated after adjusting dose or time of administration.

Physical examination can identify craniofacial abnormalities such as micrognathia, retrognathia, pectus deformities, nasal turbinate hypertrophy, and tonsillar or adenoidal hypertrophy in children with RTT as well as those with typical development – all of which can contribute to sleep-disordered breathing. Physical examination also helps direct evaluation and treatment of medical problems such as seizures, which are common in RTT. Gastrointestinal problems, such as chronic constipation and gastroesophageal reflux, occur in almost 100% in individuals with RTT and must be considered and treated as these problems are frequently associated with night awakenings and disruption of sleep. In addition, individuals with RTT may experience the same sorts of problems experienced by typically developing children and adolescents. As an example, uncontrolled or chronic nasal congestion can contribute to snoring and frequent awakenings. Nocturnal coughing as a result of postnasal drip can present with erythema and/or cobblestoning of the mucosa of the posterior pharynx. Occasionally, despite a thorough sleep history and physical examination, diagnostic studies may be indicated. Table 17.1 summarizes the available diagnostic tools that may help identify sleep problems in individuals with RTT.

Table 17.1 Diagnostic tools to help identify sleep problems in individuals with Rett syndrome

Diagnostic tool	Indication for test
Polysomnography	Sleep-disordered breathing
	Titration of positive airway pressure therapy to optimize treatment of sleep-disordered breathing
	Seizure activity during sleep
	Atypical or self-injurious parasomnias
	Periodic limb movement disorder
Sleep log/diary	Variable sleep/wake pattern
Actigraphy	Assessing multi-day rest-activity patterns
	Circadian rhythm disorders
Video and expanded EEG	Atypical behaviors
	Nocturnal seizures
	Atypical parasomnias/atypical movements

Overnight PSG is the gold standard diagnostic tool for most sleep medicine experts. This study includes EEG monitoring, pulse oximetry, oronasal airflow, abdominal and chest wall movement monitoring to record respiratory effort, leg electromyography to determine leg movements, pCO_2 monitoring, and video recording. PSG is indicated to diagnose sleep-disordered breathing such as obstructive sleep apnea, central sleep apnea, and sleep-related hypoventilation, as well as to titrate positive airway pressure in children [25]. PSG is also indicated to diagnose periodic limb movement disorder, to confirm the diagnosis of an atypical or potentially injurious parasomnia, and to differentiate an atypical parasomnia from nocturnal seizures [26]. Occasionally, video EEG and/or an expanded EEG may be helpful in identifying atypical seizures.

Sleep logs or sleep diaries are useful to determine if there are specific sleep-wake patterns from day to day as well as to identify circadian rhythm sleep disorders. They are sometimes used in tandem with actigraphy. An actigraph is a device that is worn on the wrist that estimates periods of sleep versus wakefulness based on pattern of movements. It is best utilized with a sleep log/diary, which can be particularly helpful in situations when there is artifact recorded on actigraphy monitoring.

Lastly, home sleep testing in an unattended setting may be helpful in assessing for obstructive sleep apnea using one to several physiologic parameters. Currently, there are few studies documenting the use of home sleep testing in individuals with RTT. However, home testing may be helpful in children with a high pretest probability of obstructive sleep apnea who may not tolerate being in a sleep laboratory or for whom a standard PSG is not readily available due to long wait times, transportation issues, etc. In addition, pediatric sleep labs are not universally available; many sleep labs are not experienced in studying medically complex children like individuals with RTT.

Treatment of Sleep Disorders

Treatment of sleep disorders in children with neurodevelopmental disorders in general can be challenging. Sleep problems in this population can be quite persistent if left untreated. Management begins with addressing the contribution of medical problems, primary sleep disorders, behavioral problems, and the impact of medications. Such management may improve the sleep issues, but these tend to be chronic with respect to their clinical course [4, 6, 7]. Table 17.2 illustrates the various treatment options available to treat sleep problems in individuals with RTT.

Medical problems such as epilepsy, chronic otitis media, respiratory problems such as chronic cough or allergic rhinitis, and GI abnormalities such as constipation or gastroesophageal reflux should be addressed first. Daytime behavioral problems should also be managed as they could interfere with nighttime routines and cause difficulty with winding down for bedtime. A review of any medications that have potential side effects of insomnia or daytime sleepiness has been previously noted. Timing of medication administration should also be reviewed and modified as needed.

More than one sleep problem may be present during the initial evaluation of sleep problems. Therefore, treating sleep disorders such as sleep-disordered breathing will improve overall sleep quality as well as increase total sleep time. Daytime function and behavioral problems may also improve as a result.

For obstructive sleep apnea, evaluation of the upper airway is the initial step. In children, adenotonsillar hypertrophy is the most common cause of obstructive sleep apnea. If the child is not a surgical candidate and there is significant daytime impairment, or the caregiver wishes to pursue nonsurgical options, then positive airway pressure therapy is initiated. In addition, positive airway pressure therapy may be an option if surgery is not curative and residual OSA continues to cause daytime impairment, such as daytime sleepiness or behavioral problems. This may be provided in the form of continuous positive airway pressure (CPAP) or bi-level positive airway pressure (BPAP) with or without a backup rate. Typically, the positive airway pressure therapy is delivered through a nasal interface as opposed to a full-face mask in order to prevent episodes of aspiration during sleep.

