Narcolepsy in childhood and adolescence

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ABSTRACT

The present review article discusses the most important aspects of narcolepsy in children. The main objective of this review is to describe the clinical and laboratory characteristics of narcolepsy in patients within a targeted age range and to discuss hypotheses regarding the physiopathology of this disease. Excessive daytime sleepiness is reported by up to 20% of schoolchildren and adolescents. In 10% of these cases, narcolepsy begins before the age of 10 years, whereas 30% of narcoleptic patients exhibit its initial symptoms during childhood. A delayed diagnosis might lead to severe, negative future consequences for the affected patients. Human narcolepsy is a complex disease. The association of HLA-DQB1*0602 with low hypocretin levels indicates a genetic susceptibility component. Narcolepsy is characterized by excessive daytime sleepiness and cataplexy and might be associated with hypnagogic hallucinations, sleep paralysis, and sleep fragmentation. The diagnosis of narcolepsy depends on the clinical assessment and the performance of multiple sleep latency tests preceded by polysomnography. In children, the search for secondary causes of narcolepsy is important because approximately 25% of these patients are symptomatic. The treatment of narcolepsy in children is basically symptomatic, and most cases require behavioral and pharmacological approaches. New therapeutic modalities which impede progression of the disease at the onset of symptoms have also been investigated.

Keywords: adolescent, child, narcolepsy.

INTRODUCTION

During the first few years of life, episodes of daytime sleep may be considered normal, and most children will take routine naps until they are 3 years of age. In children and adults, excessive sleepiness (ES) is defined as the tendency to sleep (or the actual occurrence of sleep) during the wakeful period, with a frequency or duration that does not correspond to a given age range, prolonged night sleep, or the necessity of a greater number of night sleep hours. ES complaints are presented by up to 20% of school-age children and adolescents. Although narcolepsy is not often diagnosed during the pediatric age range, the condition can begin before the age of 10 in 16% of the patients. Approximately 30% of narcoleptic patients exhibit initial symptoms during childhood. The phenotypic expression of narcolepsy in childhood is variable, and the onset of the disease is often monosymptomatic.

Narcolepsy should always be considered in cases where children display marked ES. Narcoleptic children can fall asleep as they talk, eat, or play, and the attacks of irresistible sleep may occur several times during the day. During the early stages of the disease, these children might have difficulty waking up in the morning at their usual times. They may also exhibit impairments in their performance at school. The differential diagnosis includes several sleep disorders that cause ES in children and adolescents. At the onset of narcolepsy, the patients may be mistakenly considered to be lazy or to have behavioral disorders. Delays in diagnosing this disease might result in severe issues during the literacy stage, psychosocial disorders, weight gain, and improper drug treatment (e.g., anticonvulsants, antipsychotics, antidepressants), among other adverse effects.

A study of narcoleptic patients in the United Kingdom demonstrated that the symptoms began during an age range of 1 to 68 years, with onset at an average age of 18 years. However, the symptoms have also been investigated.

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the diagnosis was determined at an average of 15 years after the first symptoms appeared. Delays in the diagnosis might be associated with several factors: the absence of cataplexy as the initial manifestation of the disease, which delays the search for treatment and hinders an accurate diagnosis by non-specialists; misdiagnoses in this particular age range because the symptoms are attributed to psychiatric or other neurological diseases; the failure of pediatricians to specifically request an investigation of sleep disorders; and the ignorance of pediatricians regarding the signs and symptoms of narcolepsy.

A Brazilian study demonstrated that the children and/or adolescents with ES symptoms infrequently sought medical help (i.e., 34 out of 290 patients [11.7%] over 4 years). The average age of the patients in that study was 13.5 ± 4.1 years, varying between 5 and 17 years of age, independently of their gender. The symptoms had begun an average of 3.0 ± 3.5 years before the first visit. Narcolepsy was confirmed in 13 out of 34 youths (38%). Only one adolescent sought assistance due to sleep paralysis, whereas the remainder of the patients exhibited marked ES, with 1.5 ± 2.8 minutes of sleep latency during the multiple sleep latency test (MSLT). In that sample, cataplexy was identified in 92% of the patients, sleep paralysis was identified in 23% of the patients, and hypnagogic hallucinations were identified in 46% of the patients.

