Down Syndrome

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Case Vignette

Nicky is now a 19-year-old boy with Down syndrome who has been followed in the pediatric sleep clinic since he was 9 years of age for obstructive sleep apnea. He had previously undergone an adenotonsillectomy at age 4 years. He presented to sleep clinic due to loud snoring, neck hyperextension during sleep, frequent awakenings at night, and falling asleep in school. His sleep study was consistent with obstructive sleep apnea, and he was started on continuous positive airway (CPAP) therapy. Nicky had significant difficulty with CPAP at the start. He often took it off in the middle of the night, and compliance checks were low. With assistance of behavioral psychologists and Nicky's parents, CPAP compliance gradually improved over a period of 2–3 years. He is now using it for more than 8 h nightly. His father reports that Nicky is now more awake and alert during the day. He believes that if Nicky's sleep apnea was not adequately treated, he would not be as active or as healthy and would have a lot more restless sleep. His father is constantly encouraging parents of children with DS to have them evaluated and treated for sleep apnea.

Introduction

Down syndrome (DS) is a chromosomal disorder that occurs in approximately 1 in 800–1000 live births. Most often DS results from complete trisomy of chromosome 21, due to nondisjunction during gamete formation. A small number of cases result from either complete or partial translocation of chromosome 21 to another chromosome, typically in the D (13–15) or G (21–22) group [1]. Persons with DS also experience a higher prevalence of health comorbidities including congenital, acquired, and aging-related medical conditions [2]. Guidelines for regular health maintenance and preventive medical screening have been set forth by the American Academy of Pediatrics [3]. Children and adolescents with DS experience much higher rates of sleep disorders including sleep-related breathing disorders (SRBD), sleep pattern disturbances, sleep fragmentation, and behavioral-based sleep disorders [4].

Clinical Features/Etiology

Children with DS have several clinical features which potentially lead to disturbed sleep and/or increased risk for sleep-disordered breathing [5]. Since nocturnal sleep has an important role in a child's learning as well as behavior and daytime function, it is important to diagnose and manage sleep disorders early in children who already have deficits in these areas. Sleep disruption may exacerbate learning and behavior difficulties that are already inherent to children with DS.

Sleep in children with DS has been shown to differ from sleep in typically developing children. In particular, studies of sleep architecture have shown decreased percentage of rapid eye movement (REM) sleep, decreased REM activity, increase in time to initiation of REM sleep (REM latency), more frequent night awakenings and arousals, and decreased sleep efficiency [6, 7]. The lower REM sleep in children with DS

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perhaps puts them at a disadvantage as REM sleep is thought to be functionally related to learning [8]. It is speculated to facilitate the consolidation and retrieval of prior learning.

The overall rates of sleep disturbance in children with DS range from 31% to 54%, higher than what is reported in typically developing children [4]. These sleep disturbances are not limited to sleep-related breathing disorders but also include non-respiratory and behavioral sleep disorders such as difficulties in initiating (reported in 51.8% of DS patients) or maintaining sleep (69.4%), excessive daytime sleepiness (54%), impaired circadian rhythm, and increased level of irritation or anxiety [9, 10]. These symptoms are not always brought to the attention of healthcare givers as parents may assume that these difficulties with sleep are part of their child's syndrome [9–11]. These behavioral sleep problems can have a significant impact on the child's daytime functioning, as well as the well-being of the family. It is thus useful to screen all children with DS for any evidence of sleep disturbance, including bedtime difficulties, night awakenings, excessive daytime sleepiness, or fatigue [4]. Management of these disturbances requires a comprehensive evaluation of the family's current sleep practices, as well as identification of medical and/or psychiatric disorders that can contribute to sleep difficulties.

Up to 25–30% of children and adolescents with DS also have a comorbid psychiatric or neurobehavioral condition [12]. Children with DS may manifest restless sleep and sleep pattern disturbances that can impact attention and learning, and exacerbate daytime emotional and behavior regulation [13]. Higher parent ratings of sleep disturbance correlated with greater impairment in executive function in a small, healthy cohort of adolescents and young adults with DS [14]. More specifically, a significant association between the amount of time spent in slow wave sleep and several measures of achievement and adaptive behavior has been reported [15].