Table 17.2 Treatment options available for individuals with Rett syndrome who have sleep problems

Treatment modality	Examples
Treating medical problems	
Epilepsy	Anticonvulsants
Gastroesophageal reflux	Acid suppressing medications (proton pump inhibitors, histamine type 2 receptor antagonists)
Constipation	Optimization of dietary fiber intake, laxatives, stool softeners
Allergic rhinitis	Nasal steroids, antihistamines
Treating primary sleep disorders	
Sleep-disordered breathing	Adenotonsillectomy; positive airway pressure therapy
NREM related parasomnia	Avoid periods of insufficient sleep, avoid abrupt awakening during episode; maintain good sleep habits
Periodic limb movement disorder	Iron supplementation; gabapentin
Management of daytime behaviors	Consistent daytime schedule
	Limit setting
Adequate sleep hygiene	Consistent bedtime routine
	Avoid caffeine
	Avoid strenuous or vigorous activity before bedtime
Behavioral approaches	Gradual extinction
	Scheduled awakenings
Relaxation techniques	Massage therapy
	Music therapy
	Pet therapy
	Weighted blankets
Medications	Melatonin
	Alpha agonists (clonidine)
	Antidepressants (trazodone)
	Hypnotics (zolpidem)
	Anticonvulsants (gabapentin)
	Benzodiazepines (clonazepam)
Caregiver education	Provide understanding of sleep problems
	Establish reasonable goals and expectations
	Provide resources/support groups

For NREM-related parasomnias, reassurance is provided to the caregivers that the episodes do not result in further neurologic insult and will self-resolve with improved sleep quality and sleep time. In addition, caregivers are provided with instruction to avoid abruptly awakening the individual during episodes, as this may further exacerbate parasomnias as well as increase their frequency. The caregiver can gently console the individual during the episode and then allow her to fall back asleep.

Modifying and promoting good sleep habits have been shown to dramatically improve insomnia in individuals with RTT [27]. Caregivers should maintain a consistent bedtime and wake time, incorporate a bedtime routine in which there is limited exposure to electronics, limit strenuous physical activity prior to bedtime, and limit caffeine and exposure to bright light in the evenings. Exposure to bright light after dark promotes a later bedtime with subsequent delay in sleep onset.

Behavioral approaches are beneficial in treating sleep problems in individuals with RTT. This includes extinction of the unwanted behaviors, such that a child is allowed to cry or fuss for an allotted period of time. With gradual increases in the increments of time, the individual eventually will learn to self-soothe and fall asleep without caregiver intervention. For undesired behaviors such as nocturnal laughter, confusional arousals, or nocturnal screaming, scheduled awakenings prior to the unwanted event may be helpful. This technique is especially beneficial if the timing of the unwanted behavior consistently occurs at the same time during the night. Other behavioral interventions include relaxation approaches such as massage therapy, music therapy, or pet therapy. Weighted blankets may be helpful in diminishing environmental stimuli and allow an individual to initiate sleep.

Currently, there are no medications that are FDA approved for the treatment of sleep problems in children. A few studies have shown that supplemental melatonin along with decreasing time to sleep onset also increases total sleep time and improves daytime cognitive function [28–30]. In addition, several pharmacologic agents have been used off-label in children and adults as an alternative or in conjunction with melatonin (Table 17.2).

Lastly, sleep education for caregivers is strongly recommended as it establishes an understanding and acceptance that sleep problems in individuals with RTT are common. Expectations and reasonable goals by the caregiver should be established as an initial intervention for the sleep problems. Caregivers should also feel comfortable expressing their frustration in respect to their child's sleep patterns, as most caregivers worry about their children's sleep and do not sleep well as a result.

Future Directions

Sleep problems are common in individuals with RTT contributing to poor quality of life for both individuals with RTT as well as for the caregiver(s). Sleep difficulties often present around the time of developmental regression. The genotypic and phenotypic presentations of RTT have been linked to the types of sleep problems; however, the actual mechanism contributing to sleep problems is not clear. Areas of research that can identify the exact mechanism for the sleep problems may help direct therapy. Currently, there is limited use of home sleep testing, which may benefit individuals with RTT, particularly those with significant barriers to transportation, long wait times, and developmental and behavioral issues that may prevent full PSG monitoring. Research on the use of sleep-promoting medications in individuals with RTT is necessary as this may ultimately improve overall quality of life in individuals with RTT as well as their families.

Clinical Pearls

- Individuals with RTT of all ages frequently experience sleep problems, which are oftentimes not addressed and are chronic.
- Sleep problems associated with RTT include insomnia, irregular sleep/wake schedules with daytime sleepiness, NREM-related parasomnias, and sleep-disordered breathing, including both obstructive and central sleep apnea.
- Sleep problems typically are described by caregivers as multiple nighttime awakenings, daytime napping, nighttime laughing, abnormal movements of the upper extremities, and/or nocturnal seizures.
- Evaluation of sleep problems includes a detailed history and physical examination along with evaluation of bedtime routine and description of the nighttime behavior during sleep, as well as daytime consequences as a result of poor quality sleep.
- Treatment of sleep problems includes identifying and managing primary sleep and medical problems as well as incorporating behavioral approaches in maintaining good sleep habits such as maintaining a consistent bedtime routine and avoiding daytime naps.
- Currently, there is no approved sleep-promoting medication to treat sleep problems in children. However, melatonin has been shown to be useful in individuals with RTT who have difficulty initiating and/or maintaining sleep. Off-label use of medications for sleep, such as antidepressants, hypnotic agents, and anticonvulsants, requires further study.

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