

Narcolepsy in children

Narkolepsja u dzieci

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ABSTRACT

Narcolepsy is a life-long but non-progressive neurological disorder characterized by excessive daytime sleepiness and increased presence of rapid eye movement (REM) sleep due to loss of hypocretin containing neurons located in the lateral hypothalamus. According to the International Classification of Sleep Disorders, Third Edition (ICSD-3), narcolepsy is typically associated with cataplexy and/or other REM sleep phenomena such as hypnagogic or hypnopompic hallucinations and sleep paralysis. Narcolepsy is not an uncommon disorder, but is under-recognized. The age of onset shows two peaks of presentation: in childhood and in adults. Both genetics and environmental factors may be involved in the development of narcolepsy. The history, combined with polysomnography and MSLT, remain the current gold standard in the diagnosis of narcolepsy. The levels of Hypocretin-1 are undetectable in the cerebrospinal fluid in most patients with narcolepsy with cataplexy. Early recognition and treatment can greatly improve the quality of life of patients with narcolepsy. Treatment of narcolepsy includes non-pharmacological treatment (life style changes) and pharmacological (stimulants, modafinil, sodium oxybate) against hypersomnia and anticataplectic drugs (antidepressants and sodium oxybate).

Key words: sleep, narcolepsy, cataplexy, sleepiness, children

STRESZCZENIE

Narkolepsja jest przewlekłą, niepostępującą chorobą neurologiczną charakteryzującą się nadmierną sennością w ciągu dnia oraz objawami związanymi ze zwiększeniem ilości snu z szybkim ruchem gałek ocznych (REM), spowodowaną utratą neuronów hipokretynowych zlokalizowanych w bocznej części podwzgórza. Zgodnie z Międzynarodową Klasyfikacją Zaburzeń Snu – wersją trzecią (ICSD-3) narkolepsja typowo jest skojarzona z katapleksją i/lub innymi zjawiskami związanymi ze snem REM takimi jak halucynacje hipnagogiczne i hipnopompiczne czy paraliż przysenny. Narkolepsja nie jest rzadką chorobą, często nie jest jednak rozpoznawana. Obserwowane są dwa szczyty zachorowania: w dzieciństwie i w wieku dorosłym. W etiopatogenezie narkolepsji mają znaczenie zarówno czynniki genetyczne, jak i środowiskowe. W diagnostyce narkolepsji największe znaczenie ma wywiad, a test wielokrotnej latencji snu (MSLT) poprzedzony całonocną polisomnografią uznawany jest za złoty standard w diagnostyce narkolepsji. Poziom hipokretyny-1 w płynie mózgowo-rdzeniowym u większości pacjentów z narkolepsją z katapleksją jest nieoznaczalny. Wczesne rozpoznanie i leczenie może wpłynąć znacząco na poprawę jakości życia pacjentów z narkolepsją. W leczeniu bierze się pod uwagę interwencje nefarmakologiczne (modyfikacje stylu życia) oraz farmakologiczne: stymulanty, modafinil, hydroksymaślan sodu w leczeniu nadmiernej senności oraz antydepresanty i hydroksymaślan sodu w leczeniu katapleksji.

Słowa kluczowe: sen, narkolepsja, katapleksja, senność, dzieci

INTRODUCTION

Narcolepsy is a life-long but non-progressive neurological disorder characterized by excessive daytime sleepiness and increased presence of rapid eye movement (REM) sleep due to loss of hypocretin containing neurons located in the lateral hypothalamus. According to the International Classification of Sleep Disorders, Third Edition (ICSD-3), narcolepsy is typically associated with cataplexy and/or other REM sleep phenomena such as hypnagogic or hypnopompic hallucinations and sleep paralysis [1]. People with narcolepsy usually have a sudden onset of irresistible sleep attacks during the day [2,3]. These sleep attacks are usually longer in children than in adults [4]. Cataplexy is characterized by sudden onset of bilateral muscle weakness often precipitated by emotions.

