Clinical and Therapeutic Aspects of Childhood Narcolepsy-Cataplexy: A Retrospective Study of 51 Children

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Study Objective: To report on symptoms and therapies used in childhood narcolepsy-cataplexy.

Design, Patients, and Setting: Retrospective series of 51 children who completed the Stanford Sleep Inventory. HLA-DQB1*0602 typing (all tested, and 100% positive), polysomnography or Multiple Sleep Latency Test (76%), and cerebrospinal fluid hypocretin-1 measurements (26%, all with low levels) were also conducted. Prospective data on medication response was collected in 78% using a specially designed questionnaire.

Measurements and Results: Patients were separated into children with onset of narcolepsy prior to (53%), around (29%), and after (18%) puberty. None of the children had secondary narcolepsy. Clinical features were similar across puberty groups, except for sleep paralysis, which increased in frequency with age. Common features included excessive weight gain (84% ≥ 4 kg within 6 months of onset of narcolepsy) and earlier puberty (when compared with family members), notably in subjects who gained the most weight. Streptococcus-positive throat infections were reported in 20% of cases within 6 months of onset of narcolepsy. Polysomnographic features were similar across groups, but 3 prepubertal children did not meet Multiple Sleep Latency Test diagnostic criteria. Regarding treatment, the most used and continued medications were modafinil (84% continued), sodium oxybate (79%), and venlafaxine (68%). Drugs such as methylphenidate, tricyclic antidepressants, or selective serotonin reuptake inhibitors were often tried but rarely continued. Modafinil was reported to be effective for treating sleepiness, venlafaxine for cataplexy, and sodium oxybate for all symptoms, across all puberty groups. At the conclusion of the study, half of children with prepubertal onset of narcolepsy were treated "off label" with sodium oxybate alone or with the addition of one other compound. In older children, however, most patients needed more than 2 drugs.

Conclusion: This study reports on the clinical features of childhood narcolepsy and documents the safe use of treatments commonly used in adults in young children.

Keywords: Narcolepsy, cataplexy, childhood, hypocretin, orexin, MSLT, HLA, DQB1*0602, modafinil, sodium oxybate, venlafaxine

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NARCOLEPSY-CATAPLEXY IS A COMMON DISORDER, AFFECTING 0.02% TO 0.05% OF THE POPULATION IN THE UNITED STATES. RECENT RESEARCH HAS shown that the cause of narcolepsy-cataplexy is the loss of approximately 70,000 hypothalamic neurons producing the neuropeptide hypocretin.[1-3] Hypocretin knockout mice and hypocretin receptor-2 mutated dogs have narcolepsy-cataplexy, demonstrating that the loss of hypocretin transmission causes narcolepsy.[4-6] Since 1983, it has been known that narcolepsy is associated with the HLA,[7] most specifically, allele DQB1*0602.[8-10] Because most diseases that are strongly HLA associated are autoimmune, these discoveries have led to the hypothesis that narcolepsy is caused by an autoimmune destruction of hypocretin cells. This finding was recently strengthened by the discovery that narcolepsy/hypocretin deficiency is strongly associated with T-cell receptor α polymorphisms,[11] anti-TRIB2 antibodies[12] and that streptococcus infections are a possible trigger for narcolepsy.[13]

Although narcolepsy is considered to be a disease of adulthood, most cases have their onset in childhood or adolescence.[14] Early observation in the United States[15] and Japan[16] has reported that approximately half of patients with narcolepsy had onset prior to 15 years of age, with fewer than 10% with onset prior to age 5. Similarly, in our own database of 1219 cases, although fewer than 10% are children (< 18 years of age) at evaluation, 40% reported symptom onset prior to age 15, and 2.1% had onset prior to age 5 (1.1% with cataplexy onset prior to age 5) (data not shown). With increased recognition, it is also evident that narcolepsy is diagnosed more frequently close to onset and in childhood. Early studies in the 1980s to 1990s have reported a median delay between onset and diagnosis of more than 10 years.[17]

With narcolepsy increasingly recognized in children and adolescents, there is a paucity of studies describing this population. Challamel et al.[18] reported a high frequency of secondary cases in children, especially those younger than 5 years old. From 97 cases reported, 20 were symptomatic in origin, 12 having Niemann Pick type-C, a disorder associated with cataplexy; 2 with diencephalic tumors; and 2 with other unspecified neurologic abnormalities. A few years later, Guilleminault and Pelayo[19] reported on 51 cases but found none to be secondary in etiology. These authors found that prepubertal cases were frequently misdiagnosed as seizures, cataplexy being the cause of referral. In older children, referral was secondary to sleepiness or abnormal behavior, for example, attention deficit or school-performance complaints.[19] More recently, Vendrame et al.[20] reported on the retrospective study of 125 children with a complaint of hypersomnolence, stressing the importance of sleep disordered breathing (72% of cases), delayed sleep phase syndrome (17%), and the frequency of periodic leg movements

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during sleep (16%) as more frequent causes. In this series, 20 patients (16%) had narcolepsy (defined using the multiple sleep latency test, MSLT), and only 3 reported cataplexy. Other recent narcolepsy-cataplexy case studies include a report on disease characteristics in 16 Caucasian subjects younger than 13 years old[21] and the study of 29 Chinese children.[22] Serra et al.,[23] reporting on cataplexy presentation in 23 young Italian subjects, stressed how cataplexy can be polymorphic and difficult to diagnose when close to disease onset.

Treatment studies are also lacking in this population. Studies have reported on the anecdotal use of modafinil and sodium oxybate in 35[20,24] and 22[20,25,26] children, respectively, with only 1 prepubertal subject reportedly treated "off label" with sodium oxybate.[25] Huang and Guilleminault[26] reported on the use of sodium oxybate versus baclofen, a gamma-amino-n-butyric acid $(GABA)_B$-receptor agonist, in 26 teenagers, finding both drugs to be effective in treating disturbed nocturnal sleep. Because only sodium oxybate had effects on cataplexy and daytime sleepiness, however,[26] the authors suggested that sodium oxybate had a non-$GABA_B$ mediation effect on cataplexy. A major goal of this study was to provide data on disease presentation and therapeutic response in children with narcolepsy, with an emphasis on prepubertal children. To do so, we used retrospective chart review in 51 children and prospective data collection in 40 children with narcolepsy-cataplexy.

