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Topical Review

Clinical Characteristics and Burden of Illness in Pediatric Patients with Narcolepsy

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ABSTRACT

BACKGROUND: Narcolepsy is a chronic and lifelong neurologic disorder with onset commonly occurring in childhood or adolescence, and affecting approximately 0.025% to 0.05% of the general population. The primary symptom is excessive daytime sleepiness, which is accompanied by cataplexy in 70% of patients. Other common symptoms include sleep paralysis, hallucinations upon falling asleep or waking, and disrupted nocturnal sleep. Narcolepsy is associated with a considerable burden of illness (BOI), which has been well characterized in adults, and is exacerbated by delays in symptom recognition, diagnosis, and intervention. **METHODS:** This review describes the specific characteristics and BOI of pediatric narcolepsy, using a wide range of published research data. **RESULTS:** Pediatric narcolepsy presents distinct challenges in diagnosis and management. Narcolepsy symptoms often initially manifest differently in children and adolescents versus adults, which may pose diagnostic dilemmas. Children often respond to sleepiness with irritability, hyperactivity, and poor attention, which may be misinterpreted as misbehavior or neurocognitive sequelae of other conditions. Pediatric cataplexy symptoms may include subtle and unusual facial expressions or choreic-like movements, which are not observed in adults. Insufficient sleep and circadian rhythm disorders presenting with excessive daytime sleepiness are common in adolescents, potentially confounding narcolepsy diagnosis. Pediatric narcolepsy is also associated with comorbidities including rapid weight gain, precocious puberty, and attention deficit hyperactivity disorder, and increased risk for deficits in social functioning, depression, and anxiety. School performance is also typically impaired, requiring special education services. **CONCLUSIONS:** Thus, the discrete BOI of pediatric narcolepsy underscores the need for prompt and accurate diagnosis, and appropriate treatment of this disorder.

Introduction

Narcolepsy is a chronic and lifelong neurologic disorder characterized by excessive daytime sleepiness (EDS) and cataplexy, with two distinct subtypes, narcolepsy type 1 (NT1) and narcolepsy type 2 (NT2).[1,2] Symptom onset of NT1 and NT2 typically occurs in the second or third decade of life with 50% to 65% of patients presenting before the age of 20 years.[3-8] Narcolepsy is a rare form of chronic hypersomnolence, with an estimated prevalence of 0.025% to 0.05% of the general population in the United States (US) and Western Europe.[2,4,9-11] Globally reported narcolepsy prevalence rates have ranged from as high as 0.16% in Japan and 0.28% in China

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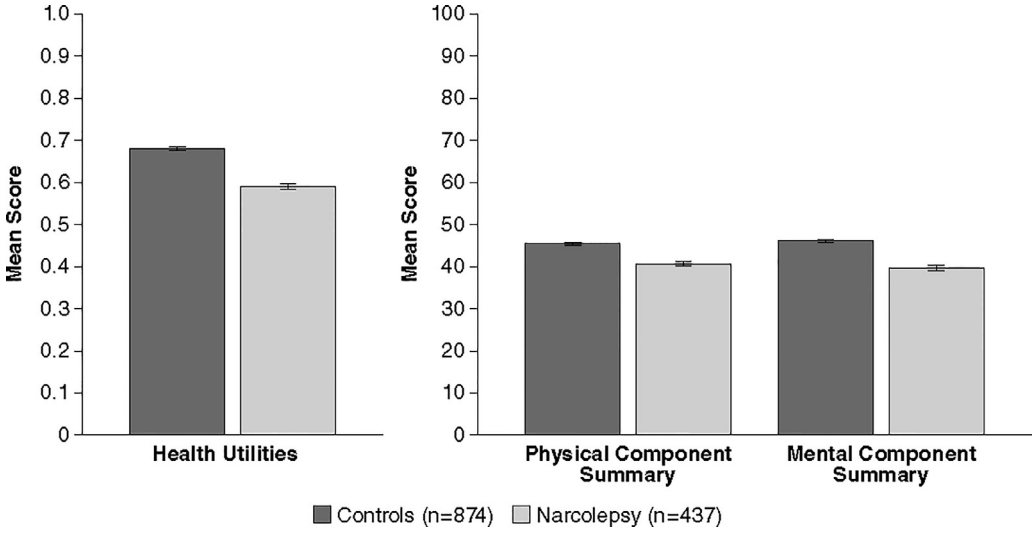

FIGURE 1.
Health-related quality of life (Medical Outcomes Study Short Form-12 and Short Form-36) for adult patients (mean age ~47 years) diagnosed with narcolepsy versus control subjects matched for age, sex, race, and multiple health and socioeconomic factors. Analysis of data from the 2011, 2012, and 2013 United States National Health and Wellness Survey. Error bars represent standard errors. All comparisons for each outcome were significant at the $P < 0.001$ level. Adapted from Flores et al.[25]

to less than 0.01% in Israeli Jews and Saudi Arabians.[1,9] Epidemiologic data suggest males may have higher prevalence of narcolepsy than females (1.6 to 1.8 versus 1); however, this difference could be related to referral bias.[1]

Pediatric narcolepsy presents a distinct set of challenges with regard to its recognition and diagnosis, its impact on patients and their parents or caregivers, and its effect on other involved individuals.[12-15] In addition, multiple studies have found that the diagnosis of narcolepsy is delayed by a mean of approximately 15 years after onset of symptoms, often likely due to poor recognition and attribution of symptoms by health care providers and leading to a wide variety of misdiagnoses, which further contributes to the burden of illness (BOI) of narcolepsy.[8,16-18] In addition, a cross-sectional survey of 1699 individuals (92% greater than 18 years old) in the US with a self-reported diagnosis of narcolepsy found that pediatric onset of symptoms was the strongest predictor of delayed diagnosis of more than year ($P < 0.0005$).[19] Multiple studies have reported that narcolepsy imposes a substantial BOI on adults in terms of reduced quality of life (QOL) and/or health-related QOL and socioeconomic costs (Fig 1).[20-25] Although fewer data are available on BOI in children with narcolepsy, recently published studies have begun to address this neglected area.[26-32]

Following a basic review of the clinical characteristics of narcolepsy, we will profile pediatric narcolepsy with a specific focus on BOI in children and adolescents with this disorder. With regard to methodology, it should be noted that any review of the clinical characteristics and BOI of a chronic pediatric disease is limited by difficulties in obtaining patient-reported data, and the absence of certain highly quantifiable adult BOI parameters such as income, employment, career, marriage, and family. However, the study of pediatric BOI raises a wide range of highly impactful developmental issues and parameters, such as schooling, socialization, and physical, psychiatric, and endocrinal growth and health, which may greatly influence later stages of life. To adjust for these factors, we have used a wide range of published research data, including observational reports, controlled studies, case studies, and reviews available through the National Library of Medicine/PubMed database.