[3]. Dream-like hallucinations are termed hypnagogic when they occur at the sleep onset, and hypnopompic at awakening from sleep. Sleep paralysis is characterized by inability to move on waking for seconds to minutes. [3].

Narcolepsy was first time described in 1877 by Karl Friedrich Otto Westphal (1833–1890). He had two cases that he presented at a Berlin Medical and Psychological Society meeting in 1877 that were then published in the Archives of Psychiatry and Nervous Disorders [5]. In 1880 the French Physician Jean-Baptiste-Edouard Gelineau (1828–1906) described the syndrome characterized by an imperative need to sleep suddenly and for brief periods, recurring at more or less close intervals, and first coined this

syndrome 'narcolepsie' [5, 6]. In 1934, Daniels published a review and emphasized the associations of excessive daytime sleepiness, cataplexy, hypnagogic hallucinations, and sleep paralysis [7]. That review is considered as one of the most insightful clinical masterpiece published to this date [8]. In 1957, Yoss and Daly called these symptoms „the clinical tetrad” [9]. In the 1950s and 1960s, the duality of sleep with rapid eye movement (REM) and non-REM sleep was recognized in normal people and sleep-onset REM was described in patients with narcolepsy [10].

Symptoms of narcolepsy typically start in childhood and young adults. Retrospective studies suggest that about half of the adults with narcolepsy had the onset of symptoms much earlier in their youth [4, 11]. The clinical severity of narcolepsy on the other hand does not depend on the age at onset [12]. The Ohayon study confirmed peak frequency of the first symptom of narcolepsy between 15 and 19 years of age for daytime sleepiness and cataplexy [11]. A clinic based study of narcoleptics in Quebec and France suggested a bimodal pattern of age of onset with a larger peak in the second decade and a smaller peak in the fourth decade [13]. Most studies suggest that Narcolepsy is more common in men as compared to women independent of age of onset [14–16]. Other case-based series have also suggested a male predominance [7, 13]. Narcolepsy has a estimated prevalence of 0.047% (from 0.05 to 0.02%), based on representative sample of five European countries in the general population using the minimal set of criteria proposed by the ICSD [15]. The Jewish population is known for its low prevalence of narcolepsy [17, 18] and an Israeli study found a prevalence at 0.00023% [19]. The study performed in Japan recorded the highest reported figure from 0.16% to 0.59% [20, 21]. Narcolepsy is not an uncommon disorder, but is one of the most often under-recognized and under-diagnosed diseases.

Both genetics and environmental factors may be involved in the development of narcolepsy. Contribution of environmental factors in the development of narcolepsy has now been well documented [22, 23].

The risk of narcolepsy in first-degree relatives is 1–2%, compared to 0.02–0.18% in the general population [22–26]. Nevertheless, genetics plays only a partial influence; even among monozygotic twins in which one has narcolepsy, the second twin is affected only approximately 25–31% of the time [27–31].

Narcolepsy has the highest human leukocyte antigens (HLA) association among all medical diseases, with the association of haplotype DRB1*1501, DQA1*0102, DQB1*0602 being the most prominent. This association varies with ethnicity; DR2 is found in 100% of Japanese, 90 to 95% of whites, and 60% of African American narcoleptic subjects with cataplexy [22, 32]. DQB1*0602 is found in 88 to 98% of narcoleptic subjects with unambiguous cataplexy, whereas it is found in only 12% of white American and 38% of African American controls [33, 34]. This allele is found in only 40% of narcolepsy without cataplexy [28].

