Williams Syndrome

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Overview of Williams Syndrome

Williams syndrome (Williams-Beuren syndrome or WBS) is a congenital disorder caused by deletions of multiple contiguous genes on the long arm of one chromosome 7 (del 7q11.23) [1]. There is a distinctive pattern of developmental delays, personality and behavior, physical phenotype, and multiorgan involvement [2, 3]. Williams syndrome is panethnic. Its incidence is approximately 1:8000, but it is likely underdiagnosed. Classically, a child with Williams syndrome is born post term, with birth weight and length in or below the lower half of the normal range.

The physical characteristics of Williams syndrome include subtle facial dysmorphism, regardless of racial background. In infancy and early childhood, the face is round or oval, sometimes with facial asymmetry, with periorbital puffiness (not edema); upward growth of the medial part of the eyebrows ("medial flare"); epicanthic folds, irides that are often blue and have a stellate, lacy pattern; strabismus; flat nasal bridge with a broad nose tip and anteverted nares; poorly defined philtrum that may be long; wide mouth; full lips with diminished or absent Cupid's bow and protuberance of the lower lip; "low-set," full cheeks; deep nasolabial creases; flat malar area; and small chin (Fig. 18.1). Nasolacrimal duct obstruction may cause excessive "tears." In later childhood and adulthood, the facies becomes long and gaunt. The body is characterized by sloping shoulders, short stature, and relatively short limbs. There may be cervical kyphosis, exaggerated lumbar lordosis, occasional scoliosis, and radioulnar synostosis (preventing rotation of the forearm). The skin is very soft with fine creases. The hair is thick and curly and becomes prematurely gray. Inguinal and umbilical hernias are common. Often there is less body fat in childhood or adolescence, due to increased resting energy expenditure. In later childhood and adolescence, patients become overweight.

The infant with Williams syndrome is hypotonic with joint laxity (except for tight heel cords) and hyperreflexia. There is early onset of feeding difficulties and failure to thrive. The infant is constantly irritable for several reasons: (1) pain from esophagitis, caused by frequent gastroesophageal reflux, compounding the feeding problems; (2) idiopathic hypercalcemia in approximately 15% (that usually resolves after infancy); (3) constipation; and (4) tactile defensiveness (irritability on being touched). By the end of the 1st year, irritability and vomiting diminish or resolve. There are still significant feeding problems, due to low tone, and difficulty chewing and swallowing coarser foods. The hypotonia and joint laxity improve in childhood. Hypertonia develops in about a third of children and is more prevalent (85%) in adults. Mild, moderate, or severe contractures develop in childhood in approximately 50%. Their gait is characteristically wide based, with the upper part of the body leaning forward and a tendency to toe-walk, even in the absence of joint contractures. Chiari I sequence (malformation) occurs, with significant displacement of the cerebellar tonsils below the level of the foramen magnum; this malformation likely occurs in Williams syndrome because of a small posterior fossa with a normal-sized cerebellum and could place affected patients at increased risk for sleep-disordered breathing.

The range of IQ in Williams syndrome is broad, with an average score of 50–60. A large number of individuals have borderline normal IQ scores, and a few are in the normal range (up to 114 in one report). However, IQ scores do not reflect the unique profile of strengths and weaknesses in