Narcolepsy symptoms and subtypes

EDS in narcolepsy in adults and children is characterized by frequent and extreme drowsiness, most often occurring during passive conditions (e.g., reading, sitting quietly in a classroom or following lunch, or riding in a motor vehicle). The sleepiness is very difficult to resist and can result in involuntary sleep bouts that may also be very brief ("micro-sleeps") or more prolonged (unplanned or inadvertent "naps"). Increased nocturnal sleep duration and planned naps can also occur. While EDS is shared in both NT1 and NT2,[33] cataplexy occurs only in NT1, also called narcolepsy with cataplexy. NT1 accounts for approximately 70% of all narcolepsy cases.[11,34] Conversely, NT2, also called narcolepsy without cataplexy, is clinically distinguished from NT1 by the absence of cataplexy symptoms, as defined in the third edition of the International Classification of Sleep Disorders, (ICDS-3; Table 1).[2] It has been estimated that 10% of patients initially diagnosed with NT2 may be reclassified to NT1 with development of cataplexy symptoms, which typically appear within five years but may be delayed up to 20 years, and can be foretold by evidence of significant hypocretin deficiency.[35-37]

Considered pathognomonic for NT1, cataplexy is characterized by abrupt and brief (typically less than two minutes in duration) episodes of loss of voluntary muscle tone, usually bilateral and ranging from a subtle sensation of weakness involving the knees or craniocervical

TABLE 1.
Diagnostic Criteria for Narcolepsy Type 1 and Type 2: International Classification of Sleep Disorders[2]

Narcolepsy Type 1
Alternate names: Hypocretin deficiency syndrome, narcolepsy-cataplexy, narcolepsy with cataplexy
Diagnostic criteria
• Criteria A and B must be met.
A. The patient has daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for at least 3 months.
B. The presence of one or both of the following:
(1) Cataplexy *and* a mean sleep latency of ≤8 minutes, and two or more sleep onset rapid eye movement periods (SOREMPs) on a Multiple Sleep Latency Test (MSLT) performed per standard techniques. A SOREMP (within 15 minutes of sleep onset) on the preceding nocturnal polysomnogram may replace one of the SOREMPs on the MSLT.
(2) Hypocretin-1 concentration in the cerebrospinal fluid (CSF), measured by immunoreactivity is either ≤110 pg/mL or less than one third of mean values obtained in normal subjects with the same standardized assay.[15]

Narcolepsy Type 2
Alternate names: Narcolepsy without cataplexy
Diagnostic criteria
• Criteria A through E must be met.
A. The patient has daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for at least 3 months.
B. A mean sleep latency of ≤8 minutes and two or more SOREMPs are found on the MSLT performed per standard techniques. A SOREMP (within 15 minutes of sleep onset) on the preceding nocturnal polysomnogram may replace one of the SOREMPs on the MSLT.
C. Cataplexy is absent.
D. *Either* CSF hypocretin-1 concentration has not been measured *or* CSF hypocretin-1 concentration measured by immunoreactivity is either greater than 110 pg/mL *or* greater than one third of mean values obtained in normal subjects with the same standardized assay.
E. The hypersomnolence and/or MSLT findings are not better explained by other causes such as insufficient sleep, obstructive sleep apnea, delayed sleep phase disorder, or the effect of medication or substances or their withdrawal.

area, with head drop and facial hypotonia (i.e., slackened jaw), to complete body paralysis leading to falls.[1,34,38] Consciousness is retained during episodes and positive motor phenomena including muscle twitching or small jerks of the face or limbs may also be observed.[1,34] Strong emotions typically trigger cataplexy episodes, most commonly laughter and surprise. Fright, anger, and startle are other potential triggers.[34,39-41] Other common symptoms of both NT1 and NT2 include sleep paralysis (inability to voluntarily initiate muscle movement except for extraocular muscles) and visual, auditory, tactile, and/or multisensory (e.g., sensed presence of an "intruder") hallucinations, both of which may be hypnagogic (while falling asleep) or more typically hypnopompic (upon waking) in terms of timing. These phenomena are thought to represent the "intrusion" of rapid eye movement (REM) sleep-related phenomena (muscle atonia and dream mentation) into the waking state.[42] NT1 is also frequently associated with disrupted nocturnal sleep, with sleep fragmentation possibly characterized by awakenings, increased motor activity, and dream enactment, resulting in a "pentad" of clinical features.[1,2]

Pathophysiology and risk factors

Although the pathophysiology of narcolepsy is not completely understood, NT1 is linked to the complete or near-complete loss of hypocretin-producing neurons of the dorsolateral hypothalamus, as measured by hypocretin-1 in cerebrospinal fluid (CSF)[43] and documented in postmortem brains.[44] Hypocretin (also termed orexin) is a neuropeptide neurotransmitter that is critical to maintaining wakefulness and arousal as well as other functions such as appetite control and energy metabolism, regulation of the neuroendocrine, cardiovascular and gastrointestinal systems, and pain modulation.[45] The natural history of NT2 and its correlation with hypocretin (orexin) loss is less clear, although approximately 10% to 30% of patients with NT2 may have reduced levels of CSF hypocretin-1,[36] and a significant reduction of hypocretin neurons has been documented in two postmortem cases.[46] A study in 171 patients with NT2 found that 24% had low CSF hypocretin (orexin) levels versus healthy control subjects.[35] Moreover, almost half of the patients in this study with low CSF hypocretin-1 levels (48%) went on to develop cataplexy in their lifetime, after a delay of four to 26 years, compared with 2% of those with normal hypocretin levels.[35]