Narcolepsy has been characterized as a disease of the REM sleep mechanism. In 1998, two independent groups

of investigators simultaneously discovered a pair of closely related neuropeptides that may provide a stabilizing influence needed to help regulation of sleep and waking [35–37]. One group named this peptide hypocretin for its presumed role in appetite whereas another group named them orexin for its possible resemblance to secretin [36, 37]. Hypocretins are synthesized in the lateral hypothalamus exclusively. The single protein precursor named pre-pro-hypocretin is enzymatically cleaved into two peptides, with high homology with each other, namely, hypocretin 1 and 2 (orexin A and B). There are two cloned hypocretin receptors, HCRT1 and HCRT2, both of which are serpentine G-protein coupled receptors. In 1999, groups of investigators found that a lack of hypocretins or their type 2 receptor can cause symptoms of narcolepsy in experimental animals [38,39]. High amplitude theta activity in the hippocampus, characteristic of REM sleep, was also prominent during cataplexy as observed in dogs [40, 41]. In 2001, it was reported that humans who have narcolepsy with cataplexy have few hypocretin neurons in the posterolateral hypothalamus, and levels of Hct-1 were undetectable in the cerebrospinal fluid (CSF) in most patients with narcolepsy with cataplexy [35,42–45]. Approximately 90% of narcoleptic subjects with cataplexy have no detectable Hct-1 in their CSF even within a few months of symptom onset [45–50]. Levels of Hct-1 < 110 pg/mL have been shown to be diagnostic of narcolepsy, while levels above 200 pg/mL are considered normal. Low CSF Hct-1 is thus highly specific (99.1%) and sensitive (88.5%) for narcolepsy with cataplexy [48]. An undetectable Hct-1 level in CSF is one of the most important diagnostic features of narcolepsy/cataplexy in children as well [46, 51, 52].

The combination of HLA antigens and hypocretin neuron loss (hypocretin deficiency) strongly points towards an autoimmune etiology. Streptococcal infections may initiate or catalyze an autoimmune response against hypocretin cells in narcolepsy [53, 54]. Post-streptococcal diseases have also been linked to brain autoimmune diseases, most notably Sydenham chorea, obsessive-compulsive disorder, and tics [55]. Recently, its autoimmune etiology was proved in narcolepsy and streptococcal infection as a trigger point of the disease was discovered [56]. However studies have shown an association to seasonal influenza, and more recently pandemic A/H1N1 2009 influenza vaccination [54, 57–60]. The recent study of Aran et al suggest that selective streptococcal infections may lead to the destruction of hypocretin neurons via molecular mimicry or super-antigen interactions with the HLA-TCR complex [53]. Thus, the autoimmune hypothesis provides a rationale for the initiation of immune-modulating therapies near disease onset in an attempt to prevent the progression of cell-loss and induce a long-lasting improvement [61–68]. If the autoimmune role in the development of narcolepsy is confirmed to be true, effective immunosuppressive therapy should be initiated at the earliest, and continued in an ongoing manner to prevent recurrence, as done in other autoimmune diseases [4, 54]. It is unclear whether this antibody mediated or cell-mediated.

CLINICAL FEATURES

The classic tetrad of narcolepsy consists of excessive daytime sleepiness, cataplexy, hypnagogic/hypnopompic hallucinations, and sleep paralysis [69]. In addition, sleep fragmentation has been recognized as a fifth but commonly present criterion in the diagnosis of narcolepsy [2]. The initial and sole manifestation of narcolepsy usually is hypersomnia followed by development of other symptoms months to years later [42,70–75].

Narcolepsy type 1 (narcolepsy with cataplexy) is highly likely in a patient with symptoms of chronic, excessive daytime sleepiness and cataplexy, since all patients with narcolepsy have chronic daytime sleepiness and cataplexy occurs in almost no other disorder. Narcolepsy type 2 (narcolepsy without cataplexy) is more difficult to diagnose because sleepiness can occur with a variety of sleep disorders, and hypnagogic hallucinations and sleep paralysis can occur with any condition that increases REM sleep pressure [1].