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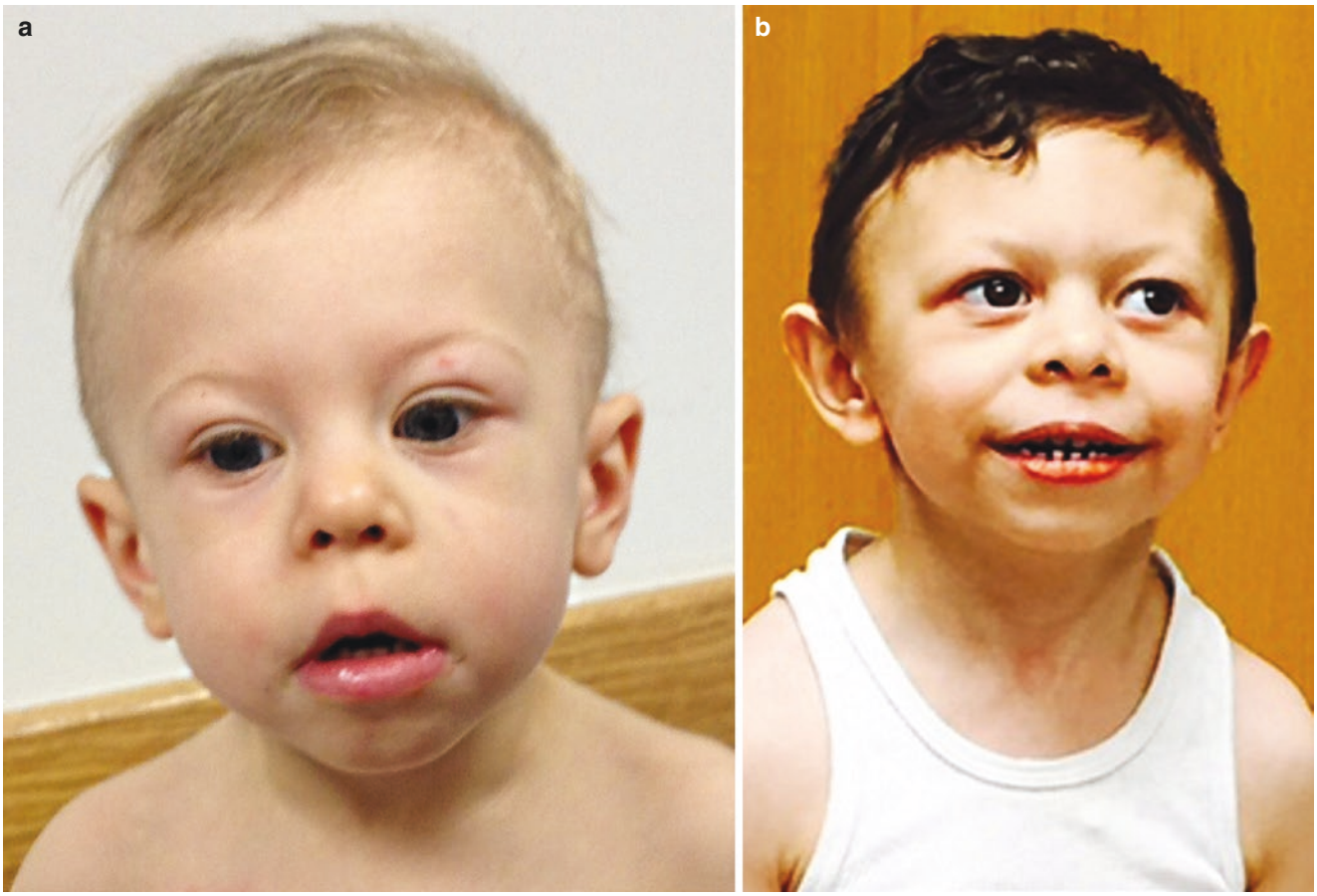

Fig. 18.1 Infant (**a**) and young child (**b**) with Williams syndrome. Note typical facial features – broad forehead, periorbital soft-tissue fullness, anteverted nares, long philtrum, decreased Cupid's bow of upper lip, "pouty"-everted lower lip, and "low-set" cheeks

cognitive skills [4, 5]. Weaknesses involve "visual-motor" skills or visual-spatial construction (spatial location and motion) and problem-solving, especially mathematics. The cognitive strengths of WBS are in verbal and auditory skills, including auditory short-term memory. Severe delays in language development are expected: first words emerge, on average, at 21 months and sentences at 3–4 years. Combination of words into phrases begins at the same stage as in typically developing children, when they know approximately 50–100 words. Most children with Williams syndrome have fluent and distinctive language at 4–5 years with emotional content; prosody is distinctive because of exaggerated emotion and rhythms and unusual, subtly inappropriate words and idioms and grammatical problems. Attention-deficit/hyperactivity disorder (ADHD), idiopathic hyperacusis, and easy distractibility affect most children.