Documented risk factors for narcolepsy include both genetic and environmental factors, with a likely combination of both. Considerable basic science evidence supports the hypothesis that the loss of hypocretin (orexin) neurons in narcolepsy has an autoimmune etiology linked to both an underlying genetic predisposition and environmental triggers in susceptible individuals, precipitating cell loss.[1,9,47] Isolated narcolepsy symptoms have been reported in up to 11% of individuals with first degree relatives who have and/or had the condition.[48] Specific genetic risks include a strong association with human leukocyte antigen DQB1*06:02, and reported correlations with T-cell receptor polymorphisms and antibodies to the protein Tribbles homolog 2.[47,49-53] Suspected environmental risk factors include H1N1 infection or specific H1N1 vaccination (namely Pandemrix) and seasonal upper airway infections, including *Streptococcal* infection, although none of these correlations are conclusive.[6,54-58] "Secondary" NT1 or NT2 may also occur in association with other neurologic conditions, injury, or genetic diseases, including traumatic brain injury involving damage to the hypothalamus, Guillain-Barre syndrome, limbic encephalitis, multiple sclerosis, congenital brain malformations, Niemann-Pick disease type C, the DNMT1 gene, and other inherited neurodegenerative conditions with broad multisystem involvement.[1,54]

Epidemiology, presentation, and symptomatology in pediatric narcolepsy

Prevalence, age of onset, gender distribution

Although multiple studies have reported on the overall prevalence of narcolepsy, the prevalence specifically in children is less well studied.[55] A large European study (approximately 280 person years of observation time) estimated the prevalence of narcolepsy to be 0.13 per 100,000 children aged less than five years, and 0.83 per 100,000 children aged five to 19 years.[55,56] Studies in pediatric cohorts (aged less than 18 years) diagnosed

with NT1 or NT2 have generally reported a mean age at onset of symptoms of approximately nine to ten years.[6,55,57-61] Occurrence in children less than five or six years old is rare,[62] with a prevalence of approximately 5% in pediatric narcolepsy cohort studies that have reported these data.[57,63] However, a study in 271 Chinese children with NT1 reported a mean age of onset of eight years, with prepubertal onset in 76% and onset at five years or younger in 15%.[64] As in adults,[1] gender does not seem to be an important factor in pediatric narcolepsy prevalence, although a slight preponderance of boys over girls has been reported.[57,59-61,65]

Clinical symptoms and presentation

The major narcolepsy symptoms in children are similar to those in adults, as described above.[66] However, the initial clinical manifestations of these symptoms may differ significantly between children and adults.[1,67] All patients with narcolepsy manifest EDS and this symptom is usually the first to appear in both children and adults; however, children may display distinct, developmentally related responses to sleepiness.[59,62,67] Children with narcolepsy have been observed to exhibit hyperactivity, irritability and emotional dysregulation, aggression, distractibility, and impulsiveness or restlessness both during the day and at bedtime. These behaviors may reflect the child's external response to an internal feeling of sleepiness and/or an attempt to resist it by engaging in self-stimulatory behavior, possibly leading to a clinical presentation that overlaps with attention deficit hyperactivity disorder (ADHD).[39,55,65,67] In preschool children, daytime napping behavior suggestive of EDS may overlap with normal, physiologic napping patterns for this age group,[62] but resumption of napping in an older child may be an initial presentation of EDS. Naps may also be longer than those in adults, lasting up to two to three hours in preschool and school-age children, and are more often nonrestorative.[12,62] Sleep "drunkenness" and extreme difficulty in arousing children in the morning, accompanied by aggressive behavior or tantrums, are additional behaviors sometimes associated with EDS in pediatric narcolepsy.[12,39,57,67]

Cataplexy in children usually presents either concomitant with EDS or within one to three years of EDS and other initial symptoms.[16,18,39,57,67] Cataplexy in the pediatric population can have different clinical features, creating diagnostic challenges.[18] One study that compared narcolepsy symptomatology in 31 children (aged 10 to 19) versus 117 adults (aged ≥20) found that almost half of the children (48.4%) did not have cataplexy symptoms and thus were diagnosed with NT2, compared with only 20.5% of adults diagnosed as NT2 ($P < 0.01$).[66] However, the mean age difference from symptom onset to diagnosis in this study was only 1.8 (±1.7) years for children versus 26.5 (±16.6) years for adults ($P < 0.001$). Therefore, cataplexy symptoms may still develop over time, especially among at-risk children (e.g., those with low CSF hypocretin-1 levels).[35,66] Studies in other cohorts have found that EDS and narcolepsy present simultaneously in childhood narcolepsy, and cataplexy symptoms often initially manifest differently in children compared with adults.[18,34,39,61] Features common in children and atypical in adults include hypotonic attacks occurring often without identifiable triggers (spontaneously), with prolonged duration, and prominent, facial and/or jaw and eyelid weakness (ptosis) with spontaneous tongue protrusion ("cataplectic facies")[39,68] often accompanied by neck extension; slurred speech; a complex array of movements, including facial grimacing; and automatic behaviors such as self-scratching and touching.[18,39,61] In particular, cataplectic facies are distinctive to the pediatric population. "Puppet" or choreic-like whole-body movements with hypotonia have also been observed.[18] These movements are also exacerbated by emotions, identifying them as variants of cataplexy.[18] These symptoms typically progress with the course of the disease to the eventual clinical presentation of classical cataplexy occurring most commonly in response to emotional triggers.[61]

Most children also develop at least one of the associated symptoms other than EDS and cataplexy, with variable reported prevalence,[55] although the "classic" pentad of symptoms (EDS, cataplexy, sleep paralysis, hypnogogic and/or hypnopompic hallucinations, and nocturnal sleep disturbances) infrequently develop simultaneously at the onset of narcolepsy symptoms in children. Rapid weight gain and precocious puberty often accompany symptoms of pediatric narcolepsy in children, and will be discussed in more detail below.[60] Other clinical characteristics include increased periodic limb movements in children,[59,69] as in adults with narcolepsy,[3] and REM sleep behavior disorder, which in pediatric narcolepsy usually only occurs in NT1 children with the most severe symptoms.[69,70]