**PHYSIOPATHOLOGY**

**Hypocretinergic system dysfunction**

Hypocretins (or orexins), which were discovered in 1998, are peptides that are exclusively produced by a well-defined set of cells located in the dorsolateral hypothalamus; these cells exhibit several projections into the cerebral cortex, brainstem, hypothalamus, and thalamus. The hypocretinergic system is predominantly excitatory and exerts effects on the monoaminergic (dopamine, norepinephrine, serotonin, and histamine) and cholinergic systems. The hypocretin-producing hypothalamic neurons are active during the wakeful period and reduce their activity during rapid eye movement (REM) and non-REM (NREM) sleep. The hypocretinergic activity progressively increases during wakefulness and during sleep deprivation to counterbalance the need for sleep, which increases proportionally with the hours of wakefulness (homeostatic factor). In narcoleptic patients, especially those with cataplexy (85% to 90%), significant reductions in the hypocretin levels were measured in the cerebrospinal fluid (CSF).

Human narcolepsy is a complex disease. The association between HLA-DQB1*0602 and reduced hypocretin levels indicates a genetic susceptibility for developing hypocretinergic neuronal injury. Genetic mutations that affect other monoaminergic systems are associated with sporadic cases of the disease, as are chromosomess 4p and 21q.

Although the presence of a positive HLA is not required for the development of narcolepsy, 88% to 98% of cataplexy cases exhibit positive HLA-DQB1*0602. However, in one study of Brazilian children, positive HLA-DQB1*0602 was found in only 29% of the patients.

Recent investigations have demonstrated that seasonality significantly affects narcoleptic children, associated with infections by Streptococcus pyogenes and H1N1 influenza as well as H1N1 vaccination. Some authors believe that infections and vaccine antigens might be important triggers of autoimmune attacks to the central nervous system (CNS). Patients carrying the HLA-DQB1*0602 allele more than likely have a unique immunological response to streptococcal infections, as do individuals with rheumatic fever.

Other genetic aspects appear to be involved in the genetics of narcolepsy. The enzyme catechol-O-methyltransferase (COMT) is responsible for most of the metabolic inactivation of dopamine in the CNS. The COMT gene is located on chromosome 21 and exhibits a single functional nucleotide polymorphism, which alters the amino acid sequence in its molecule by exchanging valine and methionine at codon 158 (Val158Met) and, in turn, results in the reduction of COMT activity. Valine (ValVa) homozygous COMT genotypes exhibit three or four times more COMT activity and, therefore, less prefrontal dopaminergic signalization than does the methionine (MetMet) genotype. Non-European populations predominantly exhibit the ValVal genotype, which is associated with differences in the intensity of neuropsychiatric symptoms among the various populations. This COMT polymorphism modulates the dopaminergic and noradrenergic neurotransmission in healthy individuals, the symptoms exhibited by narcoleptic individuals, and the response to treatment with modafinil. The MetMet polymorphism is more common among Caucasian females, and when associated with a narcoleptic phenotype, it influences the intensity of SE, sleep latency in the MSLT, and the response to modafinil. Environmental factors such as infections, pregnancy, brain trauma, and stress might precipitate the onset of symptoms in up to 50% of the cases.

No definitive explanation exists regarding the higher incidence of narcolepsy during adolescence. One hypothesis states that, in this age, some individuals respond to infections by agents such as streptococci or viruses provoke an autoimmune reaction that can elicit the symptoms of narcolepsy. However, this hypothesis should be tested as more knowledge regarding the physiopathology of narcolepsy is generated.

**CLINICAL PICTURE**

**Excessive Daytime Sleepiness (EDS)**

EDS is the initial symptom that is most commonly reported by patients. The condition occurs alone in 46.1% of the cases and is associated with other symptoms in 32.9% of the cases. It should be emphasized that EDS might be particularly difficult to recognize in children because, due to the physiological ultradian rhythm, infants usually nap in the morning and afternoon and preschoolers usually nap in the afternoon. Moreover, ES might paradoxically present in many children as an increase in motor activity, which is often mistaken for attention deficit hyperactivity disorder (ADHD). After the age of 6 years, hypersomnia should be suspected when children require daytime naps, particularly when these naps are long (duration of 30 to 90 minutes). The differential diagnosis also includes psychiatric disorders such as behavioral and oppositional-defiant disorders, depression, apathy, and mental retardation, as well as generalized absence-like epileptic seizures.