Children with Williams syndrome are very sociable – indeed, they typically show uninhibited, and often inappropriate, friendliness. In contrast to children with autism, children with Williams syndrome naturally and instantly make eye contact, even in early infancy, detect emotions in other people, and show empathy. In young children, most aggressive behavior seems to be due to frustrations in communication or in performing a given task. WBS children often perseverate with repetitive comments or questions. Despite their friendliness, often toward strangers, they suffer from tremendous anxiety and fear, even in early childhood. Disabling anxiety may be present in adults with WBS, and they may have an increased prevalence of other psychiatric disorders, including depression and obsessive-compulsive behavior.

One of the most important causes of morbidity and early death is narrowing (stenosis) of arteries. Many or all arteries are narrowed in Williams syndrome, but these stenoses may not have clinical effects. In a large series, clinically important stenosis affected peripheral (branch) pulmonary arteries (PPS) in 64%, supravalvar aorta (SVAS) 51%, aortic arch (coarctation) in 21%, and pulmonary valve in 16%. Stenoses may develop in other arteries (descending aorta, renal, mesenteric, subclavian, or cerebral arteries) even in the absence of PPS or SVAS [6]. Cardiac lesions are not uncommon: ventricular septal defect (VSD) occurs in 21% and mitral valve abnormalities (MV prolapse) in 15%. Most arterial narrowing is present at birth or early infancy.

Severe hypertension and cardiac hypertrophy, from narrowing of the great vessels, peripheral pulmonic arteries, and/or renal arteries, as well as rigidity (non-compliance) of arteries, may cause cardiac failure. Sudden death may occur and is associated with cardiac catheterization and/or anesthesia in about half of cases. Causes include deficient cardiac output from severe cardiac ventricular outflow obstructions or myocardial infarction/arrhythmia due to coronary artery stenosis. In recent decades, early diagnosis, preventive treatment, and appropriate vascular surgery have reduced morbidity and mortality. Rarely, strokes due to narrow cerebral arteries in young children or adults cause transient or permanent hemi- or para paresis, additional impairment of cognitive function, and occasionally, death. The cerebral arterial stenosis can develop in the absence of SVAS and other arterial narrowing. There is risk of sudden death with anesthesia in patients with Williams syndrome [7] that appears related to cardiac hypertrophy secondary to vascular stenosis or coronary artery stenosis [8]; anesthesia should be administered by cardiac anesthesiologists.

Other systemic involvement can affect the gastrointestinal system (gastroesophageal reflux and chronic constipation are common; rectal prolapse is less common but can be very debilitating), the renal system (increased urinary frequency in 32%, uninhibited detrusor muscle contractions or bladder dyssynergia in 10%, and radiologic "nephrocalcinosis," reported usually without renal stones or dysfunction), and teeth (small with spaces between teeth, absence of some teeth, and malocclusion). Short stature is common in Williams syndrome, sometimes evident at birth. Early puberty in males and females is common [9]. Sleep problems are prevalent and will be reviewed here.

Early diagnosis of Williams syndrome is important so that anticipatory management can help prevent severe problems and improve long-term outcomes. A multispecialty clinic for Williams syndrome patients can offer integrated, anticipatory care by medical personnel with expertise in cardiology; genetics; physical, occupational, and speech therapies; nutrition and feeding; developmental pediatrics; psychiatry; nephrology; ophthalmology; gynecology; orthopedics; neurology; neuroradiology; and sleep medicine. A list of clinics is available on the Williams Syndrome Association website, www.williams-syndrome.org.

Williams syndrome support groups, such as the Williams Syndrome Association, have been established by parents in many countries. They provide emotional support and information to patients, their families, and allied professionals; encourage research; and increase public awareness of Williams syndrome.