The diagnosis of narcolepsy type 1 requires both of the following:

1. Daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for at least three months.
2. One or both of the following:
 - Cataplexy and a mean sleep latency of ≤ 8 minutes and two or more sleep onset REM periods (SOREMPs) on a multiple sleep latency test (MSLT) performed using standard techniques. A SOREMP (within 15 minutes of sleep onset) on the preceding nocturnal polysomnogram may replace one of the SOREMPs on the MSLT.
 - CSF hypocretin-1 concentration, measured by immunoreactivity, is either up to 110 picograms/mL or $< 1/3$ of mean values obtained in normal subjects with the same standardized assay [1].

If there is clinical suspicion for narcolepsy type 2 in a patient with chronic daytime sleepiness, the diagnosis should be confirmed with:

1. The patient has daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for at least three months.
2. A mean sleep latency of ≤ 8 minutes and two or more SOREMPs on a MSLT. A SOREMP on the preceding nocturnal PSG may replace one of the SOREMPs on the MSLT.
3. Cataplexy is absent.
4. Either CSF hypocretin-1 concentration has not been measured or CSF hypocretin-1 concentration measured by immunoreactivity is > 110 picograms/mL or $> 1/3$ of mean values obtained in normal subjects with the same standardized assay.

EXCESSIVE DAYTIME SLEEPINESS

Hypersomnia usually begins with excessive daytime sleepiness and unintentional naps in the teens and early twenties [72, 73]. Sleepiness occurs regardless of the quantity of noc-

turnal sleep and is typically worse in sedentary and boring situations. The duration of the nap may vary from a few minutes to over an hour [3]. Such sleep episodes are refreshing on awakening [76]. Patients usually report dream content during these short naps [42]. During daytime, with “REM sleep intrusion”, patients can suddenly feel overwhelmingly tired and appear transiently “unaware” of their surroundings [2,70]. It may be subtle and manifest simply as difficulty getting out of bed in the morning to sudden, usually brief (10–20 min) sleep attacks during conversations, etc. [42, 77].

Disrupted nighttime sleep is common in narcolepsy and may partially contribute to excessive daytime sleepiness [42]. The inability to maintain night sleep coupled with excessive daytime sleepiness can be very frustrating to patients and family members [42]. Narcoleptic patients with the greatest sleep disturbance have more severe daytime sleepiness, but even those with good nighttime sleep also have substantial daytime sleepiness [78].

CATAPLEXY

Cataplexy is the sudden muscle weakness brought on by strong emotions, particularly joking, laughter, or anger [3, 4, 79]. Most commonly, cataplexy is caused by laughter or humorous experiences, although sometimes even the memory of a humorous event can precipitate a cataplectic attack [3, 80–83]. Cataplexy is a unique feature of narcolepsy [71, 76, 84]. The frequency of cataplexy ranges from one or two episodes per year up to dozens of episodes per day. Cataplexy occurs in 60–90% of patients with narcolepsy, and its onset follows the onset of excessive daytime sleepiness by several months to 5 years [14, 72, 73, 85]. The duration of each cataplectic episode usually range from a few seconds to 2 minutes and rarely up to 30 minutes [3]. Cataplexy represents appearance of REM sleep atonia during wakefulness [42] and is associated with an inhibition of monosynaptic H-reflexes and of the multi-synaptic tendon reflexes [3]. Severe episodes of cataplexy produce bilateral, generalized weakness sufficient to cause a fall, although usually without injury [79]. Attacks of cataplexy may be confused with atonic seizures (drop attacks), especially in children under the age of 5 years [3, 76]. More commonly, attacks of cataplexy are partial, affecting only certain muscle groups, namely neck or face [81]. During partial cataplexy attacks, the jaw may sag, the head may drop forward and speech becomes garbled [85]. “Cataplectic facies” appearing close to disease onset predated typical cataplexy triggered by emotions in some patients and in fact has been confused with sleepiness [84, 86, 87]. These abnormalities are associated with some ‘active’ movements from peri-oral to dyskinetic-dystonic movements even with stereotypic [88]. In some rare cases, symptoms of cataplexy can be seen during the course of some inherited diseases (such as Niemann-Pick disease, type C (NPC), Prader-Willi syndrome (PWS), myotonic dystrophy), Norrie disease [89–93].