The most widely studied sleep disturbance in children with DS is sleep-disordered breathing. Sleep-disordered breathing is thought to be a continuum reflecting increasing upper airway resistance (Fig. 14.1). On one end is primary snoring, which is the mildest form of sleep-disordered breathing. At the other end is the obstructive sleep apnea syndrome [16]. Upper airway resistance syndrome and obstructive hypoventilation are intermediate conditions between these two extremes. Primary snoring is defined as snoring that is not associated with gas exchange abnormalities, excessive arousals, or daytime symptoms. Obstructive sleep apnea syndrome is a disorder of breathing during sleep characterized by prolonged partial upper airway obstruction and/or intermittent complete obstruction (obstructive apnea) that disrupts normal ventilation during sleep and normal sleep patterns [17]. It has an estimated prevalence of about 1–4% in otherwise typically developing children [18]. In children with DS, the prevalence of obstructive sleep apnea (OSA) is much higher, ranging from 24% to 79% in population-based samples and up to 97%

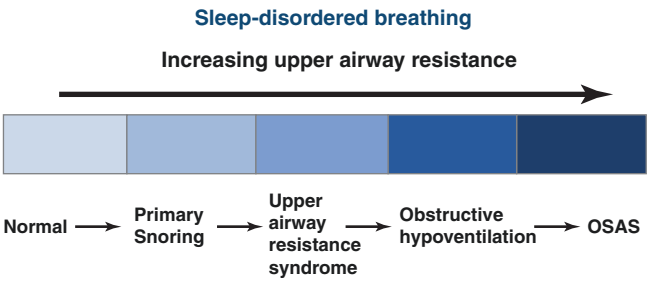

Fig. 14.1 Spectrum of sleep-disordered breathing reflecting increasing upper airway resistance

in those referred for a history of snoring [10]. This increased prevalence continues into adulthood as well, with most patients having a severe degree of OSA [19]. In typically developing children, OSA peaks between the ages of 2 and 6 years of age, corresponding to the period during which the tonsils and adenoids are largest in relation to the underlying airway size. In DS, a higher prevalence of OSA has been described even in young infants, together with correlations between OSA and prematurity, congenital heart disease, dysphagia, GERD, and other GI conditions [20, 21]. Infants with DS and GI issues, co-occurring dysphagia and CHD have a higher likelihood of also having OSA. It is recommended that at least once during the first 6 months of life, then at each well-child visit during childhood, symptoms of obstructive sleep apnea and behavioral problems that could be associated with poor sleep should be discussed with parents [3].

The etiology of obstructive sleep apnea is multifactorial, and it is thought that a combination of anatomic, neuromotor, and other factors (including racial, hormonal, metabolic, and genetic) is involved [22]. Children with DS are at higher for risk for obstructive sleep apnea because of physical, neurologic, and medical features that can contribute to a smaller upper airway, increasing their predisposition to upper airway obstruction during sleep [23, 24]. Physical features include midfacial and mandibular hypoplasia, macroglossia which may be either absolute (true macroglossia) or relative (relatively large tongue compared to the small size of their oral cavity), and lymphoid hyperplasia (including lingual tonsillar hypertrophy). In addition to these structural factors, children with DS usually have hypotonia. This decreased muscular tone throughout the body can predispose to glossoptosis, or the tongue falling back and obstructing the airway. This also contributes to hypopharyngeal collapse during sleep. In addition, obesity is a known risk factor for obstructive sleep apnea syndrome. The higher prevalence of obesity or overweight in children with DS than in the general pediatric population puts them at higher risk for OSA [25]. Hypothyroidism is another condition more commonly seen in children with DS than the general population, and which has shown some association with OSA [26]. Thyroid function should be routinely checked in children with DS diagnosed to have OSA.

Symptoms of Sleep-Disordered Breathing

- Nighttime symptoms
  - Snoring
  - Difficulty breathing
  - Restless sleep
  - Nighttime sweating
  - Enuresis
  - Sleeping in unusual positions (sitting up, bent at waist)
- Daytime symptoms
  - Mouth breathing, nasal obstruction, and hyponasal speech
  - Upper respiratory tract infection and recurrent ear infections
  - Difficulty with swallowing
  - Behavior and learning problems (inattention, impulsivity, irritability)