Sleep-Wake Patterns and Sleep Architecture

Questionnaire Studies

There are multiple questionnaire-based studies that support sleep problems in children with Williams syndrome. Mason et al. (2011) used a parent-report sleep questionnaire, adapted from Arens et al. (1998) that included 13 items to evaluate respiratory status, body/limb movements, and arousal/awakenings during sleep, as well as restless legs syndrome symptoms while awake [10, 11]. Comparing responses for 35 subjects with Williams syndrome vs. 35 typically developing matched controls, subjects with WBS were significantly more likely than controls to have difficulty falling asleep, general restlessness, repetitive leg movements, frequent and prolonged nighttime arousals, and inability to keep still before sleep [10]. Ashworth et al. (2013) used the Children's Sleep Habits Questionnaire and actigraphy (see below) to compare sleep among children with Williams syndrome, Down syndrome, and typically developing children [12]. The authors found that compared to typically developing controls, children with WBS had more sleep problems related to sleep onset delay, sleep duration, and night wakings. Children with WBS were also much more likely than typically developing children to move into another person's bed during the night, have bedwetting, and complain of body pain overnight.

Axelsson et al. (2013) compared 18 toddlers with Williams syndrome to 18 typically developing children (over the age range of 18–48 months). Parents completed questionnaires including the Brief Infant Sleep Questionnaire, Child Behavior Checklist, Infant Sleep Vignettes Interpretation Scale, Pittsburgh Sleep Quality Index of Parents, MacArthur Communicative Development Inventory for Infants – Words and Gestures, and the Major (ICD-10) Depression Inventory [13]. Based on these parent responses, children with WBS had shorter nighttime sleep duration, more night wakefulness, more night wakings, and later bedtimes and took longer to settle compared with age-matched typically developing children. There were no significant differences found in measures of maternal sleep quality and mood between mothers of typically developing and Williams syndrome children. However, up to 50% of mothers in both groups had scores indicative of poor sleep quality. In addition, the sleep quality scores of the mothers of the children with Williams syndrome were significantly related to their children's night wakefulness and night wakings [13].

Annaz et al. (2011) focused on school-aged children, surveying parents of children with Williams syndrome (ages 6–12 years, n = 64), comparing findings with 92 age-matched controls [14]. The instruments used included the Child Sleep Habits Questionnaire and sections of the

Pediatric Sleep Clinic Questionnaire. The authors reported that children with Williams syndrome were significantly more affected by sleep disturbances including bedtime resistance, sleep anxiety, sleep onset delay, frequent night waking, and excessive daytime sleepiness. Exploring changes with chronological age, the authors found that the subjects with Williams syndrome had decreases in sleep problems with age at a much slower rate in comparison with typically developing children.

Given that sleep problems are common in children with developmental disabilities as well as in the general population, it is important to compare questionnaire findings across different groups, so that control groups also include subjects with other special needs. Einfeld et al. used the Developmental Behavior Checklist to assess sleep, among other parameters [15]. The study included 70 subjects with Williams syndrome (average age 9.2 years) and 454 control subjects with intellectual disabilities (average age 12 years). The control group tended to have more severe intellectual disability than the Williams syndrome group. For the category of sleep ("sleeps little/disturbed sleep"), subjects with Williams syndrome were not significantly different than controls [15]. Ashworth et al. (2013) compared scores for the Children's Sleep Habits Questionnaire between children with Down syndrome and children with WBS and found that children with Down syndrome had significantly increased bedtime resistance, sleep anxiety, parasomnias, and sleep-disordered breathing. Moreover, the Children's Sleep Habits Questionnaire total score was significantly higher for those children with Down syndrome compared to subjects with Williams syndrome [12].