Diagnostic criteria and challenges

In children as in adults, narcolepsy is formally diagnosed and designated as either NT1 or NT2, based on clinical evaluation and physical examination, symptoms, and the results of objective sleep testing and/or CSF hypocretin-1 assay, according to the criteria established by the ICDS-3 (Table 1).[2]

Although the ICSD-3 generally recommends the same criteria for diagnosis in adults and children, it has also issued several caveats with regard to developmental issues in the pediatric population, including differences in symptomatology from adult presentation, as described above (see **Epidemiology, Presentation, and Symptomatology in Pediatric Narcolepsy:** *Clinical Symptoms and Presentation*), and limited ability of especially younger children to articulate some symptoms, particularly sleep paralysis and hallucinations.[2] Both clinical characteristics of narcolepsy and sleep testing results may also differ between prepubertal patients and adolescents (Table 2).

The primary sleep diagnostic tools used to supplement the clinical evaluation and help confirm the diagnosis include a nocturnal polysomnogram/polysomnography (PSG) followed by a Multiple Sleep Latency Test (MSLT). The latter is a series of five 20-minute nap opportunities separated by two-hour intervals that is conducted on the

TABLE 2.
Characteristics of Patients With Pediatric Prepubertal Versus Adolescent Onset of Narcolepsy*[12,18,60]

Symptom/Characteristic	Prepubertal Onset	Adolescent Onset
Excessive sleepiness	Sleep "attacks" more constant and of longer duration	Less frequent and shorter naps
MSLT results	Longer mean sleep latency, MSLT more commonly negative	Shorter mean sleep latency, MSLT more commonly false-positive due to adolescent sleep phase delay, poor sleep hygiene, and chronic sleep deprivation
Cataplexy	More severe (may indicate more severe course of disease)	Less severe
Sleep paralysis	Less prevalent and severe	More prevalent and severe
Negative motor phenomena†	More common	Less common

* All relative terms (e.g., more and less) refer to the onset age group versus the other onset age group.
† Partial or generalized hypotonia, ptosis, and tongue protrusion.

day after the PSG and documents whether the patient meets criteria for narcolepsy in terms of both sleep propensity (mean sleep onset latency <8 minutes) and rapid initiation of REM sleep (the presence of sleep onset rapid eye movement periods or SOREMPs on two or more of the naps), which is considered the most pathognomonic objective feature of NT2.[2] A REM period occurring within the first 15 minutes of the nocturnal PSG may be counted as one of the SOREMPs. Interpretation of the PSG and MSLT in the pediatric population, however, is not necessarily straightforward and may be complicated by multiple factors that can produce either false-negative or false-positive results. These include the lack of established normative values for the MSLT in prepubertal children, the fact that severely sleep-deprived adolescents without narcolepsy can have a very short mean sleep onset latency and even SOREMPs, and difficulties children may have understanding or complying with testing instructions.[12,71]

Other factors may influence the MSLT results such as comorbid sleep disorders, including obstructive sleep apnea and periodic leg movement disorder, which may increase sleepiness; concomitant use of (or withdrawal from) REM suppressing medications such as many antidepressants; and current substance use. In some cases of "emerging" narcolepsy in children, the MSLT may need to be repeated several times before a clear diagnosis can be made. A CSF hypocretin-1 concentration of ≤110 pg/mL or less than one third of mean values in normal subjects is the biological marker of NT1; however, this test is currently not widely used due to limited availability and the need to conduct a lumbar puncture.[34,72] Because cataplexy is absent in NT2 and thus SOREMPs are not required for the diagnosis, this form of narcolepsy is particularly difficult to diagnose[36] as EDS alone may indicate other conditions such as sleep deprivation or idiopathic hypersomnia. Indeed, studies indicate MSLT is less reliable for diagnosis of NT2 than for NT1, and often requires repeat testing when NT2 is suspected.[73–75] A diagnostic algorithm for NT2 diagnosis (nonspecific to age) has been proposed (Fig 2).[36]

Interpretation of clinical evaluation and symptomatology is also particularly difficult in pediatric narcolepsy, with high potential for misinterpretation.[65,76,77] For example, the distinction between "sleepiness" and "fatigue," as in adults, is not always clear. Thus, EDS in children, especially when combined with symptoms of attentional, behavioral, and emotional dysregulation, may be misinterpreted as "laziness," depression, chronic fatigue syndrome, or endocrine problems such as hypothyroidism. Cataplexy episodes can be confused with normal falls, clumsiness, seizures, or neuromuscular disorders, and hypnagogic hallucinations are sometimes misinterpreted as nightmares or "night terrors" or even as evidence of psychosis in children and adolescents.[12,18,65,76–79] The behavioral symptoms commonly associated with EDS in children with narcolepsy, such as irritability, emotional lability, poor attentiveness in school, aggressiveness, insomnia, hallucinations, or social withdrawal, may be misinterpreted as ADHD, conversion disorder, oppositional defiant disorder, depression or schizophrenia.[2,26,65,76,80] Indeed, the child's teacher is frequently one of the first to report problems eventually leading to narcolepsy diagnosis, including poor attention span, hyperactivity, distractibility, learning problems and academic underperformance, especially in comparison to the child's general cognitive ability (Table 3).[65,67] Emerging study data also suggest that psychiatric and/or neurodevelopmental disorders such as ADHD, oppositional defiant disorder, and depression may be comorbid with narcolepsy in some patients,[26,31,80,81] as discussed below (see **Burden of Illness (BOI) of Pediatric Narcolepsy: Correlates and Comorbidities:** *ADHD and Other Neurologic/Psychiatric Comorbidities*).