METHODS

Patients

All patients gave written assent with parental consent for the study; those who were no longer under the age of 18 provided written consent. The local institutional review board of Stanford University approved the study. Patients were 51 successive children with a major complaint of excessive daytime sleepiness and cataplexy, all meeting International Classification of Sleep Disorders-2 criteria for narcolepsy with cataplexy. Patients were from the United States, and all were either evaluated at the Stanford Sleep Disorders Center from 2001 to 2009 or had participated in research and had been followed for a mean of 4.6 ± 0.5 years (mean ± SEM). Although a few patients first presented with sleepiness and cataplexy-like symptoms, not meeting the strict definition of International Classification of Sleep Disorders-2 for cataplexy upon presentation, all children subsequently developed definitive cataplexy (triggered by laughing and joking). Cataplexy-like symptoms not typically triggered by emotions, such as tongue thrusting and cataplectic gapes, are common close to onset[23] and generally develop into typical events triggered by laughing within a year.

Baseline Evaluation

All patients provided a blood sample for HLA-DQB1*0602 typing (all subjects were HLA positive) and completed the Stanford Center for Narcolepsy Sleep Inventory (SSI). The SSI is a previously validated questionnaire predictive of cataplexy; it also evaluates for the presence and severity of various other narcolepsy symptoms, such as sleepiness, napping, disturbed nocturnal sleep, sleep paralysis, and hypnagogic hallucinations.[14,27]

The SSI questionnaire was completed by the patient, family members or by a combination of the patient and family members, together with a first consent form. Age, sex, and demographic characteristics were also collected. Body mass index was calculated, and most patients were asked to undergo a nocturnal polysomnogram (73%) followed by an MSLT (76%) or/and CSF hypocretin-1 evaluation (26%, all with low CSF hypocretin-1 concentrations).

Follow-up Evaluation

From 2008 to 2009, we attempted to recontact the 51 families by phone and asked whether they were willing to participate to a follow-up interview. A total of 40 families (78%) could be recontacted, accepted, and returned a questionnaire and a newly signed consent form, approved by the Institutional Review Board (in addition to the first consent form, signed by all 51 families). They were then asked to complete a 9-page follow-up questionnaire (see supplementary information) focused on descriptions of disease onset and experience with prior therapies. Data collected in this follow-up questionnaire included dates of appearance of each symptom, number of physicians seen prior to diagnosis (and date of diagnosis), associated disorders, impact of the disease on school performance, existence of a streptococcus throat infection prior to onset of narcolepsy symptoms, evolution of body weight around disease onset, date of puberty if applicable (for boys age of "sparse rather than few pubic hair," for girls "age of first menarche," in comparison to a same-sex sibling or parent), therapies tried (comprehensive list), effects on each symptom (no change [0], decrease [-], increase [+], mild [1], moderate [2], or large [3] effect), side effects (listed categories, including dizziness, nausea, headache, nervousness, anxiety, tremor, leg cramps, somnambulism, early awakenings, constipation, weight gain, weight loss, dry mouth, irritability, insomnia, hypertension, tics, diarrhea), and continuation of medication (stopped medication and why).

Data and Statistical Analysis

Data from both the SSI and the supplementary questionnaire were collated. One of our goals was to contrast patients before, during, and after puberty. Patients were thus separated into three groups, children with prepubertal onset (n = 27, including 24 children with narcolepsy diagnosed prior to puberty and 3 with narcolepsy diagnosed after puberty; 19 with follow-up questionnaire data available), children with onset of narcolepsy symptoms and evaluation while undergoing puberty (n = 15, all within one year of puberty, 14 with follow-up questionnaire data), children with postpubertal onset of narcolepsy and studied after puberty (n = 9, 7 with questionnaire data). These three groups were compared for all variables, but, when most appropriate, data were reported for all three groups combined. Data are reported as means ± SEM or percentage, as appropriate. Statistical comparisons were conducted using analysis of variance across 3 groups, χ^2 tests, or Fisher exact tests, with posthoc comparison when appropriate.

RESULTS

Clinical Characteristics

Table 1 compares clinical characteristics across the three groups. The clinical picture of all three groups was very comparable, except for severity of cataplexy, which was lower in children

with prepubertal onset of narcolepsy, compared with children with peripubertal and postpubertal onset of narcolepsy ($P < 0.05$) and for prevalence and severity of sleep paralysis that increased significantly across puberty groups ($P < 0.05$, trend test). Sleepiness was the first symptom to occur in most cases. Cataplexy occurred within 3 months of onset in 85% of cases (Table 1).

More children with prepubertal onset were African American (versus peripubertal and postpubertal groups combined, $P < 0.05$, Table 1). Strikingly, weight gain was a prominent feature of childhood narcolepsy in all ages (82%-86% gained at least 4 kg within 6 months of onset). Comparing age of puberty (as defined earlier) between patients and a same-sex sibling or parent, we found that puberty occurred earlier in narcoleptic patients diagnosed before and during puberty in comparison to family control **($P = 0.058$).** Interestingly, earlier puberty was related to weight gain; puberty occurred roughly 1 year earlier in patients reporting a weight gain over 10 kg than in control subjects, versus 0.3 years when the weight gain reported was less than 10 kg ($P < 0.01$, Table 1). Of note, however, earlier puberty occurred even when puberty preceded onset (and weight gain) (71% of cases), ruling out simple weight gain as a cause of early puberty (detailed data not shown).

Table 2 reports on the polysomnography and diagnostic characteristics of the three groups. Although results were similar across groups, we found that 15% of prepubertal children (n = 3) did not have a positive MSLT, a significantly larger number than the other two groups combined ($P < 0.05$). The 3 children with a negative MSLT were all prepubescent at testing, including a girl who was 5.5 years old at diagnosis, a 6.1-year-old boy (both Caucasians seen within 8 months of onset, with undetectable CSF hypocretin-1 concentration), and a 10.4-year old boy (African American, 2.5 years after onset). The 5.5-year-old girl with undetectable hypocretin had essentially a normal MSLT (mean sleep latency = 11.5, 0 sleep-onset rapid eye movement [REM] periods, and a normal REM latency at night of 88 minutes). All other children had a positive MSLT (mean sleep latency ≤ 8 min, ≥ 2 sleep-onset REM periods). Mean sleep latency on the MSLT was lowest in postpubertal children (Table 2); a shorter sleep latency on the MSLT has also been reported in normal children during and after puberty. Interestingly, we also found an increased periodic limb movement index in children with an older postpubertal onset of symptoms but not in younger subjects (Table 2).