Objective Assessments

Actigraphy is a noninvasive technique that provides objective assessments of activity levels, from which sleep-related parameters can be derived. Advantages of actigraphy include ease and simplicity of recording and feasibility of recording data over multiple days in the home environment. Ashworth et al. included actigraphy in their study, with the actigraph being worn on the non-dominant wrist for a week in study subjects; concurrent sleep diaries were completed to support analyses of actigraphy data. Compared to typically developing children, children with Williams syndrome had earlier bedtimes and longer sleep latencies, although there was a wide interindividual variability in the latter parameter. The mean sleep latency of 48 min in the Williams syndrome subjects was twice that of both typically developing and Down syndrome subjects [12]. Interestingly, children with Down syndrome had multiple actigraphy measures supporting sleep disturbance that were significantly different compared to both the typically developing and Williams syndrome subjects, including night wakings, wake after sleep onset, sleep efficiency, moving time, and fragmentation. As the authors suggest, sleep-disordered breathing (e.g., obstructive sleep apnea) could have been an important factor resulting in sleep disturbance that was not objectively assessed in the study [12]. Thus, while both developmental disorder groups were found to have sleep problems, actigraphy measures showed differing profiles between subjects with Down syndrome versus Williams syndrome.

In a study of adolescents and adults with Williams syndrome, 95% reported feeling tired, and approximately 35% had excessive daytime sleepiness, based on the commonly used Epworth Sleepiness Scale score cutoff of 10 or greater [16]. Mean sleep onset latency was prolonged at 37.7 min, and sleep efficiency was decreased compared with normal values (average 74%). This study's limitations included the absence of a control group and no polysomnography data to support actigraphy results. The authors also noted potential biases associated with self-report data, specifically related to the personality features of individuals with Williams syndrome (strong desire to please others and give answers that they think others want to hear) [16].

There have been few studies using overnight polysomnography to assess sleep architecture and other parameters in children with Williams syndrome. Arens et al. (1998) studied seven subjects with Williams syndrome described by parents as often or always having symptoms suggestive of a movement arousal sleep disorder and ten age-matched controls. They found that the subjects with Williams syndrome had significantly increased wake after sleep onset (as a percentage of total sleep time), decreased Stage 1–2 (N1/N2) sleep, and increased Stage 3–4 (N3) sleep compared to controls; however, no significant differences were seen in total sleep time, sleep efficiency, sleep latency, or arousal/awakening indices [11]. A subsequent study of 35 subjects with Williams syndrome and 35 gender, ethnicity, and age-matched typically developing subjects (age range of 2–18 years) showed that children with Williams syndrome had significantly decreased sleep efficiency, with a mean difference between matched pairs of 4.5%. Wake after sleep onset was also statistically greater in Williams syndrome [10]. The authors also found that slow-wave (N3) sleep was increased as a percentage of total sleep time compared to controls, with a mean difference of 4.6%; there were no significant differences in N1, N2, or REM sleep between the two groups [10]. Gombos et al. (2011) performed two consecutive full-night polysomnograms on nine Williams syndrome subjects ages 14–28 years and nine matched controls; the first night was used for acclimation to polysomnography, so that only the data from the second night were analyzed [17]. They found that Williams syndrome subjects had decreased total sleep time, decreased total sleep efficiency, increased wake time after sleep onset, and increased slow-wave sleep and

decreased REM sleep as percentages of total sleep time. The authors also observed that sleep in their Williams syndrome subjects appeared qualitatively more fragmented in general, with more awakenings and less cyclic sleep architecture than in typically developing subjects. However, there were no significant differences between the two groups in the number of sleep cycles, average REM period duration, or average sleep cycle duration [17]. Taken together, these studies support increased wake after sleep onset (which may in turn result in decreased sleep efficiency) and increased slow-wave (N3) sleep as consistent findings in subjects with Williams syndrome from early childhood through young adulthood.