In adolescents, narcolepsy symptoms such as sleepiness, mood dysregulation, and inattention may be labeled as behaviors related to "hormonal changes" in puberty.[82] Delayed sleep-wake phase disorder is a common circadian-rhythm disorder in adolescents in which the preferred nocturnal sleep onset and morning wake times are both significantly delayed and thus result in significant EDS when the individual is required to wake for regular morning activities such as school at a time which conflicts with their circadian clock; these manifestations may also mimic narcolepsy.[59] Furthermore, the average high school student obtains far less than the 8.5 to 10 hours of sleep recommended for optimal functioning and as a result, EDS is extremely common in this population.[83] However, EDS symptoms associated with insufficient sleep and sleep-phase delay typically are reduced or even disappear when the adolescent is able to obtain enough sleep to meet sleep needs over a period of time (e.g., on school vacations and during the summer) thus helping to differentiate these conditions from narcolepsy.[59]

In addition to PSG and MSLT assessments, prolonged recording of rest and/or activity behavior by actigraphy is

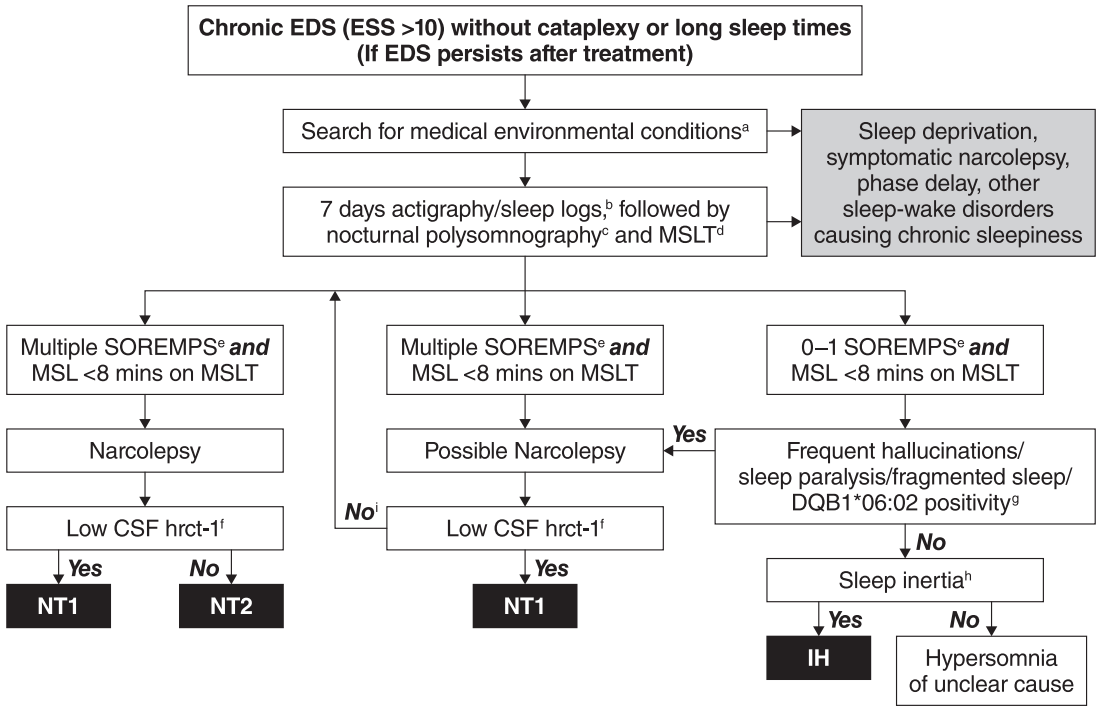

FIGURE 2.
Proposed algorithm for the diagnosis of NT2 and its differential diagnoses. CSF, cerebrospinal fluid; EDS, excessive daytime sleepiness; ESS, Epworth Sleepiness Scale; hcrt-1, hypocretin-1; IH, idiopathic hypersomnia; MSL, mean sleep latency; MSLT, Multiple Sleep Latency Test; NT1, narcolepsy type 1; NT2, narcolepsy type 2; SOREMP, sleep onset rapid eye movement period. Adapted from Baumann et al.[36] [a]In patients with an atypical history or neurological deficits, other causes of narcolepsy-like findings should be considered, and a brain magnetic resonance imaging should be performed. Children with NT2 should receive a more extensive workup for unusual causes of sleepiness (e.g., tumors, metabolic disorders, and seizures). [b]Sleep logs or preferably actigraphy over 14 days should be performed before the polysomnography (PSG) and MSLT to exclude insufficient sleep syndrome. [c]During the nocturnal PSG, the patient should be permitted their habitual amount of sleep. [d]MSLT should be performed according to American Academy of Sleep Medicine guidelines, and medications that might alter sleep pressure or rapid eye movement sleep should be discontinued well in advance. [e]According to International Classification of Sleep Disorders, third edition criteria, one SOREMP within 15 minutes of sleep onset on the preceding nocturnal PSG can be included in the total SOREMP count. [f]In patients without cataplexy, CSF hypocretin is recommended to distinguish NT1 from NT2. [g]A clinical evaluation of frequent hypnagogic and/or hypnopompic hallucinations, frequent sleep paralysis, fragmented nocturnal sleep, or positive HLA DQB1*06:02 typing may increase the likelihood of NT2. [h]Sleep inertia, the need for multiple alarm clocks, and long but unrefreshing daytime naps are more indicative of idiopathic hypersomnia. [i]In patients with normal hypocretin levels, the MSLT should be repeated, preferably after a period of documented sleep extension.

not only a useful, objective, and reliable tool to rule out circadian phase disorders in children with EDS,[2,84] but also promises to be an objective marker in the diagnosis of NT1 in adults and in children.[84,85] Moreover, since actigraphy is a noninvasive method that provides circadian measures collected in the subject's natural environment for long periods, it represents a particularly valuable approach to assess pediatric patients at baseline and to monitor the subjective efficacy of and adherence to therapeutic interventions (pharmacologic and nonpharmacologic). Regardless of the diagnostic approach, the failure to screen for EDS and identify potential causes, and failure to diagnose narcolepsy accurately prolongs and exacerbates the associated scholastic, psychosocial, and psychiatric problems associated with narcolepsy in children.[65,67,76]

