Narcolepsy in Children

Description/Etiology
Narcolepsy is a lifelong sleep disorder of uncontrolled rapid eye movement (REM) sleep that is characterized by four phenomena: hypersomnia (i.e., excessive daytime sleepiness), cataplexy (i.e., sudden loss of muscle tone triggered by extreme emotion or excitement), sleep paralysis (i.e., inability to move just before falling asleep or immediately upon awakening), and hypnagogic and hypnopompic hallucinations (i.e., vivid visual or auditory hallucinations at sleep onset or upon waking which may be very frightening). Disturbed nighttime sleep is not uncommon. Not all four phenomena need be present for diagnosis.

In narcolepsy of childhood, hypersomnia is often the only characteristic manifesting as recurrent attacks of instantaneous REM sleep (i.e., dream state). These attacks can be very brief (5–10 minutes) and may occur in unusual situations. Cataplexy, less common in children, is manifested by total body paralysis and a sudden fall to the floor or partial paralysis involving particular muscle groups (e.g., jaw drop, arm weakness), during which the patient maintains consciousness. Hypnagogic and hypnopompic hallucinations can occur with nighttime or daytime sleep and consist of vivid, frightening, dreamlike experiences.

Although the presence of narcolepsy in childhood is common, narcolepsy is not usually diagnosed until the teen years or adulthood because its signs and symptoms are frequently overlooked or misdiagnosed for many years. The peak period of onset is during the teenage years (e.g., 13-19 years of age). When brief episodes of hypersomnia are the only childhood symptom, the disorder is often mistaken for normal childhood napping, inattentiveness, low intelligence, depression, or laziness. Cataplexy is commonly mistaken for epilepsy (i.e., a brain disorder involving repeated, spontaneous seizures). Sleep paralysis is a nonspecific symptom that is often overlooked because it is estimated that over half of the world’s population has experienced it at least once. Hypnagogic and hypnopompic hallucinations are easily mistaken for nightmares or panic attacks.

The etiology of narcolepsy is unknown, but theories involving genetic autoimmune disease and hypothalamic dysfunction have been established. The genetic autoimmune theory is based on the presence of human leukocyte antigen (HLA) type DQB1*0602 in 85–95% of patients with cataplectic narcolepsy, and the increased prevalence of the antigen in first degree relatives. The theory of hypothalamic dysfunction is derived from the fact that 75% of narcoleptic patients have no detectible hypocretin-1 (Hcrt-1), a naturally occurring hypothalamic neurotransmitter that helps control the sleep-wake cycle. Narcolepsy has also been associated with brain injury (e.g., from head trauma), CNS disorders (e.g., multiple sclerosis [MS]), and brain tumors.

There are several methods for definitive diagnosis, including nighttime polysomnography (PSG) to identify immediate onset of REM sleep (sleep-onset REM) indicating narcolepsy; multiple sleep latency test (MSLT) to identify rapid onset of daytime napping (< 5 min) with sleep-onset REM; HLA typing for the presence of biologic marker HLA type DQB1*0602; and cerebrospinal fluid (CSF) analysis to detect low levels of Hcrt-1, also known as orexin-A, a hypothalamic neuropeptide. Narcolepsy should be differentiated from other disorders in which cataplexy occurs including Niemann Pick type C, Norrie disease, Coffin-Lowry syndrome, and Prader-Willi syndrome.

First-line pharmacologic treatments for narcolepsy in children include modafinil and sodium oxybate, which are administered off-label in children under 16 because their safety has
not been established in this age group. Second-line medications include stimulants (e.g., methylphenidate for children aged 6 and up), tricyclic antidepressants (e.g., clomipramine for children aged 10 and up), selective serotonin reuptake inhibitors (SSRIs; e.g., fluoxetine for children aged 8 and up), and serotonin and norepinephrine reuptake inhibitors (SNRIs; e.g., venlafaxine for children aged 6 and up). Irritability has been reported in patients taking modafinil, venlafaxine, and sodium oxybate. Sodium oxybate is further associated with weight loss, while venlafaxine has been associated with weight gain and constipation (Aran et al., 2010).

Treatment with I.V. immunoglobulin (IVIG) has recently been shown to improve symptoms in children with recent onset cataplectic narcolepsy and is an area for further study. In addition, children with narcolepsy are encouraged to adhere to scheduled sleep periods during the day to minimize narcoleptic events. Lifelong pharmacologic treatment is required to manage the condition. Referral to a sleep specialist and/or neurologist is necessary for proper management of childhood narcolepsy.

### Facts and Figures
The incidence of narcolepsy in Western Europe is 25–50 per 100,000. Narcolepsy is somewhat common in childhood but is frequently overlooked or misdiagnosed. Typically, there is an average of 15 years between onset of symptoms and definitive diagnosis. Hypersomnia is often the only manifestation in children. Incidence is 2–50% in first-degree relatives. Only 10–20% of patients demonstrate all four narcoleptic phenomena.