Sleep paralysis and hypnagogic/hypnopompic hallucinations:

Sleep paralyzes are brief episodes of an inability to move, occurring during awakening or upon falling asleep [3, 76].

Sleep paralysis occurs due to persistence of REM sleep atonia after awakening [42]. Episodes are more common in the first two hours of night sleep and tend to occur more often again in the morning hours [94]. The prevalence of sleep paralysis in narcoleptic patients is around 25% (from 17% to 66%) [9, 95, 96]. The children are fully aware of this state and able to recall the event which usually lasts seconds to minutes and end spontaneously or, sometimes, after sensory stimulation [42, 96]. Fifty percent of the episodes can be associated with hypnagogic or hypnopompic hallucinations [96]. Children are often reluctant to talk about these events [97].

Hypnagogic/hypnopompic hallucinations occur in approximately 60% of patients with narcolepsy [14, 98]. These are typically very vivid visual, auditory dreams or out-of-body experiences and are usually frightening [85, 99]. Hypnagogic/hypnopompic hallucinations are exacerbated by fatigue and emotion, often associated with sleep paralysis or cataplexy.

Sleep paralysis and hypnagogic/hypnopompic hallucinations do not affect all patients with narcolepsy and can be transitory.

Additional symptoms:

Disrupted nighttime sleep may be seen in association with difficulty in falling asleep, and the patients may be misdiagnosed as having insomnia [74]. Frequent awakenings are also described, possibly associated with periodic limb movements [69]. Sleep terrors, frequent nightmares, and bruxism can be seen in patients with narcolepsy [99, 100]. Some studies in narcoleptic patients suggest abnormalities in REM sleep motor regulation, with an increased frequency of REM sleep without atonia, and PLMS, when compared to controls [101]. The presence of REM sleep without atonia associated with prominent motor behavioral manifestations associated with dreaming during REM sleep is the key feature of a condition called REM sleep behavior disorder (RBD) [2].

Depression has also been reported in 30–50% of narcoleptic patients [100, 102, 103]. It must be borne in mind that mood disorders may also be masked by antidepressant therapy used to treat symptoms of the disease [104].

Obesity is very common in narcolepsy, but often overlooked [72, 105]. In children, the weight gain occurs quickly and suddenly after the onset of other symptoms of narcolepsy [4, 106, 107]. These patients have been found to have significantly greater body mass index (BMI) across various ethnic groups and cultural backgrounds [72]. Changes in eating behavior, leptin modulation, and lower basal metabolism may explain the positive energy balance [105, 108].

Because of the increased weight, obstructive sleep apnea is a frequent co-existing disorder with narcolepsy with prevalence ranging from 9.8–19% on polysomnographic studies [78, 109]. Children suffering from headaches were noted to have a higher prevalence of excessive daytime sleepiness, narcolepsy, and insomnia than children without headaches [110]. The prevalence of migraine in narcoleptic patients is also increased [111, 112].

Diagnosis of narcolepsy.

Evaluation of children with narcolepsy may require assessment by a sleep physician in a pediatric sleep disorder center. The diagnosis of narcolepsy is not easy and specific diagnostic tools should be used. A detailed sleep history is crucial in evaluating patients with EDS. The history, combined with polysomnography (PSG) and multiple sleep latency test (MSLT), remain the current gold standard in the diagnosis of narcolepsy [42, 113]. Sleep logs give an estimate of the number, duration, and timing of daily episodes of nocturnal sleep, daytime naps, and wake periods. They are frequently used before the PSG and MSLT and may reveal evidence of chronically insufficient sleep [114].

Subjective measures of EDS consist of validated scales for quantifying sleepiness. Three clinical sleep scales have been used to assess sleepiness: Stanford Sleepiness Scale (SSS) [115], Epworth Sleepiness Scale (ESS) [116], and Pediatric Daytime Sleepiness Scale (PDSS) [117]. PDSS is a recently introduced validated measure for assessing sleepiness in children [117]. SSS and ESS are 2 extensively used sleep scales used to assess sleepiness in adults.