TABLE 3.
Schooling and Psychosocial Problems in Children with Narcolepsy[27,65,67,76]

Poor attention and concentration
Irritability and emotional lability
Memory deficits
Tardiness and forgetfulness
Being disciplined and embarrassed for falling asleep
Stigmatization by school personnel as lazy, "dull," and unmotivated
Evaluation by school counselors for behavioral problems and consideration for enrollment in special education classes
False accusations of drug abuse
Aversion to going to school because of conflicts with teachers and peers
Absenteeism, dropping out of school
Difficulty with athletics due to cataplexy or sleepiness
Social isolation and decreased participation in after-school activities
Bullying, feelings of shame and fear of ridicule

BOI of pediatric narcolepsy: Correlates and comorbidities

Weight gain and precocious puberty

Studies have documented multiple clinical correlates and comorbidities of narcolepsy in children that may have a significant impact on BOI, including elevated body mass index compared with control subjects.[60,80,81,86–88] Rapid weight gain coinciding with the onset of other

pediatric narcolepsy symptoms, such as EDS, and subsequently resulting in obesity has been among the most long-standing and consistently observed correlates.[6,26,57,60,80,87,89] However, only one study described the time relation between NT1 onset and weight increase.[88] Reported obesity rates have ranged from approximately 25% to 75% of children with narcolepsy,[80,86-89] and body mass index has been shown to be significantly higher in pediatric narcolepsy patients versus control subjects.[80,86] While weight gain and obesity have been primarily documented in NT1, they have also been reported in NT2, although at slightly lower rates.[80] Hypothesized causes of obesity in pediatric narcolepsy include decreased binding of the appetite-suppressing hormone leptin in the hypothalamus due to reduction of leptin receptors in hypocretin (orexin) neurons, leading to hyperphagia, and altered energy homeostasis with a decreased basal metabolic rate.[86,90] Some data suggest that obese children with narcolepsy may have lower sleep efficiency, are at higher risk for sleep apnea, and have higher rates of fatigue and school absenteeism versus nonobese children with narcolepsy.[91]

Precocious puberty (early onset compared with developmental norms in girls and boys) has been correlated with NT1 in several studies,[87,88,92] and in one study was reported to occur in 17% of children with NT1 versus 1.9% in obese control subjects.[87] Patients with precocious puberty in this study were younger age at onset and/or diagnosis of NT1, and weight gain or obesity was not associated with an increased risk of precocious puberty.[87] However, another study found that early puberty was associated with weight gain, although it did not appear to be an independent association.[60]

ADHD and other neurologic/psychiatric comorbidities

A 2015 study compared scores on an ADHD rating scale in children younger than 18 years with NT1 (n = 86) or NT2 (n = 33) versus 67 healthy control subjects.[80] In this study, total scores on the ADHD rating scale were significantly higher in both NT1 patients (14.2%; $P < 0.001$) and NT2 patients (12.2%; $P < 0.01$) versus control subjects (6.4%), with no significant difference between NT1 and NT2.[80]

Another study of 38 pediatric patients with narcolepsy, including 31 post-H1N1 vaccination (PHV) patients and seven non-PHV patients, reported an overall ADHD prevalence of 28%, based on ADHD rating scale scores, which was approximately four times the rate in the general population (Sweden).[81] This study also reported elevated rates of major depression, anxiety disorder, and oppositional defiant disorder in PVH patients, compared with reference rates in the general pediatric population.[81] The most frequent psychiatric symptom was temper tantrums, present in 94% of PHV patients and 71% of non-PHV patients. While none of the patients had mental disability, based on Wechsler intelligence scales, scores for the Verbal Comprehension Index and the Working Memory Index were significantly lower in the PHV group compared with normal reference values.[81] The investigators hypothesized that these psychiatric and cognitive deficits could be secondary to sleepiness or other aspects of sleep dysregulation, or to neurologic decrements related to the pathology of narcolepsy and hypocretin (orexin) loss.[81] In addition, a Danish registry study found that rates of psychiatric disorders were significantly higher in 243 patients with narcolepsy aged <19 years, both before and after their diagnosis, versus 970 matched control subjects ($P < 0.0001$ for all comparisons).[93] This study also reported significantly higher rates of endocrine, nutritional, and metabolic disease both before and after diagnosis in the narcolepsy patients versus control subjects ($P = 0.001$ for both time periods).

BOI: The patient's perspective

While few qualitative studies on the BOI of narcolepsy for children and adolescents have been published, the existing data help characterize the impact of narcolepsy from the patient and caregivers point of view. A study in 40 prepubertal patients aged ≥ seven years who were given a brief psychiatric interview found that 90% of the patients wanted to hide their symptoms from peers and 90% were ashamed of their symptoms.[65] In addition, 80% of these patients had feelings of helplessness with their symptoms; 83% regarded their symptoms as significant hindrances to acceptance in school, athletics, and social activities; and 20% had potential symptoms of reactive depression, including loss of appetite, withdrawal from social interaction, crying episodes, loss of interest in activities, or loss of self-esteem.[65] Another study used semistructured interviews of approximately 90 minutes' duration with nine adolescents and young adults (mean age 20.8 years) diagnosed with narcolepsy.[82] Study participants described such negative experiences as teachers throwing things at them to wake them up; falling at a dance due to cataplexy; lacking adequate energy to perform at a full-time job; inability to drive and falling asleep on public transport; and being teased by other children (e.g., being made to laugh so he or she would fall).[82] A supplementary figure illustrates the self-expressed thoughts, feelings, and experiences of an eight-year-old girl with narcolepsy who is a patient of one of the authors (JAO).

BOI: Impact on academic performance and cognition

A summary of the methods and results of published studies of the impact of narcolepsy on school performance, QOL, and other domains of BOI for children is presented in Supplemental Table 1.