Table 1—Clinical characteristics of narcolepsy by puberty status

	All patients (n = 51)	Prepubertal onset (n = 27)	Peripubertal onset (n = 15)	Postpuberty onset (n = 9)
Demographics				
Age, y				
At first symptom	10.3 ± 0.5 (51)	7.5 ± 0.4 (27)	12.3 ± 0.6 (15)	15.3 ± 0 .6 (9)
At diagnosis	11.8 ± 0.5 (51)	9.3 ± 0.5 (27)	13.6 ± 0.6 (15)	16.4 ± 0.5 (9)
Females	43 (51)	41 (27)	53 (15)	33 (9)
Race				
Caucasian	75 (51)	67 (27)	87 (15)	67 (9)
African American	14 (51)	22 (27)[b]	0 (15)[b]	11 (9)[b]
Weight and puberty[a]				
BMI at diagnosis	25.2 ± 1.2 (40)	21.8 ± 1.4 (16)	26.1 ± 1.2 (15)	29.4 ± 5.0 (9)
Weight gain at onset of symptoms				
Excessive[c]	84 (38)	82 (17)	86 (14)	86 (7)
kg[c]	9.9 ± 1.1 (38)	8.5 ± 1.8 (17)	10.6 ± 2.4 (14)	12 ± 2.7 (7)
Age at puberty, y				
All	12.2 ± 0.2 (33)	11.9 ± 0.4 (12)	12.3 ± 0.6 (14)	12.6 ± 0.7 (7)
Boys	12.7 ± 0.3 (20)	12.4 ± 0.3 (8)	13.4 ± 0.8 (7)	12.3 ± 0.5 (5)
Girls	11.4 ± 0.5 (13)	11.0 ± 0.7 (4)	11.1 ± 0.5 (7)	13.5 ± 2.5 (2)
In comparison with same-sex sibling or parent, according to sex				
All	-0.7 ± 0.2 (31)	-0.4 ± 0.2 (10)	-0.8 ± 0.4 (14)	-0.6 ± 0.5 (7)
Boys	-0.6 ± 0.2 (19)	-0.3 ± 0.2 (7)	-0.5 ± 0.5 (7)	-1.0 ± 0.4 (5)
Girls	-0.8 ± 0.4 (12)	-0.7 ± 0.7 (3)	-1.1 ± 0.6 (7)	0.5 ± 1.5 (2)
In comparison with same-sex sibling or parent, according to weight gain[d]				
≥ 10 kg	-1.0 ± 0.38 (16)			
< 10 kg	-0.3 ± 0.12 (14)			
Symptoms				
EDS				
Affected, %	100 (51)	100 (27)	100 (15)	100 (9)
Severity[e]	17.2 ± 0.5 (41)	17.1 ± 0.8 (27)	17.4 ± 0.9 (15)	17.0 ± 1.0 (9)
Cataplexy				
Affected, %	100 (51)	100 (27)	100 (15)	100 (9)
Severity[f]	6.8 ± 0.2 (51)	6.4 ± 0.4 (27)[b]	7.4 ± 0.3 (15)[b]	7.1 ± 0.4 (9)[b]
Hypnagogic hallucinations				
Affected, %	66 (50)	62 (26)	67 (15)	89 (9)
Severity[f]	3.6 ± 0.4 (34)	3.5 ± 0.5 (16)	3.4 ± 0.4 (10)	4.1 ± 0.8 (8)
Sleep paralysis				
Affected, %	55 (51)	44 (27)[b]	60 (15)[b]	78 (9)[b]
Severity[f]	3.4 ± 0.6 (28)	2.3 ± 0.5 (12)[b]	4.0 ± 1.26 (9)[b]	4.3 ± 1.6 (7)[b]
Disturbed nighttime sleep				
Affected, %	92 (51)	85 (27)	100 (15)	100 (9)
Severity[f]	4.6 ± 0.5 (47)	4.4 ± 0.6 (23)	4.7 ± 0.6 (15)	4.7 ± 0.8 (9)
Presenting symptom was EDS, %	85 (39)	85 (20)	92 (12)	71 (7)
Cataplexy appeared within 2 months of onset, %	82 (39)	85 (20)	75 (12)	86 (7)

Data presented as mean ± SEM or percentage (number of subjects). [a]Puberty is defined as the age of first menarche for girls and of sparse pubic hair for boys; [b]$P < 0.05$ prepubertal vs peripubertal and postpubertal; [c]Weight gain during the first 6 months from onset of symptoms of narcolepsy. Excessive weight gain was defined as at least 4 kg gain in 6 months. Body mass index (BMI) and weight gain were measured before onset of any treatment; [d]P Value = 0.009; [e]Severity of excessive daytime sleepiness is based on the modified Epworth Sleepiness Scale score; [f]Severity among those subjects who had this symptom.

Comorbidities and Medical History

We next evaluated comorbidities and medical history (Table 3). Time from onset to diagnosis