PSG and MSLT

At least two weeks prior to these studies, all central nervous stimulants, sedative-hypnotics, and antidepressants should be discontinued so as not to adversely affect the results [42, 113]. This overnight study with sleep efficiency over 75% is followed the next day by the multiple sleep latency test (MSLT) in which a patient is given four or five opportunities to nap every 2 hours to assess the degree of sleepiness and timing of REM sleep onset [118]. Overnight polygraphic sleep records also exclude parasomnias as a cause of fragmented and non-restorative nocturnal sleep and/or verify REM behavior disorder as one of the possible symptoms of narcolepsy [4, 119]. Nocturnal PSG is also obtained to rule out other sleep disturbances such as sleep-disorder breathing and periodic limb movements of sleep [120]. The polysomnogram should confirm sufficiently long nocturnal sleep (at least 6 h) with the possible presence of a short REM sleep latency [3]. A SOREMP on the preceding nocturnal polysomnogram may replace one of the SOREMPs on the MSLT [1]. The PSG may demonstrate frequent arousals and wakefulness after sleep onset [42].

Details of the protocol have been recently described [76, 113]. On the basis of polysomnographic recording, REM sleep which occurring within 15 minutes of sleep onset is considered a sleep onset REM period (SOREMP) [113, 121]. The mean sleep latency (MSL; arithmetic mean of sleep onset of all naps) is an index of severity of sleepiness [76]. MSL scores under 8 minutes are generally considered to be in the pathological sleepiness range; those over 10 minutes are considered normal in adults [3]. Patients with narcolepsy usually have MSL of less than 8 minutes, whereas healthy children show an MSL of 15 to 20 minutes [113].

The naps of narcoleptic patients often include REM sleep [22], and the occurrence of these sleep-onset REM periods (SOREMPs) in two or more naps is highly sugges-

tive of narcolepsy [2, 113, 121, 122]. The combination of two sleep-onset REM periods and an MSL of less than 5 min are estimated to have a sensitivity of 70% but a specificity of 97% for narcolepsy [113, 121, 122].

Limitations of the MSLT in children are the lack of normative data in this population, the last nap effect (increased arousal because of the anticipation of going home on completion of this extensive testing), and motivation (to remain awake or attempt to sleep) [120].

MWT

The Maintenance of Wakefulness Test (MWT) is indicated to assess the efficacy of treatment in patients with narcolepsy. MWT, the mirror image of the MSLT, is a validated objective measure of the ability to stay awake for a defined time [123]. Motivation of the patient to stay awake is the key for the interpretation of the results [113]. The MWT consists of 4 trials performed at 2-hour intervals, with the first trial beginning about 1.5 to 3 hours after the patient's usual wakeup time, each lasting 40 minutes [113]. Details of the protocol have been recently described [113]. Normal values of MWT are more than 30 minutes, whereas the test is considered abnormal when it is less than 10 minutes [113, 121, 124]. Pediatric normative values are not available [124].

Hypocretin-1 CSF level

Laboratory tests such as cerebrospinal fluid (CSF) hypocretin-1 analysis and human leukocyte antigen (HLA) typing are useful but at present are not considered mandatory for a diagnosis of narcolepsy [76, 125].

CSF Hcr-1 testing should be considered in the following situations, when MSLT is difficult to conduct or to interpret in complex cases, and in children [76]: (1) equivocal MSLT results; (2) children younger than 8 years; (3) individuals taking psychotropic medications (e.g. anti-cataplexy agents or stimulants); (4) individuals who cannot afford formal sleep testing; and (5) individuals with severe or complex psychiatric, neurological, or medical disorders which could compromise the validity of the MSLT results [42, 126].