**Cataplexy**

In a Brazilian study, cataplexy appeared as a single symptom in approximately 5% of the cases and was associated with other symptoms in 39%. According to the literature, cataplexy occurs in 80.5% of the patients with idiopathic narcolepsy. Cataplexy usually appears after the onset of EDS and might be mistaken for syncope, atonic-type epileptic seizures, or psychological symptoms. Because of its high prevalence, assess-
ment of the presence of cataplexy is of paramount importance, although pediatricians often have difficulty recognizing the condition. The frequency of cataplectic episodes tends to decrease with age[18].

Hallucinations

Hypnagogic (at the onset of sleep) and hypnopompic (at the end of the nighttime sleep) hallucinations occur in two-thirds of individuals with narcolepsy. Usually, these hallucinations are visual; more rarely, their nature is tactile, auditory, or somatosensory. The hallucinations might reflect everyday scenes, animals, life events, family members, or other persons, and the episodes are sometimes accompanied by sleep paralysis, which terrifies the children even more. When these episodes are misdiagnosed, they might be mistaken for hallucinatory psychotic symptoms, temporal lobe epilepsy, night terrors, nightmares, or panic attacks[12,14].

Sleep Paralysis

Episodes of sleep paralysis occur in 60% of the individuals with narcolepsy, and the frequency is variable, eventually occurring daily. Moaning, difficulty breathing, chest tightness, paresthesias such as pins and needles, or anesthesia of the limbs might occur together with paralysis. These episodes usually last a few seconds and spontaneously end when the children are touched or moved. These patients may also learn to recover their motor activity by moving their eyes or breathing slowly. When these episodes are misdiagnosed, they might be mistaken for psychiatric symptoms, intense fatigue, or certain neuromuscular diseases[5].

Other associated characteristics

Certain additional signs and symptoms are recognized to be associated with narcolepsy, including sleep fragmentation with frequent awakenings, which occurs in up to one-third of the patients.

Narcoleptic children exhibit important differences in their behavioral features, emotional status, quality of life, educational development, and the impact of the disease on their families[18]. EDS appears to be a common limiting factor in these patients’ quality of life. Narcoleptic patients are often considered to be lazy and are eventually discriminated against by their families, schoolmates, and friends. Furthermore, the accurate diagnosis of narcolepsy is important because many of these patients are inaccurately treated for depression[13].

A higher body mass index (BMI) is increasingly found among adults and in approximately 25% of children with narcolepsy compared to individuals without this disease[16]. A tendency to gain weight appears inherent to childhood narcolepsy and the early manifestation of this disease, and a correlation between hypocretin and leptin levels has been discovered. Leptin is a peptide hormone secreted by adipocytes and is associated with the feeling of satiety.

Several other sleep disorders might coexist with narcolepsy during childhood, including night terrors, nightmares, obstructive sleep apnea (OSA), periodic limb movement disorder (PLMD), restless leg syndrome, muscular disorder, or REM sleep behavior disorder.

Narcolepsy is seldom associated with hypothalamic tumors. However, cases associated with precocious puberty, hyperandrogenism, and insulin resistance have been reported[17].

Some authors suggest that children with narcolepsy and cataplexy develop a complex movement disorder that resolves over time. However, it is not yet known whether this movement disorder is associated with low hypocretin-1 levels or with the alteration of another neurotransmitter[18].

DIAGNOSIS

The diagnosis of narcolepsy is established according to clinical symptoms. However, an accurate diagnosis might be difficult at the disease onset and in cases where the ES episodes are short. The use of sleep diaries written by the patients and/or their caretakers might be very helpful, as are questionnaires for the assessment of sleepiness, such as the Epworth Sleepiness Scale modified for children[12,16] and the Pediatric Daytime Sleepiness Scale (PDSS)[19], which can be applied to patients as young as 11 years of age.