Periodic Limb Movements in Sleep

Periodic limb movements in sleep are determined by overnight polysomnography and are scored from surface anterior tibialis electromyography leads using standardized criteria for movement amplitude, duration, and frequency. Since periodic limb movements may disrupt sleep in some children, Arens et al. wondered if restless sleep in some patients with Williams syndrome could be related to these movements. Indeed, the authors found an association between periodic limb movements in sleep and Williams syndrome. In a subset of children with Williams syndrome who were screened for possible movement arousal disorder, the mean periodic limb movement index was fivefold greater in the group with Williams syndrome compared to the control group (14.9 vs. 2.8); in addition, the periodic limb movement arousal and periodic limb movement-awakening indices were significantly higher than in the control group. Five of the Williams syndrome subjects were treated with clonazepam, and an immediate and sustained improvement was noted by parents in four of these. After 3–6 months of treatment, three Williams syndrome patients underwent repeat polysomnography, during which significant decreases in the periodic limb movement index, period limb movement arousal index, and periodic limb movement-awakening index were seen [11].

A subsequent study of children with Williams syndrome and controls found significant correlations between parental reports of repetitive leg movements during sleep and periodic limb movements in children with Williams syndrome on polysomnography [10]. The study, however, did not show that the periodic limb movement index and periodic limb movement arousal index differed significantly between the group with Williams syndrome and controls [10]. A contributor to the discrepancy between the studies may have been referral bias, as the only children with Williams syndrome described by parents as often or always having symptoms supportive of a movement arousal disorder had polysomnography in the Arens et al. study [11]. In another study, Gombos et al. reported that subjects with Williams syndrome had a significantly higher number of leg movements per hour, but the leg movements did not meet criteria for being described as periodic. Ultimately, the periodic limb movement indices were low in both groups, and there was no significant difference between them [17]. Goldman et al. (2009) reported in their study of adolescents and adults with Williams syndrome that 13.6% of 23 subjects had unpleasant leg sensations when lying down at night, suggestive of restless legs syndrome symptoms. Individuals with restless legs syndrome in the general population often have periodic limb movements in sleep, but polysomnography was not included as part of the study, so the prevalence of periodic limb movements in sleep could not be assessed in their subjects [16].

Sleep-Disordered Breathing

The respiratory parameters in the Arens et al. study were overall normal in subjects with Williams syndrome compared to control subjects, including the apnea index, apnea/hypopnea index, baseline oxyhemoglobin saturation, and saturation nadir. While the mean end-tidal CO_2 value was mildly elevated in subjects with Williams syndrome compared to control subjects, it was still within the normal range. One subject with Williams syndrome was noted to have mild upper airway obstruction associated with transient oxyhemoglobin desaturation to 88% [11]. Similarly, in the Mason et al. study, the mean obstructive apnea-hypopnea index, the number of subjects with an obstructive apnea-hypopnea index >1 event per hour, and total apnea-hypopnea index were not significantly different between subjects with Williams syndrome and controls. Those subjects, however, were found to have greater respiratory-related arousals than control subjects, and such arousals may contribute to decreased sleep efficiency [10].

EEG Features

Gombos et al. (2011) reported that EEG spectra during sleep in subjects with Williams syndrome showed higher delta and slow-wave activity over the frontopolar leads bilaterally in terms of both absolute and relative power compared to age- and sex-matched typically developing controls. The authors also noted a region-independent decrease in relative alpha and sigma power. The delta activity and slow-wave activity increases in subjects with Williams syndrome might have been related to increased slow-wave sleep, but the authors suggested that these changes could also have reflected fatigue or delayed maturation [17]. Subsequently, further analyses of sleep EEG in subjects with Williams syndrome compared to controls suggested a decrease in alpha/low sigma power,

as well as a redistribution of 8–16 Hz EEG power toward faster frequencies, which was felt to be a characteristic feature of Williams syndrome [18]. More recently, Bódizs and colleagues studied 21 subjects with Williams syndrome across a range of ages (6–29 years) and compared these to 21 typically developing subjects matched for age and sex. The authors reported an accelerated age-dependent sleep architectural impairment affecting sleep efficiency, wake after sleep onset, and wake time [19].