Table 2—Biologic markers and sleep studies in childhood narcolepsy

	All patients (n = 51)	Prepubertal onset (n = 27)	Peripubertal onset (n = 15)	Postpubertal onset (n = 9)
HLA DQB1*0602 positive, %	100	100	100	100
CSF hypocretin concentration				
Low, %	100 (12)	100 (6)	100 (5)	100 (1)
Value	4.5 ± 2.2 (13)	6.1 (6)	3.4 (6)	0 (1)
Nighttime polysomnography				
Sleep efficiency, %	86 ± 1.6 (34)	86.4 ± 2.1 (17)	85.2 ± 3.1 (12)	86.9 ± 2.3 (5)
REM latency				
Value, min	94 ± 18.5 (33)	77 ± 20.2 (19)	144 ± 39.2 (11)	60 ± 20.7 (6)
< 20 min	41 (37)	42 (19)	27 (11)	57 (7)
AHI	2.2 ± 0.7 (36)	2.2 ± 0.7 (20)	3.5 ± 2.0 (10)	0.6 ± 0.4 (6)
Sleep stage, % of TST				
1	7.1 ± 1.7 (24)	6.6 ± 1.6 (14)	4.5 ± 2.9 (6)	12.8 ± 4.0 (4)
2	55.1 ± 8.3 (23)	61.7 ± 12.7 (13)	47.4 ± 5.9 (6)	49.2 ± 5.4 (4)
3/4	27.5 ± 3.4 (23)	28.6 ± 3.8 (13)	34.2 ± 5.2 (6)	15.9 ± 1.3 (4)
REM	16.7 ± 1.7 (23)	17.4 ± 1.7 (13)	12.6 ± 3.1 (6)	20.2 ± 3.4 (4)
TST, min	410 ± 12 (22)	411.8 ± 17 (10)	428.0 ± 27.2 (7)	384.0 ± 30.5 (5)
PLMS Index, no./h	6.7 ± 2 (22)	5.0 ± 1.9 (13)[a]	3.3 ± 1.1 (7)[a]	15.5 ± 6.1 (5)[a]
MSLT				
MSL, min	2.5 ± 0.4 (39)	2.8 ± 0.6 (21)	2.4 ± 0.6 (11)	1.5 ± 0.4 (7)
SOREMPS, %	83.8 ± 4.5 (39)	80.5 ± 7.5 (22)	83.5 ± 7.7 (10)	100.0 (7)
Positive results[b], %	92 (39)	85 (21)[c]	100 (11)[c]	100 (7)[c]

Data are presented as average ± SEM or percentage (number of subjects, if the number is different from the total group number). CSF refers to cerebrospinal fluid; AHI, apnea-hypopnea index; TST, total sleep time; PLMS, periodic limb movements of sleep. [a]P < 0.05 postpubertal versus prepubertal and peripubertal; [b]Positive Multiple Sleep Latency Test (MSLT): mean sleep latency (MSL) ≤ 8 minutes and at least 2 sleep-onset rapid eye movement (REM) periods (SOREMP); [c]P < 0.05 prepubertal versus peripubertal and postpubertal

did not differ by age groups, and a similar number of medical consultations (~4.0) were needed prior to diagnosis. Families of prepubertal patients reported 33 misdiagnoses (9, emotional disturbances; 6, normal maturational behaviors; 5, infection; 3, epilepsy; 3, other sleep disorders; and 7, other disorders). Families of peripubertal and postpubertal patients reported 32 misdiagnoses (11, normal maturational behaviors; 9, emotional disturbances; 3, infection; 3, epilepsy; 2, other sleep disorders; and 4, other disorders). As reported recently,[28] we also found a high prevalence of streptococcal throat infections prior to onset, most notably in prepubertal and peripubertal children (Table 3, $P < 0.05$ combined vs postpubertal children). Other findings were unremarkable. Of note, 66% reported social difficulties, and 72% reported a decrease in the academic performance after disease onset, with significant improvement in academic performance but not for social problems with appropriate treatment.

Use of Medications and Therapeutic Response

Table 4 reports on the use and continuation of medications. We found that the most commonly used and continued medications were modafinil and sodium oxybate, followed by venlafaxine (Table 4). The high rate of use for these medications reflects usage at Stanford University for adult narcoleptic patients as well. Continuation of both modafinil and sodium oxybate was remarkably high (71%-100%) and did not differ across puberty groups. Continuation for venlafaxine was moderate (58%-83%) and higher than for fluoxetine (25% overall), tricyclic antidepressants (13%), or other selective serotonin reuptake inhibitors (0%). The continuation rates of modafinil, sodium oxybate, and venlafaxine were individually higher than those of any other drugs tried ($P < 0.01$). Methylphenidate was also commonly tried, but continuation rates were low (0% for Ritalin, 20% for Concerta). Atomoxetine also had a moderate continuation rate, having been tried in 6 patients and remaining in use in 2 patients after having been tried (33%).

Tables 5 and 6 report on the effects of sodium oxybate, modafinil, and venlafaxine, the most commonly used compounds. In Table 6, prepubertal children were contrasted with peripubertal and postpubertal children. Modafinil and venlafaxine were used sooner than sodium oxybate in prepubertal children but not as much in peripubertal and postpubertal children (number of medications used prior to this medication) (Table 6). Sodium oxybate was self-reported as being effective for all narcolepsy symptoms (including insomnia, hypnagogic hallucinations, and sleep paralysis) (Table 5). These effects did not differ across groups except for the effect of sodium oxybate on hypnagogic hallucinations, which was lower in prepubertal children in comparison with others ($P < 0.01$, data not shown). In contrast, modafinil and methylphenidate were reported to be effective only for sleepiness (Table 5). Interestingly, venlafaxine was reported to be primarily effective for cataplexy and had minor effects on sleepiness, sleep paralysis, and hypnagogic hallucinations, all inferior to those reported after the use of sodium oxybate. These compounds had very similar effects in prepubertal versus peripubertal and postpubertal children (data not shown).

Side effects were collected using retrospective questionnaire responses (Table 6). Irritability was the most common side effect of both modafinil and venlafaxine and a common side effect of sodium oxybate. This side effect was also more commonly reported in prepubertal versus older children (Table 6) ($P < 0.01$). Nausea and weight loss were the most commonly reported side effects for sodium oxybate in all groups (Table 6). Sodium oxybate had more side effects in prepubertal versus older children (Table 6; $P = 0.058$), and a larger number of prepubertal children stopped this medication due to side effects (18%), in comparison with in older children (0%) (Table 6). We found no effects of sodium oxybate treatment in prepubertal children on the occurrence of subsequent puberty. Indeed, of 11 children who started sodium oxybate prior to puberty, 4 have undergone puberty (1 girl, 3 boys, average age at puberty 12 years), and 7 are still prepubertal (4 girls, 3 boys; average current age, 11.6 years). The average age at puberty of the 4 subjects who have been treated all along with sodium oxybate (12

years) is similar to that of all other children (12.2 years).