Obstructive sleep apnea causes both nighttime and daytime symptoms. Snoring and difficulty breathing are the most common nighttime symptoms of OSA. The snoring in children with DS is usually loud and occurs nightly. It is present in almost all children with DS who have sleep apnea. Parents may describe increased respiratory effort associated with lack of airflow. Some parents may describe this as struggling to breathe and restlessness during sleep. Other symptoms include secondary nocturnal enuresis, sweating, and sleeping in unusual positions such as with the neck hyperextended, sleeping propped up on several pillows, or sleeping in a sitting position (Fig. 14.2). Daytime symptoms are usually related to adenotonsillar hypertrophy and include mouth breathing and hyponasal speech in which the child sounds as if he has nasal congestion. Children with OSA may also exhibit behavior and learning problems. Symptoms of attention-deficit/hyperactivity disorder and mood irritability are common among children with OSA.

Diagnosis of obstructive sleep apnea is done using polysomnography. This entails an overnight stay in a sleep laboratory, during which time various physiologic parameters are measured simultaneously. As children with DS may not tolerate the monitoring sensors used during a study, it is useful to introduce what to expect prior to the test, to enable some degree of preparation and possibly better tolerance of the procedure. A sleep study is indicated if a child with DS exhibits the symptoms of obstructive sleep apnea, especially when other risk factors such as obesity are present on examination. In addition, it is recommended that all children with DS (regardless of the presence or absence of symptoms) undergo a sleep study by age 4 years [3], since there is usually poor correlation between parent report of symptoms of sleep-disordered breathing and polysomnogram results [15].

Untreated obstructive sleep apnea poses the risk of neurocognitive, behavioral, cardiovascular, and metabolic consequences [27]. As children with DS already have deficits in these areas, OSA may result in more profound effects in these children. Children with DS and OSA/sleep pattern disturbances demonstrated lower verbal IQ scores and more cognitive inflexibility compared to those without OSA [28]. A possible relationship between OSA severity (AHI) and communication skill has been recently noted as well [29]. Most of these studies are from small, clinically ascertained samples.

It is tempting to speculate that undiagnosed sleep-related breathing disorders (SRBD) or other sleep disturbances are also causally related to neurobehavioral disorders in this vulnerable and susceptible population, but this has not been conclusively demonstrated nor has it been well studied. Whenever behavior problems involving mood, irritability, anxiety, inattention, distractibility, loss of developmental skills (regression), hypo- or hyperactivity, and fatigue manifest in children without a prior history, focused questioning about sleep patterns and hygiene and diagnostic testing for sleep apnea should be considered. As reported by us previously, children with DS and comorbid neurobehavioral disorders manifest a high incidence of sleep disturbances according to parent report. Even in the absence of diagnostic testing by overnight polysomnogram, a majority of these children appeared to benefit from psychotropic medications given at bedtime to improve insomnia and sleep consolidation in addition to daytime maladaptive behaviors [30, 31]. Laboratory-based investigation of larger cohorts needs to be undertaken in order to tease apart the separate contributions of hypoxemia, disturbed breathing, and sleep fragmentation in children with DS both with and without neurobehavioral problems.

Previously unpublished data obtained from children with DS 3–13 years of age presenting to our outpatient clinic for initial evaluation suggests the following:

- In a cohort of DS children with externalizing disruptive behavior problems, 16/38 (42%) also had OSA on overnight polysomnogram. While 22/38 (58%) did not have OSA, half of those without OSA (11/22) manifested >7/h spontaneous arousals on overnight polysomnogram.
- As expected, in this same cohort, children with OSA had a higher apnea-hypopnea index (AHI), more central apneas (CA), and a higher arousal index (ArI) compared to those without OSA.
- According to the parent-reported Sleep Disturbance Scale for Children [32], none of the six subscale scores differed significantly between those children with and without OSA.

Fig. 14.2 Children with Down syndrome and unusual sleep positions, including sleeping "folded over" (clamshell position) (**a**) and also sleeping with neck and upper trunk in hyperextension (**b**)

- On the parent-reported Aberrant Behavior Checklist (ABC-C), all children scored high on the hyperactivity and irritability scales, consistent with our previous findings in children with ADHD and disruptive behaviors [31]. However, significant differences were not apparent between those with and without OSA.