Endocrine Markers

Sniecinska-Cooper et al. (2015) determined melatonin and cortisol levels in children with Williams syndrome to explore a possible relationship between the circadian rhythm of the expression of these hormones and sleep patterns [20]. The authors compared 25 children with Williams syndrome with 27 typically developing controls matched for age and gender. For each subject, saliva was collected at three time points over a day (4–6 PM, shortly before customary bedtime and after awakening for the day). The levels of salivary cortisol and melatonin were analyzed by enzyme-linked immunoassays. Sleep patterns were analyzed by actigraphy and the Children's Sleep Habits Questionnaire. The authors found high individual variability in the amount of melatonin secreted in both groups, and no significant differences between the groups in samples collected in the afternoon or at bedtime. Comparing the ratios between bedtime and afternoon samples, there was a less pronounced rise in melatonin levels before sleep in the group with Williams syndrome compared with the typically developing group. A similar cortisol ratio evaluation showed that the group with Williams syndrome had less of a drop in cortisol at bedtime, as well as a higher normalized value of cortisol at bedtime. From a sleep standpoint, subjects with Williams syndrome had significantly increased sleep latency, increased movement time, increased wake time, and more sleep fragmentation on actigraphy compared to controls. On the Children's Sleep Habits Questionnaire, parents reported that 15% of subjects with Williams syndrome previously had sleep problems, and 65% had current sleep problems (23% of these children occasionally). None of the parents of typically developing children indicated that subjects currently or previously had sleep problems. In summary, the authors concluded that abnormalities in secretion of melatonin and cortisol may be underlying factors or contribute to sleep problems in individuals with Williams syndrome [20].

Management

The approach to assessment and management of sleep disorders in children with Williams syndrome should include, where appropriate, overnight polysomnography for evaluation of primary sleep disorders (such as obstructive sleep apnea and/or periodic limb movements in sleep). In turn, if an intrinsic sleep disruptor is found, then management should be initiated; there may be a role for follow-up overnight polysomnography to monitor treatment response or interim progression. After assessing for primary sleep disorders and excluding medical issues (e.g., pain, gastroesophageal reflux, etc.), parents of children with Williams syndrome should be provided with education and guidelines for behavioral intervention. This approach may mirror steps recommended for families of children with other neurodevelopmental disabilities and include creating a quality sleeping environment, promoting self-soothing skills that allow the patient to initiate sleep and maintain sleep independently, adopting a consistent sleep/wake schedule, and optimizing parent-child interactions [21].

There are no sleep medications that have been trialed specifically in the Williams syndrome population through designated studies. As with other children who have neurodevelopmental disorders and sleep issues, melatonin can be tried. It would be reasonable to start with a low dose (0.5–1 mg) at bedtime for hypnotic effect and titrate as needed. Over-the-counter preparations of melatonin that include other active ingredients should be avoided, and extended release melatonin preparations could be considered for children with sleep-maintenance insomnia features [21, 22]. Wasdell et al. (2007) reported the first randomized, placebo-controlled crossover study to demonstrate that controlled-release melatonin is an effective and safe means of treating sleep initiation and maintenance issues in children with neurodevelopmental disorders. Controlled-release melatonin 5 mg (initial trial) increased total sleep duration by approximately 30 min and shortened sleep latency by about the same amount. In the subsequent open label portion of the study, doses as high as 15 mg were used in some subjects [22].

Future Directions

For the child in the office with Williams syndrome, the evaluation and treatment of sleep problems is an important component of overall management. Indeed, optimizing sleep may expand developmental potential and greatly improve quality of life for the patient and the patient's family. Future research should be aimed at teasing out the genetic contribu-

tions to disturbed sleep in Williams syndrome. For example, circadian rhythms may be disturbed, as reflected by endocrine studies, leading to disrupted sleep patterns. Further work is needed to validate the techniques of saliva collection in younger children for cortisol and melatonin assays [23]. Similarly, endocrine studies might be confirmed in larger subject groups. Further assessment of daytime sleepiness as it relates to endocrine changes is needed, as well as determining actual endocrine values during sleep.