Table 4 reports on current treatment combinations in these children. About half of our prepubertal cohort was currently treated with sodium oxybate without any other additional treatment or with the addition of only one compound. In older children, however, most patients needed more than 2 drugs, and only 14% to 28% used sodium oxybate alone or with 1 other compound ($P = 0.013$).

Table 3—Evaluation and diagnostic features in childhood narcolepsy

	All patients (n = 51)	Prepubertal onset (n = 27)	Peripubertal onset (n = 15)	Postpubertal onset (n = 9)
Time from onset to Diagnosis, y	1.5 ± 0.3 (51)	1.8 ± 0.44 (27)	1.3 ± 0.26 (15)	1.1 ± 0.4 (9)
Medical consultations prior to diagnosis, no.	3.9 ± 0.3 (36)	3.9 ± 0.33 (16)	3.9 ± 0.55 (13)	4 ± 0.45 (7)
Events occurring prior to onset of symptoms[a]				
Streptococcal infection, %				
Fever & sore throat	59 (39)	68 (19)	46 (13)	57 (7)
Positive throat culture[b]	21 (39)	26 (19)	15 (13)	14 (7)
Antistreptolysin O titer ≥ 200 IU/mL	58 (38)	63 (19)	67 (12)	29 (7)
Travel, %	13 (39)	16 (19)	8 (13)	14 (7)
Minor head trauma, %	13 (39)	16 (19)	8 (13)	14 (7)
Comorbidities occurring				
Before onset of narcolepsy symptoms, %				
Allergies	30 (40)	32 (19)	21 (14)	43 (7)
Asthma	18 (40)	21 (19)	14 (14)	14 (7)
Developmental delay	10 (40)	16 (19)	0 (14)	14 (7)
ADD, learning disabilities	12.5 (40)	5 (19)	7 (14)	43 (7)
After onset of narcolepsy symptoms, %				
Depression or Anxiety	20 (40)	11 (19)	29 (14)	29 (7)
ADD, learning disabilities	10 (40)	16 (19)	0 (14)	14 (7)
Social difficulties[c]	66 (39)	58 (19)	62 (13)	100 (7)
Decreased academic performance[d]	72 (39)	63 (19)	69 (13)	100 (7)
Academic performance improved to level before disease onset with appropriate treatment	46 (28)	25 (12)	55 (9)	71 (7)

Data are presented as mean ± SEM (number of subjects) or as percentage (number of subjects) when applicable. [a]In the 6 months prior to onset; [b]Positive throat culture for *Streptococcus pyogenes*; [c]Fewer friends compared with older siblings when they were at that age or with peers if there are no older siblings; [d]Compared to their own grades before disease onset and compared with peers and older siblings when they were at that age.

DISCUSSION

In this study, we systematically gathered data in a cohort of 51 children with narcolepsy-cataplexy. We found that the clinical and polysomnographic picture of narcolepsy-cataplexy was similar across puberty groups, with the exception of sleep paralysis and periodic limb movements of sleep, which were more common in the older age groups. As reported by others,[21,29] a striking weight gain was frequently reported in children around onset (8-12 kg within 6 months), and, though usually occurring after puberty, weight gain correlated with earlier onset of puberty. Indeed, children having gained more than 10 kg had puberty 1 year earlier than matched controls, versus only 4 months earlier when gaining less than 10 kg. This last result suggests that weight gain and early puberty are somehow related, but not because weight gain triggers puberty. This may reflect a broader hypothalamic dysfunction around onset, as suggested by Plazzi,[30] or a simple correlation with disease severity. In all cases, we strongly advocate careful monitoring and prevention of weight gain and its aggressive treatment through the use of medications (e.g., sodium oxybate treatment often associated with weight loss) and the restoration of preonset exercise routines. We also found that the MSLT was an adequate tool to diagnose narcolepsy in peripubertal and postpubertal children[19] but that the test occasionally failed to be useful in young prepubertal children (younger than 7 years) and close to disease onset (2 cases within 8 months of onset). In 1 case, the MSLT (and REM sleep latency at night) results were normal, yet the patient had bona fide cataplexy and low CSF hypocretin-1 concentrations, ruling out a diagnosis of conversion disorder. Encouragingly, we found that, in our population, a mean of 1 to 2 years and 4 office visits were needed prior to diagnosis, values much lower than were reported several years ago,[17] thus suggesting increased awareness of the condition. Similar to former reports in children[19] and adults,[31] narcolepsy was frequently misdiagnosed, with behavior and depressive symptoms (emotional disturbances or within normal maturation behaviors) being common misdiagnoses. One of the most interesting aspects of this study was the collection and analysis of systematic data on narcolepsy therapies in this population. Whereas the treatment of narcolepsy is well codified in adults, less is known regarding narcolepsy therapies in children,[32,33,25,34] and virtually nothing is known about the "off label" use of sodium oxybate in prepubertal children (only 1 case reported by[25]). In this study, we found that modafinil, venlafaxine, and sodium oxybate, 3 therapeutic agents commonly used in the treatment of adult narcolepsy, could be used successfully in children of all ages. Of note, narcolepsy-cataplexy symptoms were severe enough to require ongoing medications in all patients but 1. Therapeutic effects similar to those that have been previously reported in adults were found in children. Modafinil was reported to be effective only on sleepiness and has no effect on cataplexy. Venlafaxine was reported to be primarily effective in treating cataplexy, with a minor effect on sleepiness. Sodium oxybate was reported to be effective on all symptoms, including disturbed nocturnal sleep. Special caution is needed, however, with the off-label use of sodium oxybate in this population. We recommend starting with 60 to 90 mg/kg per day (on an empty stomach, divided in 2 doses—1 at bedtime and the second 2.5-