Diagnostic confirmation requires long follow-up periods and the performance of an MSLT that has been preceded by polysomnography (PSG) on the prior night.

PSG is indicated whenever narcolepsy is suspected; this test enables the exclusion of other causes of ES and other sleep disorders that might coexist with narcolepsy, such as OSA and PLMD. MSLT is recommended for children who are at least 8 years of age and for adolescents. False negative results can be obtained at the onset of the disease, whereas false positive results might appear in adolescents due to the physiological delay in their sleep rhythm phase, poor sleep hygiene, or chronic sleep deprivation. In younger children, the diagnosis is mainly based on the clinical history and the exclusion of other diagnoses, when possible[20].

Twenty-four-hour video-PSG monitoring performed with an extended EEG montage (international 10-20 system for EEG) is suggested for children who are of preschool age. This technique allows for the identification and distinction between sleep and cataplectic episodes and their differential diagnosis from epileptic seizures[22,23].

Narcoleptic patients might exhibit REM sleep within 15 minutes from the test onset. The sleep efficiency is usually high (above 90%); however, sleep fragmentation might occur, caused by an increased number of awakenings. Reduced REM sleep latency among adolescents might suggest a diagnosis of narcolepsy. In general, the number of REM sleep episodes decreases in narcoleptic patients, and their sleep latency increases progressively with increasing age.

MSLT yields quantitative data on the degree of sleepiness and qualitative information on the nature of the wake-sleep transition, i.e., from the wakeful state to NREM or REM sleep. In narcolepsy, a direct transition from the wakeful state to REM sleep is a common finding, as is the occurrence of REM sleep immediately after the sleep onset (SOREMP = “sleep onset REM period”). The occurrence of two or more SOREMPs might not be observed at the early stages of narcolepsy in children or teenagers; consequently, several tests are required to establish a definitive diagnosis[20]. The PSG and MSLT results that are obtained from adults must be adjusted to prepubertal children (between 8 and 11 years of age), who are usually alert during the daytime. Opinions diverge as to the sleep latency values in pre-adolescents, which vary between 15.5 and 18.8 minutes but might also be higher than 20 minutes[20].

Notably, the discontinuation of all CNS stimulant medications, hypnotics, antidepressants, and other psychotropic

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agents is required for the performance of PSG. All of these medications must be discontinued at least two weeks prior to the exam because they can alter the sleep architecture.

A recent study of a population of narcoleptic children, for whom PSG and MSLT data were available, revealed reductions in the sleep latency (average of 5.3 +/- 3.6 minutes) and the REM sleep latency (14.4 +/- 23.0 minutes) [16]. MSLT demonstrated an average latency of 3.5 +/- 2.4 minutes, and all of the children exhibited two or more SOREMPs. During the tests, attempts were made to trigger cataplexy. Laughter was the main triggering factor, and anger, tickling, and surprise were less frequent elicitors. The cataplectic episodes lasted 1 to 180 seconds with several manifestations: knee weakness; neck flexion; drooping of the eyelids, jaw, or arms; chest flexion; decreased ability to smile or facial hypomimia, slurred speech; and irregular breathing.

Drooping eyelids, facial hypomimia, an open mouth with stuck out tongue characterize a “cataplectic facies,” which was observed in 35% of the patients. This clinical manifestation was more frequently associated with an early onset of cataplexy, increased BMI, and a higher number of SOREMPs. Further intercritical manifestations included repetitive automatic behaviors such as touching certain body parts, scratching, or head shaking. All of these manifestations improved with specific treatments and were thus considered to be cataplectic equivalents.

HLA-DQB1*0602 testing is a useful diagnostic tool in children, whereas its diagnostic sensitivity is higher in patients with narcolepsy accompanied by cataplexy, among whom the condition is present in up to 95% of individuals compared with approximately 25% of the general population. However, the diagnostic specificity is low. A positive HLA-DQB1*0602 result is an additional piece of data that indicates a diagnosis of narcolepsy, especially in the early stage of the disease. Moreover, the test may be performed on patients at any age.