As with other parameters including EEG spectral power changes, it will be critical to determine what changes in sleep patterns may be unique to Williams syndrome (in the setting of 7q11 haploinsufficiency) versus non-specific changes seen broadly in populations of children with neurodevelopmental disabilities. Additional studies are needed to replicate findings that support or define characteristic sleep-related Williams syndrome phenotypes. While general approaches to management of sleep problems in Williams syndrome are certainly helpful, targeted interventions in the future could be introduced to improve sleep and daytime functioning more specifically in children with Williams syndrome based on a knowledge of downstream genetic effects.

Case Vignette

Sally is an 11-year-old girl with a history of Williams syndrome, insomnia issues, and obstructive sleep apnea.

Her history includes adenotonsillectomy at age 2 years for obstructive sleep apnea symptoms. An overnight polysomnogram performed in the months after surgery showed borderline/mild obstructive sleep apnea (obstructive apnea-hypopnea index 1.7 events per hour). Because of her developmental issues, she was placed in a self-contained classroom for her main courses. She repeated the first grade and had a one-on-one specialist in the classroom. She has received multiple services at school as well as privately, including speech therapy, occupational therapy, and social skills training.

At age 5 years, she was seen in the sleep center for anxiety around bedtime, when she would cry and scream for up to an hour. Her mother began allowing Sally to fall asleep in her parents' bed, where she would fall asleep quickly and remain until morning. On nights when she was able to fall asleep in her own bed, Sally would typically wake overnight and move into her parents' bed, again staying for the night. She did not have symptoms at that time of snoring, paradoxical effort, gasping in sleep, or witnessed apneas. If she did not get adequate sleep, she was reported to be irritable and fatigued the following day. Overall, she had hyperactivity and poor concentration during the day. Given her anxiety and sleep onset association insomnia, behavioral recommendations were made, including setting up a separate bed in the parents' room and stressing the importance of sleeping in her own bed, whether in her room or her parents' room. It was also recommended that the family use a timer to let her know how long she should remain in her bedroom before being allowed to move into her parents' room. It was to start at 3 min, and if Sally cried out prior to timer going off, it would be reset; her parent would check on her during the 3 min interval as a positive reinforcement. It was also suggested that the patient have playtime during the day in her room to help lessen her anxiety there. Melatonin was added and helped with sleep onset issues. She gradually developed greater independence, falling asleep more quickly, and sleeping in her bedroom most nights. Melatonin was subsequently discontinued, and behavioral recommendations included the use of a "good morning light" (a bedroom lamp set with a timer for the desired wake time) in order to help her understand when she was permitted to leave her room in the morning.

At age 10, Sally had developed increased snoring and difficulty breathing during sleep and underwent repeat overnight polysomnography to assess for obstructive sleep apnea. The study demonstrated sleep architecture findings of decreased sleep efficiency (due to an increased sleep latency and multiple awakenings), and increased arousals and awakenings, with many arousals related to respiratory events. There was severe obstructive sleep apnea, with an obstructive apnea-hypopnea index 25.5 obstructive events per hour (normal <1.5 events per hour). Central apneas and periodic breathing were not increased. Baseline oxyhemoglobin saturation was normal; the oxyhemoglobin saturation nadir was mildly abnormal. The periodic limb movement index was normal.

Sally was evaluated in the sleep center office for continuous positive airway pressure (CPAP) therapy initiation. After an interval of desensitization for mask use habituation, she was placed on an empiric regimen of 5 cm H_2O CPAP. She then underwent a CPAP titration that showed resolution of obstructive sleep apnea on CPAP 9 cm H_2O. Her mother reported that Sally's behavior was improved on CPAP, and download of the home machine showed excellent adherence; her mother reported, however, that she was placing the patient's CPAP mask after the patient was asleep and

struggled put the mask back on after the patient awoke overnight. It was decided that her mother would make CPAP part of the "tuck-in" routine at bedtime, and Sally would try to fall asleep with the mask on. She also was to practice wearing her CPAP mask while awake (such as while watching television). Her CPAP use improved gradually, such that the most recent download of her home machine showed use for 30 consecutive nights, with an average use of over 7 h per night.

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