Management

The first line of treatment for childhood obstructive sleep apnea is adenotonsillectomy [33], including among children with DS. Adenotonsillectomy is indicated if a child has obstructive sleep apnea documented on an overnight sleep study, has some degree of adenotonsillar hypertrophy, and has no contraindications to surgery [33]. In children with DS, adenotonsillectomy for OSA also leads to improvement in OSA, but not to the same degree as in typically developing children [34, 35]. Adenotonsillectomy in typically developing children is curative in about 80% [36]. In contrast, about 50–73% of children with DS will have persistent obstructive sleep apnea following adenotonsillectomy [35], requiring further treatment.

Children with DS may require a higher level of care in the immediate postoperative period, as they are at higher risk for postoperative complications. Potential complications of adenotonsillectomy for OSA include complications related to anesthesia, bleeding, pain, fever, infection, and pulmonary edema. Children with DS are also at risk for respiratory complications such as upper airway obstruction and oxygen desaturations, in addition to potentially needing a longer period to tolerate adequate oral intake, leading to longer hospital stays [37]. The American Academy of Pediatrics recommends admitting children at high risk to a hospital for observation following surgery for OSA, including those with DS [33]. In addition, evaluation with a follow-up sleep study after adenotonsillectomy is recommended in children with DS [38], given the higher likelihood of incomplete cure. This study should be done 6–8 weeks after surgery to allow for adequate healing of the surgical site.

In those with a significant degree of OSA persisting after surgery, further airway evaluation through flexible endoscopy, sleep video fluoroscopy, cine computed tomography (CT), or cine sleep magnetic resonance imaging (MRI) may be done to identify other sites or causes of airway obstruction that may be amenable to further surgery [39, 40]. In children with DS, there may be multiple sites of persistent obstruction and may include adenoid regrowth, glossoptosis, lingual tonsillar hypertrophy, and/or hypopharyngeal collapse [11]. Surgical procedures which may be done include revision adenoidectomy, lingual tonsillectomy, uvulopalatoplasty, genioglossus advancement, tongue reduction or radio

frequency ablation of the tongue base, rapid maxillary expansion, and tracheostomy [41, 42].

For children with DS who are not candidates for surgery, or in whom OSA has persisted after surgery, positive airway pressure (PAP) therapy is used. Two modes of PAP therapy can be used to treat obstructive sleep apnea: continuous PAP (CPAP) and bi-level PAP. A CPAP machine delivers air at a constant pressure through a nasal mask to keep the airways open. Bi-level PAP has two pressures set, an inspiratory and an expiratory pressure. Both CPAP and bi-level PAP have been shown to be effective in childhood OSA [43], but CPAP is used more commonly. PAP therapy significantly decreases the number of obstructive apneas and improves oxygenation, snoring, and sleepiness. As PAP therapy entails the use of a nasal mask during every sleep period, compliance is often suboptimal. Initiating PAP therapy may be particularly difficult in children with developmental disabilities, such as in Nicky's case, above. As such, behavioral therapies have been developed, with about 75% of children successfully tolerating PAP after behavioral intervention [44] (Fig. 14.3). Ideally, behavioral training for PAP therapy in children with developmental disabilities should begin prior to PAP therapy initiation by involving a behavioral therapist even during the initial mask fitting. The therapist can also help identify the type of distraction and reinforcement contingencies that can be used for the child [45]. In instances when a behavioral therapist is not available, the family can also work with a respiratory therapist who has significant experience working with children with DS. It is typically recommended that the child be taught first to tolerate the mask while awake, prior to attempting to use it during sleep. Ongoing parental education and support throughout all stages of therapy is a prerequisite to successfully implementing PAP therapy in children.

In addition to behavioral therapy for the child, adherence may be improved by minimizing side effects from PAP use. Complications from PAP use include those related to an ill-fitting mask such as skin breakdown and eye irritation from air leak. Nasal symptoms such as congestion or irritation may be improved by providing heated humidification with the machine [46].

Compliance Information 2/13/2015 - 5/13/2015

Compliance Summary

Date Range	2/13/2015 - 5/13/2015 (90 days)
Days with Device Usage	90 days
Days without Device Usage	0 days
Percent Days with Device Usage	100.0%
Cumulative Usage	30 days 11 hrs. 39 mins. 55 secs.
Maximum Usage (1 Day)	9 hrs. 48 mins.
Average Usage (All Day)	8 hrs. 7 mins. 46 secs.
Average Usage (Days Used)	8 hrs. 7 mins. 46 secs.
Minimum Usage (1Day)	1 hrs. 37 mins. 30 secs.
Percent of Days with Usage >= 4 Hours	97.8%
Percent of Days with Usage > 4 Hours	2.2%
Total Blower Time	30 days 11 hrs. 39 mins. 55 secs.