Although few studies have evaluated the impact of narcolepsy on intellectual functioning and learning with use of formal neuropsychologic assessment measures, multiple reviews and observational studies have noted that narcolepsy is associated with impaired school performance, which may be further exacerbated by the sequelae of misdiagnosis and delayed diagnosis for these students (Table 3).[12,27,62,65,67] Academic performance appears to deteriorate over time as schoolwork becomes more complex and challenging[67]; as success in school (and life) is also associated with success in interpersonal

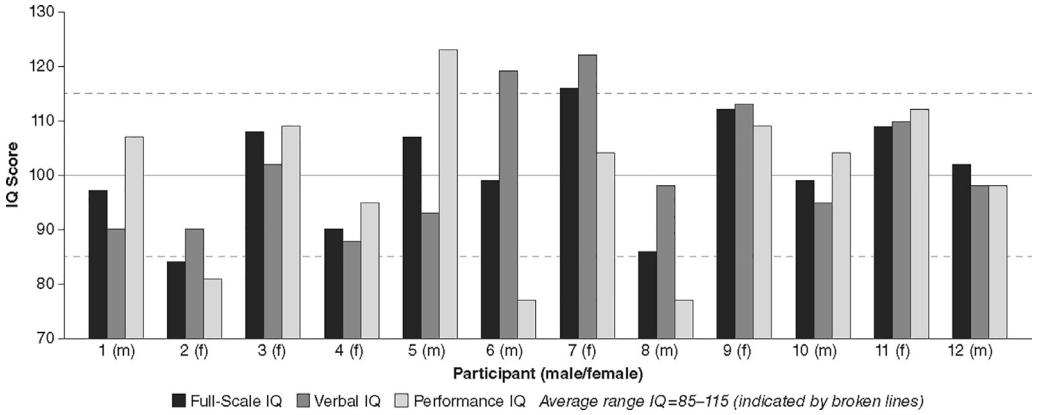

FIGURE 3.
Full-scale, verbal, and performance intelligence quotient scores (Wechsler Intelligence Scale for Children-III-UK) for each participant in a trial of 12 patients with narcolepsy aged 7 to 16 years (median age 10 years). Reproduced with permission from Taylor & Francis Ltd (www.tandfonline.com): Dorris et al.[29] © 2008.

relationships, the fact that narcolepsy is associated with psychosocial problems is equally concerning.[67]

In contrast, the few studies that applied formal neurocognitive assessment measures have consistently reported intact cognitive function, with mean full-scale intelligence quotient (IQ) within the average range, despite academic struggles (Supplemental Table 1).[27,29,30] One study that evaluated 12 children referred to a narcolepsy clinic found that while no distinct cognitive impairments or domain-specific weaknesses were observed, significant differences were found for Verbal versus Performance scores in five (42%) patients, as compared with 24% of normal children, suggesting an uneven cognitive profile for some patients (Supplemental Table 1 and Fig 3).[29]

Another study of 13 children with NT1 also found that while all patients had normal full-scale IQ (mean and/or median not reported), there were significant disparities in Verbal versus Performance IQ (Supplemental Table 1).[30] In this sample, seven of 13 patients (53.8%) reported a history of academic failure. Other studies have evaluated academic performance in the context of overall QOL, and reported similar, consistent evidence of impaired function at school among children and adolescents with narcolepsy versus healthy control subjects (Supplemental Table 1).[26,28,31,32] For example, a study of 117 patients with narcolepsy (95 with NT1, 22 with NT2), which evaluated academic performance on the basis of interviews with children and their parents, reported higher rates of school difficulties among the narcolepsy patients versus 69 control subjects[31] (Fig 4).

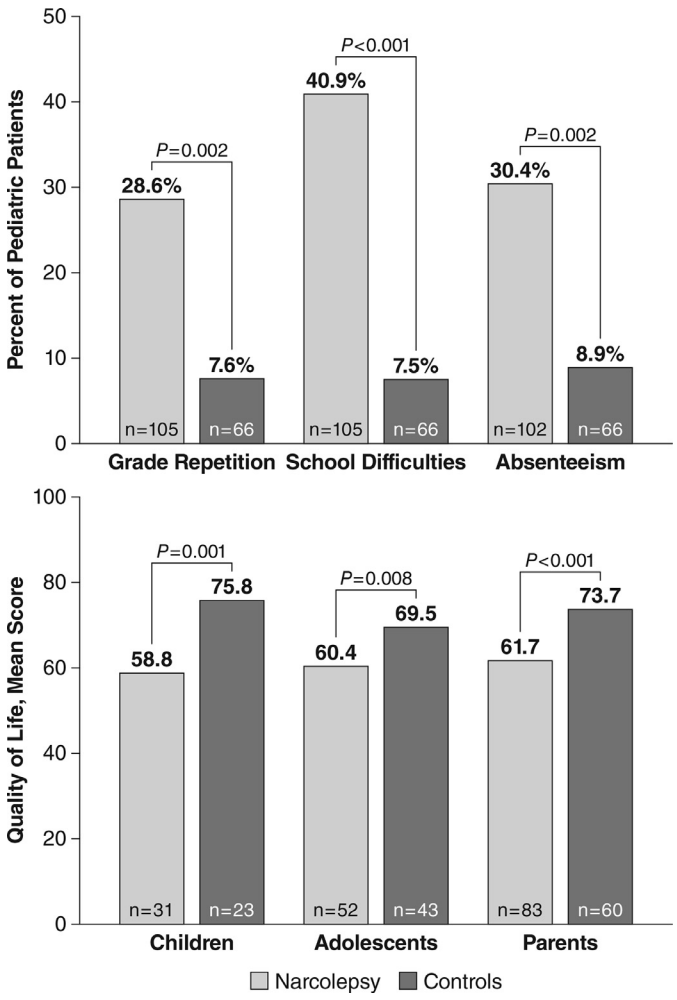

FIGURE 4.
Academic performance and health-related quality of life (HR-QOL) scores from a study in 117 children with narcolepsy (95 [81%] with NT1, 22 [19%] with NT2; mean age 11.6 [±3.1] years) versus 69 healthy control subjects. Age appropriate or modified versions of the Vécu et Santé Perçu par l'Enfant or de l'Adolescent were used to measure HR-QOL. Adapted from Inocente et al.[31]