The measurement of hypocretin-1 in the CSF is invasive, exhibits a low sensitivity in cases without cataplexy, and is available at few institutions. Hypocretin levels lower than 110 pg/ml yield a high diagnostic specificity. The measurement of hypocretin in the CSF is particularly useful for the diagnosis of patients who are taking psychotropic (anti-cataplectic or stimulant) agents that cannot be discontinued, patients with diseases that interfere with the performance of the MSLT, children younger than 8 years of age, or individuals who exhibit difficulties complying with the MSLT instructions.

Actigraphy is a diagnostic technique that allows the performance of a longitudinal assessment of the sleep-wake cycle over several days or weeks [25]. However, its pediatric use has not yet been validated.

DIFFERENTIAL DIAGNOSIS

Investigation of secondary causes of narcolepsy is crucial in children because one-fifth to one-third of cases are symptomatic for diseases such as Niemann-Pick disease type C, Norrie disease, Prader-Willi syndrome, Moebius syndrome, multiple sclerosis, CNS tumors, and brain trauma (particularly involving hypothalamic localization) [14,29].

Among the main differential diagnoses of narcolepsy in children (Table 1), Klein-Levine Syndrome (KLS) is the most prominent. KLS is characterized by recurrent episodes of sleepiness, hyperphagia, mental disorders, and increased serum pro-lactin. These episodes last between 12 hours and 3 or 4 weeks (usually 4 to 7 days), and the intervals between episodes might last months or years. During crises, patients sleep for long periods (18 to 20 hours) and awake (still feeling sleepy) only to eat voraciously. In addition, sexual behavior disorders, aggressiveness, memory disorders, depressive symptoms, and hallucinations might occur. During the intervals between episodes, the patients appear to be fully normal and usually do not have any memory of their crises. SKL is a rare disease that is more frequent among males, and its etiopathogenesis is unknown. SKL must be distinguished from disorders accompanied by intermittent sleepiness (such as third-ventricle tumors, encephalitis, and brain trauma) and from psychiatric disorders.

Circadian rhythm disorders and sleep deprivation represent another important category in the differential diagnosis. Children and adolescents might exhibit marked sleep-rhythm disorders and sleep deprivation; moreover, adolescents with poor sleep hygiene often exhibit an exacerbation of the well-established pattern of physiological phase delay. These patients experience excessive morning sleepiness (due to insufficient sleep) while in the classroom; notably, their symptoms lead to dozing and poor school performance and can be misdiagnosed as narcolepsy. The differential diagnosis is established by collecting detailed information on the adolescents’ sleep schedules, which often requires the use of sleep diaries or actigraphy and the monitoring of their habits and lifestyles [26].

TREATMENT

The treatment of narcolepsy in children is basically symptomatic, and a combination of behavioral and pharmacological approaches is necessary in most cases.

Behavioral treatment

Non-pharmacological therapies for narcolepsy in children are crucial to achieve adequate control of the disease. The chronic nature of narcolepsy, provision of appropriate information to teachers and school coordinators, professional counseling, and explanations regarding the risks associated with driving and performing sports are among the features that must be thoroughly discussed with these patients and their parents. Psychological or psychiatric assistance is often required, particularly for patients who develop depressive symptoms. Furthermore, the establishment of routines that specifically include regular sleep schedules and naps that are scheduled for the periods of marked daytime sleepiness should always be recommended [27].

Possible side effects of chronic medication should be monitored, and these adverse events include the following: the development of tolerance and potential addictions, systemic arterial hypertension, liver dysfunction, and psychiatric symptoms (irritability, nausea, headache, sleeplessness, anorexia, depression, anxiety, mania, and psychosis). Special attention must be paid to the appearance of psychotic symptoms when amphetamines, methylphenidate, or modafinil are used [28].

Pharmacological treatment

No double-blind placebo-controlled trials that target the treatment of narcolepsy in children have been conducted. Stimulants (methylphenidate) and wakefulness enhancers (modafinil) are the first-choice drugs for the treatment of EDS.
Table 1. Differential diagnosis of narcolepsy in children and adolescents.