Table 4—Use and continuation of medications in childhood narcolepsy

Individual drugs	All patients (n = 40)	Prepubertal onset (n = 19)	Peripubertal onset (n = 14)	Postpubertal onset (n = 7)
Modafinil (Provigil)	93 → 78; (84)	84 → 68; (81)	100 → 93; (93)	100 → 71; (71)
Sodium oxybate (Xyrem)	85 → 68; (79)	89 → 68; (76)	79 → 64; (82)	86 → 86; (100)
Venlafaxine (Effexor)	70 → 48; (68)	63 → 37; (58)	71 → 57; (73)	86 → 57; (83)
Methylphenidate (Ritalin)	63 → 0; (0)	74 → 0; (0)	57 → 0; (0)	43 → 0; (0)
Methylphenidate (Concerta)	25 → 5; (20)	37 → 5; (14)	14 → 0; (0)	14 →14; (100)
Fluoxetine (Prozac)	30 → 7.5; (25)	37 → 0; (0)	21 → 14; (66)	29 → 14; (50)
Other SSRIs[a]	15 → 0; (0)	11 → 0; (0)	21 → 0; (0)	14 → 0; (0)
Tricyclic antidepressants[b]	20 → 2.5; (13)	11 → 0; (0)	21 → 7; (33)	43 → 0; (0)
Atomoxetine (Strattera)	15 → 5; (33)	5 → 5; (100)	29 → 7 (25)	14 → 0; (0)
Others[c]	7.5 → 0; (0)	5 → 0; (0)	0 → 0; (0)	29 → 0; (0)
Current treatment combinations				
No pharmacologic therapy	2.5	5	0	0
Monotherapy				
Sodium oxybate only	10.0	16	7	0
Modafinil only	5.0	5	7	0
Double therapy				
Sodium oxybate + modafinil	17.5	26	7	14
Sodium oxybate + atomoxetine	2.5	5	0	0
Sodium oxybate + methylphenidate	2.5	5	0	0
Sodium oxybate + venlafaxine	2.5	0	0	14
Modafinil + venlafaxine	22.5	21	29	14
Modafinil + clomipramine	2.5	0	7	0
Triple therapy				
Sodium oxybate + modafinil +venlafaxine	20.0	16	21	29
Sodium oxybate + modafinil + fluoxetine	5.0	0	7	14
Sodium oxybate + modafinil + atomoxetine	2.5	0	7	0
Sodium oxybate + methylphenidate + venlafaxine	2.5	0	0	14
Quadruple therapy				
Sodium oxybate + modafinil + venlafaxine + fluoxetine	2.5	0	7	0

Data are displayed as the percentage of children who ever used a drug → percentage of children currently using the drug (Continuation rate). [a]Selective serotonin reuptake inhibitors (SSRIs) other than fluoxetine, ie, citalopram (2 patients), paroxetine (2), escitalopram (1), sertraline (1); [b]Protriptyline (4 patients), amitriptyline (2), imipramine (1), clomipramine (1); [c]Lisdexamfetamine (1 patient), bupropion (1), duloxetine (1).

Table 5—Pharmacologic treatment of childhood narcolepsy: effects and side effects of the various medications used in 40 children with narcolepsy[a]

	Effect on sleepiness	Effect on insomnia	Effect on cataplexy	Effect on hypnagogic hallucinations	Effect on sleep paralysis	Side effects
Modafinil	1.9 ± 0.1 (36)	0.0 ± 0.1 (31)	0.2 ± 0.1 (33)	0.1 ± 0.1 (22)	0 ± 0 (22)	39% (36)
Sodium oxybate	2.1 ± 0.1 (31)	2.8 ± 0.1 (31)	2.1 ± 0.1 (33)	1.9 ± 0.2 (20)	2.0 ± 0.2 (10)	55% (31)
Venlafaxine	0.4 ± 0.1 (24)	0.0 ± 0.1 (24)	2.1 ± 0.1 (26)	0.5 ± 0.3 (15)	0.6 ± 0.3 (11)	48% (25)
Methylphenidate (Ritalin; Concerta)	1.5 ± 0.1 (19) 1.9 ± 0.2 (8)	-0.1 ± 0.1 (14) 0.0 ± 0.0 (7)	0.2 ± 0.1 (18) 0.0 ± 0.0 (8)	0.1 ± 0.2 (10) 0.0 ± 0.0 (4)	0.0 ± 0.0 (5) 0.0 ± 0.0 (4)	81% (16) 50% (6)
Fluoxetine	0.0 ± 0.1 (10)	-0.1 ± 0.1 (8)	0.9 ± 0.2 (11)	0.0 ± 0.0 (5)	0.0 ± 0.0 (4)	70% (10)

[a]On a scale of -3 to 3, -3 is maximal negative effect, 0 is no effect, and 3 is maximal positive effect. Data are presented as mean ± SEM (number of subjects).

4 hours later) and increasing the dose every 1 to 2 week until effective or the development of significant side effects (maximal dose—180 mg/kg per day, up to 9 gm). Enuresis is not uncommon at the beginning of treatment and mandates reducing the dose and starting the titration more slowly, as some habituation occurs. Depending on age, the 2 nightly doses may be administered by the parents or may be prepared at bedtime. In rare cases, patients may be asked to take the first dose only after a first sleep cycle or the total nightly dose may be divided in 3. A goal is to ensure consolidated undisturbed sleep of age-adequate duration and no residual sedation in the morning.

Main side effects for these medications were also similar to those reported in adults. Irritability was reported with all medications in 38% to 69% of cases. Modafinil, in particular, was well tolerated and was almost never stopped after initiation of therapy. It is our experience that modafinil alone is rarely sufficient as a treatment for narcolepsy-hypocretin deficiency. Weight loss was reported as a side effect of sodium oxybate in 20% to 25% of children treated with this medication but almost never as the result of modafinil (0%-6%) or venlafaxine (0%) (Table 6). Weight gain and constipation were reported when using venlafaxine only. Because sodium oxybate has been reported to increase growth-hormone release in adults,[35] we feared that the drug would trigger premature puberty. Not only did our data not support this hypothesis (sodium oxybate was used in 19 prepubertal cases in this study), but we also found a strong relationship between

acute weight gain around onset of symptoms and premature puberty. Because one of the side effects of sodium oxybate was weight loss, it is possible that sodium oxybate treatment, instead, mitigates premature puberty associated with weight gain, although additional follow-up data will be needed before confirming this hypothesis. In contrast, it is worth mentioning that the use of venlafaxine, fluoxetine, and stimulants in children has been associated with a slightly slower growth rate in large-scale clinical trials.[36,37] As in adults, however, we advocate caution in using sodium oxybate in children with sleep disordered breathing.[38,39] In these cases, we advocate the use of continuous positive airway pressure, with appropriate titration, when using sodium oxybate; monitoring of compliance with continuous positive airway pressure therapy; and retesting for sleep disordered breathing if significant weight loss occurs.