### Risk Factors
Risk factors include having a first-degree relative with narcolepsy, head trauma, CNS, and brain tumors. At least one copy of major histocompatibility complex, class II, DQ beta 1 (HLA-DQB1) seems to be needed for narcolepsy to develop. Other haplotypes of HLA contribute to type 1 diabetes and celiac disease (Lernmark, 2016).

### Signs and Symptoms/Clinical Presentation
Primary signs and symptoms include hypersomnia, cataplexy, sleep paralysis, and hypnagogic and/or hypnopompic hallucinations. Other signs and symptoms that may occur include automatic behavior (i.e., no recollection of performed activities, which often presents in children as sloppy handwriting), periodic leg movements during sleep (PLMS), depression, obesity, and obstructive sleep apnea (OSA).

### Assessment
- **Patient History**
  - See Description/Etiology, above
  - Assess the patient’s drug history
  - Assess for OSA
  - Ask the patient or the patient’s parents about the child fidgeting, rolling the tongue around the mouth, or pinching him- or herself to stay awake
- **Physical Findings of Particular Interest**
  - Moments of intense laughter, excitement, anxiety or fear can precipitate cataplexy
- **Laboratory Tests That May Be Ordered**
  - HLA typing will identify the presence of biologic marker HLA type DQB1*0602
  - CSF analysis to detect for low Hcrt-1 (≤ 110 pg/ml is positive for narcolepsy)
- **Other Diagnostic Tests/Studies**
  - Nighttime polysomnography (PSG) will identify sleep-onset REM indicating narcolepsy and may be used to assess for nocturnal epilepsy (i.e., a disorder in which the patient experiences seizures at night while asleep) if the condition is suspected
  - Multiple sleep latency test (MSLT) will identify rapid onset of daytime napping (< 5 minutes) with sleep-onset REM—Compared to children with narcolepsy, but without PLMS, children with both narcolepsy and PLMS have shorter mean sleep latency and greater sleep disturbance (Jambhekar et al., 2011)

### Treatment Goals
- **Identify Narcolepsy in Children, Administer Medications, and Prevent Injury**
  - Observe for hypersomnia and cataplexy; document reports of sleep paralysis and nightmares/hallucinations; report findings to the treating clinician
• Administer medications for narcolepsy (e.g., modafinil, clomipramine), as prescribed. and monitor for adverse effects (e.g., weight loss/gain, headache, nausea, irritability, disturbed nocturnal sleep, and parasomnias [sleepwalking])
• Encourage adherence to scheduled sleep periods to minimize narcoleptic events; allow for adequate nighttime sleep, and encourage a nutritious diet and exercise to prevent obesity and related obstructive sleep apnea
• Monitor for fall risk in patients with narcolepsy due to cataplexy or hallucinations; institute fall precautions per facility protocol

Provide Emotional and Social Support to Patients with Narcolepsy
• Assess anxiety level and coping ability of the patient with narcolepsy and parents/family; encourage discussion about narcolepsy, medication regimen, potential complications (e.g., fall risk), and the need for ongoing medical surveillance
• Request a referral to a social worker for local resources for tutoring and homework assistance, and for Internet support groups (e.g., http://narcolepsynetwork.org)
• Request a referral to a mental health clinician to help children with narcolepsy cope with an upsetting and often frightening disorder

Food for Thought
• Investigators in France who evaluated the off-label use of sodium oxybate in 27 children ranging in age from 6 to 16 years found the drug was well-tolerated in the majority of the sample with ameliorations in cataplexy, hypersomnia, and nocturnal sleep disturbance reported. In about 15% percent of children, sodium oxybate was discontinued due to persistent nausea or sleep loss (Lecendreux et al., 2012)
• Researchers in a 2013 study reported that H1N1 vaccination with Pandemrix should be avoided, as it can be a precipitating factor in the development of narcolepsy in children (Szakacs, 2013)
  • Though this has been seen across multiple countries, authors of a meta-analysis of 12 such studies across Europe found that many of these studies had significant methodological limitations that were not fully addressed
  • Care should be taken to ensure that patients and their parents, guardians, and care-takers do not develop a negative attitude towards all vaccines as a result of the association of the Pandemrix vaccine with narcolepsy (Ahmed, et al., 2016)

Red Flags
• Venlafaxine, modafinil, and sodium oxybate have been associated with a lower growth rate in children in large-scale clinical trials (Aran et al., 2010)
• Sodium oxybate (gamma hydrobutyrate or GHB) is a known drug of abuse and has been used as a date-rape drug

What Do I Need to Tell the Patient/Patient’s Family?
• Advise that most patients with narcolepsy are able to manage their condition with adherence to appropriate pharmacologic treatment: Lifelong treatment is probable
• Encourage children to wear a medical-alert bracelet: Educate family members and friends about narcolepsy and how to react during a sleep attack or cataplexy

References