<table>
<thead>
<tr>
<th>Causes of insufficient sleep</th>
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<tr>
<td>1. Behavioral</td>
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<tr>
<td>2. Sleep onset association disorder</td>
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<td>3. Social adjustment disorder</td>
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<td>4. Lack of limits</td>
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<td>5. Chronic sleep deprivation</td>
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<td>6. Idiopathic sleeplessness (diagnosis of exclusion)</td>
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<td>7. Circadian Rhythm Disorders</td>
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<td>8. Sleep phase delay</td>
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<td>9. Non-24-hour sleep-wake cycle or free-running cycle</td>
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<td>10. Irregular sleep-wake pattern</td>
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<tr>
<td>11. Sleep fragmentation</td>
</tr>
<tr>
<td>12. Behavioral</td>
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<tr>
<td>13. Sleep association disorder</td>
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<tr>
<td>14. Parasomnias</td>
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<tr>
<td>15. Sleep respiratory disorders</td>
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<tr>
<td>16. Other clinical causes</td>
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<tr>
<td>17. Environmental</td>
</tr>
<tr>
<td>18. Increased need of sleep</td>
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<tr>
<td>19. Narcolepsy</td>
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<tr>
<td>20. Occasional or transient hypersomnia</td>
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<tr>
<td>21. Recurrent hypersomnia</td>
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<tr>
<td>22. Depression</td>
</tr>
<tr>
<td>23. Kleine-Levine Syndrome</td>
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<tr>
<td>24. Relation to menstrual cycles</td>
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<tr>
<td>25. Idiopathic hypersomnia</td>
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</tbody>
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Modafinil has only been approved in Northern Hemisphere countries for children who are older than 12 years. Its initial dosage is 100 mg/day to avoid adverse effects such as headache, irritability, and nausea. The dosage must be gradually increased and can be divided into two daily doses. In adults, the average dosage varies between 200 and 400 mg/day. The use of modafinil must be avoided after 14:00h, due to its long half-life of 12-13 hours. Few studies of the use of this drug in children have been conducted.

Currently, modafinil appears to be safe for the treatment of children with narcolepsy; however, certain allergic reactions have been reported. Angioedema, severe skin rashes, and Stevens-Johnson syndrome have been reported, but these adverse effects to modafinil are not frequent and do not differ significantly from their prevalence in the general population. Modafinil must be discontinued at the first sign of a skin rash because children exhibit the highest risk of allergic reactions. Allergic reactions in several organs and systems, including myocarditis, hepatitis, cosinophilia, leukaemia, thrombocytopenia, and asthenia, have also been reported. No clinical markers are available to predict these adverse effects.

Methylphenidate can be used in either immediate-release or controlled-release formulations at a dosage of 0.5-1 mg/kg/day (to a maximum of 60 mg/day) in two or three doses after meals to avoid gastric symptoms.

Low-dose tricyclic agents (amitriptyline, imipramine, clomipramine) or dually selective inhibitors (such as the serotonin reuptake inhibitor venlafaxine with an initial, low dose of 37.5 mg/day) are indicated for the treatment of cataplexy, sleep paralysis, and hypnagogic hallucinations. Selective serotonin reuptake inhibitors (SSRI), such as fluoxetine (10-20 mg/kg), are used in the treatment of cataplexy.

Nocturnal sleep fragmentation seldom occurs in narcoleptic children and can be treated with benzodiazepines (clonazepam, 0.2-0.5 mg/day) and non-benzodiazepine hypnotics (zolpidem, zopiclone, or zaleplon) in children who are older than 12 years, using smaller dosages than those for adults.

Lecendreux et al. treated one 10-year-old narcoleptic child with high doses of an intravenous immunoglobulin, and the patient exhibited a significant improvement during the first months of treatment. A recent study demonstrated that treatment with an immunoglobulin within 9 months of the onset of narcolepsy is efficacious. The low hypocretin-1 levels of patients with narcolepsy and cataplexy indicate an autoimmune condition; thus, early immune intervention might be beneficial. Conversely, treatment with prednisolone did not appear to affect the expression of the disease in an 8-year-old patient. Early treatment might alter the natural course of narcolepsy; however, additional controlled trials of immunosuppressants are necessary to confirm this hypothesis.

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