Interestingly, we also found that prepubertal cases used fewer medications, compared with older children. Although half of the prepubertal cases used sodium oxybate alone or in association with a single drug, typically modafinil, only 14% and 28% of the other groups used sodium oxybate plus 1 medication, and many more needed a combination of 3 medications. It is tempting to speculate that increased medication load with age reflects increased work and social pressure in older children. Indeed, it is our experience, as that of others,[40] that a well-controlled sleep schedule with sufficient nocturnal sleep and proper napping (1-2 per day) reduces medication use and is easier to enforce in younger children prior to puberty. It is likely that older children with narcolepsy experience increased sleep need and sleepiness across adolescence, as has been reported in normal children, and that this maturation interacts with the disease, mandating an increased use of medication during this difficult period of increased workload.

Table 6—Pharmacologic treatment of narcolepsy based on onset of symptoms related to puberty: use, side effects, and reasons for discontinuation

	Modafinil (Provigil)	Sodium oxybate (Xyrem)	Venlafaxine (Effexor)
Prepubertal onset of narcolepsy (n = 19)			
Number of medications tried prior to this medication	0.9 ± 0.25 (16)	3.8 ± 0.6 (17)	1.1 ± 0.5 (12)
Months started after diagnosis	9.8 ± 3.1 (16)	26 ± 4.8 (17)	21 ± 6.6 (12)
Maximum dose, mg/d	333 ± 32 (16)	7200 ± 400 (17)	79 ± 16 (12)
Duration of treatment, mos.	46 ± 6 (16)	36 ± 4.1 (17)	20 ± 7 (12)
Side effects, %	38 (16)	69 (16)	55 (11)
Irritability	25 (16)	19 (16)	36 (11)
Dry mouth	6 (16)	12 (16)	9 (11)
Nausea	0 (16)	19 (16)	0 (11)
Weight loss	6 (16)	25 (16)	0 (11)
Weight gain	0 (16)	0 (16)	18 (11)
Headaches	19 (16)	6 (16)	0 (11)
Constipation	0 (16)	0 (16)	9 (11)
Others	6 (16)[a]	13 (16)[b]	0 (11)
Withdrawal due to, %			
Side effects	6 (16)	18 (17)	8 (12)
Lack of efficacy	19 (16)	0 (17)	25 (12)
Cost	0 (16)	6 (17)	0 (12)
Peripubertal or postpubertal onset of narcolepsy (n = 21)			
Number of medications tried prior to this medication	2.1 ± 0.6 (21)	3.4 ± 0.6 (17)	3.0 ± 0.4 (15)
Months started after diagnosis	7.5 ± 2.5 (21)	17 ± 4.8 (17)	13.3 ± 3.8 (15)
Maximum dose, mg/d	353 ± 22 (20)	8100 ± 360 (17)	103 ± 13 (15)
Duration of treatment, mos.	62 ± 6.2 (20)	52 ± 6.1 (17)	59 ± 7.4 (15)
Side effects, %	40 (20)	40 (15)	43 (14)
Irritability	10 (20)	0 (15)	14 (14)
Dry mouth	10 (20)	0 (15)	7 (14)
Nausea	10 (20)	13 (15)	7 (14)
Weight loss	0 (20)	20 (15)	0 (14)
Weight gain	0 (20)	0 (20)	29 (14)
Headaches	5 (20)	5 (20)	0 (14)
Constipation	0 (20)	0 (20)	7 (14)
Others	10 (20)[c]	5 (20)[d]	0 (14)
Withdrawal due to, %			
Side effects	0 (20)	0 (20)	12 (17)
Lack of efficacy	15 (20)	15 (20)	12 (17)
Cost	0 (20)	5 (20)	0 (17)

Data are presented as mean ± SEM or percentage (number of subjects if different from total in the group). [a]Early waking (1); [b]Chest pain, tachycardia, fainting (1), bed wetting (1); [c]Insomnia (1), tremor and hypertension (1); [d]Somnambulism (1)

Our study suffers from several important limitations. First and foremost, the study is retrospective in design, and the results reflect prescription habits at the Stanford Center for Narcolepsy. For example, the low continuation rate of methylphenidate, selective serotonin reuptake inhibitors, and tricyclic antidepressants likely partially reflects the preferential use of venlafaxine and modafinil in our practice. Second, although in most cases medications were used sequentially, in some cases it may be difficult for the family to attribute efficacy or side effects to specific medications in the context of polypharmacy. Finally, patients were educated about the expected therapeutic and side effects of each drug, and because the study was retrospective in design and therefore "open-label" in nature, placebo and nocebo effects cannot be excluded. Due to these limitations and the current paucity of safety data with sodium oxybate, modafinil, and venlafaxine in young children, we recommend the use of these drugs under strict monitoring and by experienced physicians only. Nonetheless, this study reports on the experience of 1 center treating a significant number of children, documenting the safe use and efficacy of narcolepsy medications in this rarely studied population.