BOI: Impact on QOL and behavior

No instruments to measure health-related QOL specifically in pediatric narcolepsy were available until 2017, when the NARQoL-21 was developed and reported to have promising psychometric qualities.[94] Previous studies of the BOI of pediatric narcolepsy have used general, validated measures of pediatric QOL and health-related QOL as well as behavioral measures (Supplemental Table 1).[95-99]

Among four published studies identified for this review that evaluated QOL in pediatric narcolepsy using measurement scales for children, results have been mixed (Supplemental Table 1). The study in 117 patients with narcolepsy (described above in the section on academic performance), which evaluated the QOL with the Vécu et Santé Perçue de l'Adolescent, reported significantly lower scores overall and in most subdomains of health-related QOL (Fig 4).[31] Similarly, a study of 33 patients with central hypersomnia, including 18 with narcolepsy (seven with NT1 and 11 with NT2), found that the participants with central hypersomnia had significantly lower scores for overall QOL and all subdomains, except for Emotional Functioning, versus control subjects, as determined via the Pediatric Quality of Life Inventory 4.0 Generic Core Scales.[32] A study of 42 patients with NT1 and 18 with EDS of uncertain etiology also reported that both patients with NT1 and EDS had significantly worse scores than control subjects (n = 23) on the Child Health Questionnaire for Mental health; however, no differences were seen for Physical and Global health domains.[28] The fourth study also found that patients with NT1 (n = 29) and control subjects (n = 39) had similar scores in three of four Pediatric Quality of Life Inventory 4.0 Generic Core Scale domains (physical, emotional, and social), although NT1 patients had significantly lower scores for School Functioning ($P < 0.001$) and Psychosocial Health Summary ($P = 0.01$).[26]

Findings for behavioral measures, reported in four studies, have been more consistent (Supplemental Table 1). Of two small studies that conducted behavioral evaluation without control groups, one (n = 12) reported clinically significant problems in each of the various domains of the Achenbach Child Behavior Checklist (parent reported) for approximately 15% to 50% of patients,[29] and the other found worse-than reference mean values for at least one domain of the Strengths and Difficulties Questionnaire in eight of 13 (62%) patients.[30] The study in 42 patients with NT1 and 18 with EDS of uncertain etiology, also noted above, reported significantly worse scores versus healthy control subjects and compared with reference mean values, for Total and subdomain scores ($P \leq 0.01$).[28] The fourth study of this group also reported significantly worse Achenbach Child Behavior Checklist Total and specific domain values in patients with NT1 (n = 29) versus control subjects (n = 39) ($P \leq 0.02$).[26]

Among other results, one QOL study reported significantly higher rates of depression in patients with NT1 versus control subjects ($P < 0.01$),[28] although another study found that the rate of depression was not significantly higher in patients with narcolepsy (NT1 and NT2) versus control subjects (25% versus 15.6%).[31] The study of 33 patients with central hypersomnia also found that measures of wellness (higher rates of injury, less overall physical activity, and time spent on homework) were significantly worse ($P < 0.05$) in the patients versus control subjects.[32]

Future directions

The emerging research on BOI of pediatric narcolepsy in children supports long-time clinical observations that narcolepsy is a particularly difficult condition for children and families to cope with, especially given the frequent long lag time to diagnosis and treatment, the lifelong nature of the disorder, uncertainty regarding natural history and prognosis and limited treatment options in pediatric narcolepsy. The low prevalence of narcolepsy in children and general lack of public awareness of this disorder further exacerbates the sense of isolation that many of these children and families may feel, and when coupled with health care providers' often limited knowledge regarding the disorder as well societal perceptions that equate "sleepiness" with "laziness" and increased need for sleep with physical or moral "weakness," further delays diagnosis. Thus, the development of tailored educational programs and screening tools, targeting medical providers and the general public, as well as teachers, school nurses, school counselors and other adults involved in promoting child health and functioning, would be critical to improving QOL and reducing BOI in pediatric narcolepsy. Policies at the district, county, statewide, and national levels may include school-based individual education plans ("IEPs" in the US and Europe in various languages) which ensure that students with narcolepsy, as with other medical disabilities, receive the appropriate environmental and academic accommodations. Standardized requirements for driving licensure in adolescents with narcolepsy, including selection of measurement tools to assess sleepiness and "fitness to drive" requirements for compliance with prescribed medications, and alternative strategies such as napping, are needed.

There are also many clinical research questions regarding BOI in children with narcolepsy that need to be answered. For example, although cognitive function seems largely intact in children with narcolepsy, some inconsistencies across cognitive domains have been identified and should be further investigated. Little is known about how the onset of NT1 in very young children may impact neurodevelopment or alter the trajectory of behavior, mood, and cognitive regulation. The impact of pharmacologic treatment of both EDS and cataplexy on cognitive domains such as executive functions, behavioral domains such as impulse control, and emotional domains including anxiety and depressive symptoms and self-esteem, should be explored. Moreover, little is known about the impact of nonpharmacologic interventions such as scheduled naps, sleep extension, increased physical activity, changes in nutrition, strategic caffeine use, or yoga and mindfulness in children and adolescents with narcolepsy, or about the specific factors which influence compliance with medication regimens. The role of substance abuse, particularly self-medication of sleepiness, among adolescents and its potential to complicate narcolepsy detection and diagnosis is a neglected area of research that should be further investigated.

Conclusions

Narcolepsy may impose a substantial BOI on children, particularly when it remains undiagnosed and untreated for many years. Tailored education campaigns are needed to increase narcolepsy disease recognition and to improve time to diagnosis; heighten attention to symptoms associated with narcolepsy, which may include

impaired school performance, social function, and increased risk of psychiatric disorders; and to improve implementation of screening procedures. Additional studies are also needed to evaluate more fully the extent of BOI of narcolepsy in children and adolescents, correlates of specific components of narcolepsy-associated BOI, the potential risk of substance abuse among adolescents with narcolepsy, and implications in adulthood for nonrecognition and undermanagement of childhood narcolepsy.

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Supplementary materials

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