Hours of Usage

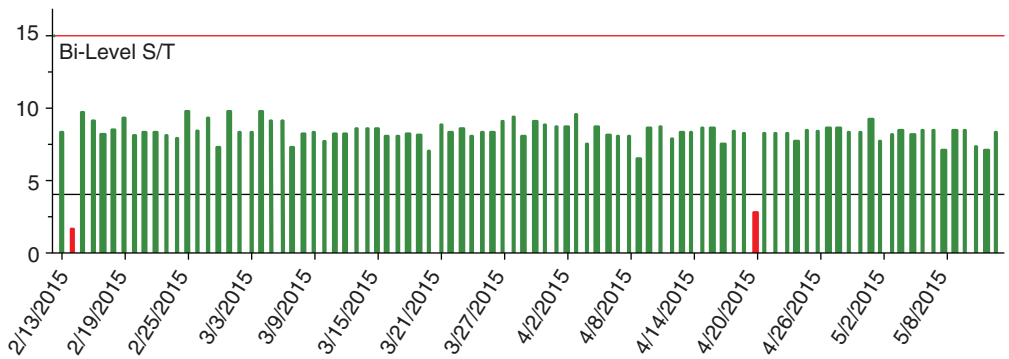

Fig. 14.3 PAP compliance card download on a previously noncompliant child with Down syndrome following behavioral therapy showing that the child used his PAP machine on all days, with an average daily use of more than 8 h

Weight loss is an important aspect of the management of obstructive sleep apnea in obese children. Thyroid function should be checked and hypothyroidism should be treated if present. Symptoms related to gastroesophageal reflux, or reactive airway disease also require aggressive management. The use of intranasal steroids is an option for those with mild OSA who have contraindications to surgery and in those with mild residual OSA following adenotonsillectomy [33].

Summary

In summary, children with DS are higher risk for both behavioral and physiologic sleep problems. Parents may not routinely bring these sleep disturbances to attention with the belief that these are inevitable consequences of the syndrome. Management of these sleep disorders impacts the child's health as well as overall functioning of the family.

Clinical Pearls

- Children with Down syndrome are at higher risk for sleep-disordered breathing (SDB).
- Both respiratory and non-respiratory sleep disorders are more common in children with Down syndrome compared to typically developing children.
- Children with Down syndrome should be screened for sleep disorders during each well-child visit beginning in infancy.
- Obstructive sleep apnea in children with Down syndrome is less often cured by adenotonsillectomy than in typically developing children.
- Children with evidence of sleep disturbance/fragmentation without SDB often benefit from both behavioral and medical therapies that promote sleep consolidation.

Future Directions

An initial sleep study to screen for sleep-disordered breathing is recommended starting at age of 4 years for children with DS who are not symptomatic. For children under 4 years, it is reasonable to screen based on presence of symptoms, risk factors, or other comorbidities. The next frontier may be adults with DS over 21 years of age and guidelines for rescreening based on risk factors.

Research is also needed to establish whether children with DS exhibit improvement in behavior or neurocognitive functioning following treatment for OSA. We believe this is true for some symptoms, but not clearly demonstrated as of yet. Further, type of treatment presents another variable: surgical treatment vs. CPAP vs. medication, to address issues with sleep consolidation and potentially daytime behavior targets. Hypoglossal nerve stimulation, an implantable medical device used in select populations as an alternative to CPAP for treatment of OSA, is starting at this writing in clinical trials for people with DS and OSA also. Studies using airway management are needed. Our clinical experience is that the behaviors most likely to improve are fatigue, mood, irritability, oppositional resistance, impulsivity-hyperactivity, and some disruptive behaviors. In terms of neurocognitive domains (executive function), improvement in attention, organization, and initiative are most likely. The behaviors that are less likely to improve include symptoms of autism spectrum disorder, self-injurious behaviors, obsessive-compulsive disorder, stereotypy, and severe ADHD or disruptive behaviors. More studies are needed to address pharmacologic management of sleep in this population, as most of the above behaviors can show a nice response to a well-chosen medication.

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