DISCLOSURE STATEMENT

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REFERENCES

1. Peyron C, Faraco J, Rogers W, et al. A mutation in a case of early onset narcolepsy and a generalized absence of hypocretin peptides in human narcoleptic brains. Nat Med 2000;6:991-7.
2. Thannickal TC, Moore RY, Nienhuis R, et al. Reduced number of hypocretin neurons in human narcolepsy. Neuron 2000;27:469-74.
3. Crocker A, Espana RA, Papadopoulou M, et al. Concomitant loss of dynorphin, NARP, and orexin in narcolepsy. Neurology 2005;65:1184-8.
4. Chemelli RM, Willie JT, Sinton CM, et al. Narcolepsy in orexin knockout mice: molecular genetics of sleep regulation. Cell 1999;98:437-51.
5. Lin L, Faraco J, Li R, et al. The sleep disorder canine narcolepsy is caused by a mutation in the hypocretin (orexin) receptor 2 gene. Cell 1999;98:365-76.
6. Hara J, Beuckmann CT, Nambu T, et al. Genetic ablation of orexin neurons in mice results in narcolepsy, hypophagia, and obesity. Neuron 2001;30:345-54.
7. Juji T, Satake M, Honda Y, Doi Y. HLA antigens in Japanese patients with narcolepsy. All the patients were DR2 positive. Tissue Antigens 1984;24:316-9.
8. Mignot E, Kimura A, Lattermann A, et al. Extensive HLA class II studies in 58 non-DRB1*15 (DR2) narcoleptic patients with cataplexy. Tissue Antigens 1997;49:329-41.
9. Matsuki K, Grumet FC, Lin X, et al. DQ (rather than DR) gene marks susceptibility to narcolepsy. Lancet 1992;339:1052.
10. Mignot E, Lin L, Rogers W, et al. Complex HLA-DR and -DQ interactions confer risk of narcolepsy-cataplexy in three ethnic groups. Am J Hum Genet 2001;68:686-99.
11. Hallmayer J, Faraco J, Lin L, et al. Narcolepsy is strongly associated with the T-cell receptor alpha locus. Nat Genet 2009;41:708-11.
12. Cvetkovic-Lopes V, Bayer L, Dorsaz S, et al. Elevated Tribbles homolog 2-specific antibody levels in narcolepsy patients. J Clin Invest 2010;120:713-9.
13. Aran A, Lin L, Nevsimalova S, et al. Elevated anti-streptococcal antibodies in patients with recent narcolepsy onset. Sleep. 2009;32:979-83.
14. Okun ML, Lin L, Pelin Z, Hong S, Mignot E. Clinical aspects of narcolepsy-cataplexy across ethnic groups. Sleep 2002;25:27-35.
15. Yoss RE, Daly DD. Narcolepsy in children. Pediatrics 1960;25:1025-33.
16. Honda Y, Asaka A, Tanimura M, Furusho T. A genetic study of narcolepsy and excessive daytime sleepiness in 308 families with a narcolepsy or hypersomnia proband. . In: Guilleminault C, Lugaresi E, eds. Sleep/Wake disorders: Natural History, Epidemiology and Long Term Evolution. New York, NY: Raven; 1983:187-99.
17. Morrish E, King MA, Smith IE, Shneerson JM. Factors associated with a delay in the diagnosis of narcolepsy. Sleep Med. Jan 2004;5(1):37-41.
18. Challamel MJ, Mazzola ME, Nevsimalova S, Cannard C, Louis J, Revol M. Narcolepsy in children. Sleep 1994;17(8 Suppl):S17-20.
19. Guilleminault C, Pelayo R. Narcolepsy in prepubertal children. Ann Neurol 1998;43:135-42.
20. Vendrame M, Havaligi N, Matadeen-Ali C, Adams R, Kothare SV. Narcolepsy in children: a single-center clinical experience. Pediatr Neurol 2008;38:314-20.
21. Dahl RE, Holttum J, Trubnick L. A clinical picture of child and adolescent narcolepsy. J Am Acad Child Adolesc Psychiatry 1994;33:834-41.
22. Han F, Chen E, Wei H, et al. Childhood narcolepsy in North China. Sleep. 2001;24:321-4.
23. Serra L, Montagna P, Mignot E, Lugaresi E, Plazzi G. Cataplexy features in childhood narcolepsy. Mov Disord2008;23:858-65.
24. Ivanenko A, Tauman R, Gozal D. Modafinil in the treatment of excessive daytime sleepiness in children. Sleep Med 2003;4:579-82.
25. Murali H, Kotagal S. Off-label treatment of severe childhood narcolepsy-cataplexy with sodium oxybate. Sleep 2006;29:1025-9.
26. Huang YS, Guilleminault C. Narcolepsy: action of two gamma-aminobutyric acid type B agonists, baclofen and sodium oxybate. Pediatr Neurol 2009;41:9-16.
27. Anic-Labat S, Guilleminault C, Kraemer HC, Meehan J, Arrigoni J, Mignot E. Validation of a cataplexy questionnaire in 983 sleep-disorders patients. Sleep 1999;22:77-87.
28. Koepsell TD, Longstreth WT, Ton TG. Medical exposures in youth and the frequency of narcolepsy with cataplexy: a population-based case-control study in genetically predisposed people. J Sleep Res 2009 Aug 31. [Epub ahead of print]
29. Kotagal S, Krahn LE, Slocumb N. A putative link between childhood narcolepsy and obesity. Sleep Med 2004;5:147-50.
30. Plazzi G, Parmeggiani A, Mignot E, et al. Narcolepsy-cataplexy associated with precocious puberty. Neurology 2006;66:1577-9.
31. Kryger MH, Walid R, Manfreda J. Diagnoses received by narcolepsy patients in the year prior to diagnosis by a sleep specialist. Sleep 2002;25:36-41.
32. Peterson PC, Husain AM. Pediatric narcolepsy. Brain Dev 2008;30):609-23.
33. Wise MS, Lynch J. Narcolepsy in children. Semin Pediatr Neurol 2001;8:198-206.
34. Guilleminault C, Pelayo R. Narcolepsy in children: a practical guide to its diagnosis, treatment and follow-up. Paediatr Drugs 2000;2:1-9.
35. Takahara J, Yunoki S, Yakushiji W, Yamauchi J, Yamane Y. Stimulatory effects of gamma-hydroxybutyric acid on growth hormone and prolactin release in humans. J Clin Endocrinol Metab 1977;44:1014-7.
36. Emslie GJ, Heiligenstein JH, Hoog SL, et al. Fluoxetine treatment for prevention of relapse of depression in children and adolescents: a double-blind, placebo-controlled study. J Am Acad Child Adolesc Psychiatry 2004;43:1397-405.
37. Charach A, Figueroa M, Chen S, Ickowicz A, Schachar R. Stimulant treatment over 5 years: effects on growth. J Am Acad Child Adolesc Psychiatry 2006;45:415-21.
38. Feldman NT. Clinical perspective: monitoring sodium oxybate-treated narcolepsy patients for the development of sleep-disordered breathing. Sleep Breath 2010;14:77-9.
39. George CF, Feldman N, Inhaber N, et al. A safety trial of sodium oxybate in patients with obstructive sleep apnea: acute effects on sleep-disordered breathing. Sleep Med 2010;11:38-42.
40. Wise MS. Childhood narcolepsy. Neurology 1998;50(2 Suppl 1):S37-42.