HLA typing

HLA typing has been recommended as an adjuvant test for patients with narcolepsy [127]. Its sensitivity is highest in patients with narcolepsy and cataplexy [42]. The presence of the DQB1*0602 haplotype makes the diagnostic probability of narcolepsy much more likely, though DQB1*0602 negativity does not exclude it. [128]. Twenty five percent of the normal population has a positive DQB1*0602 haplotype.

TREATMENT

Undoubtedly, narcolepsy is a lifelong disabling disorder [3]. At present, there is no cure for narcolepsy, with resultant significant impairment in the quality of life. For most patients, chronic sleepiness is the most disabling symptom [79]. Once symptoms of narcolepsy are established, treatment is generally required [75]. Individuals with EDS experience impaired alertness and decrements in performance across many areas of life [129–131]. Therefore, treatment should be individualized based on the severity of symptoms

[132]. According to generally accepted opinion, there is no specific treatment for narcolepsy in children in comparison with adults [4, 97, 133]. Current management of narcolepsy involves a combination of behavioral and pharmacologic therapies [75].

Behavioral intervention

Lifestyle changes are however rarely sufficient to adequately control the symptoms of narcolepsy and, therefore, in most patients, must be combined with pharmacological management to optimally control the daytime sleepiness [42, 132].

Some non-pharmacological interventions can enhance the therapeutic effect such as regular sleep wake schedules and planned naps [4]. Good sleep habits, the avoidance of sleep deprivation and/or irregular sleep patterns, are important for many patients. Two 15-minute daytime naps can temporarily reduce sleepiness and improve alertness, especially in patients with more severe sleepiness; however these attacks returns after a few hours of remaining awake [42, 134, 135]. Maintaining a consistent sleep–wake schedule, and time for exercise in the morning can help control EDS [3, 42, 75]. The combination of scheduled naps and regular nocturnal sleep times produced significant reduction in severity of sleepiness and duration of daytime sleep in treated narcoleptics [136].

Dietary modification can also help in maintaining wakefulness [42]. Foods high in refined sugars and carbohydrates tend to produce more EDS [42]. Caffeine in sodas and coffee can serve as a stimulant. In older children and adults 400–600 mg of caffeine (3–4 cups of coffee) is needed for an effect [42]. Meals at scheduled times, avoidance of alcohol and certain types of food is also recommended [137].

Pharmacological Treatment

The main goal of pharmacologic treatment for narcolepsy is to keep the patient alert during the day and reduce episodes of cataplexy while also minimizing the incidence of undesirable side effects and adverse events [132]. Recent practice parameters generated by the American Academy of Sleep Medicine and European Federation of Neurological Societies address the pharmacologic options available for treatment of sleepiness caused by narcolepsy using an evidence-based approach [138].

Daytime sleepiness

Several medications are available for treating daytime sleepiness in narcolepsy patients.

Psychostimulants

Methylphenidate is a dopamine and catecholamine reuptake inhibitor, thereby increasing the amount of these neurotransmitters in the synaptic cleft [42]. There was a study showing significant improvement in dosages of 10, 30, and 60 mg/day compared with the baseline [139]. In children, the American Academy of Child and Adolescent Psychiatry (AACAP) recommends that treatment with methylphenidate be initiated with 5 mg dosed in the morning and a second dose at around noon due to its short half-life with upward titration by 5–10 mg/day at weekly intervals up to maximum total dose of 60 mg/day [104, 140]. It does have some

anti-cataplectic action too. Methylphenidate showed good to excellent response in 68% [30] of cases and mild to moderate improvement in 90% of cases [104]. Methylphenidate is not registered for treatment of narcolepsy in Poland, so must be used off label.

The dextroamphetamine and methamphetamine are effective treatments of excessive daytime sleepiness in short-term use (up to 4 weeks) at starting doses of 15–20 mg increasing up to 60 mg/day [141–143]. There is no evidence of abuse and addiction in narcoleptic patients [144]. At low doses the main effect of amphetamine is to release dopamine and to a lesser extent norepinephrine and serotonin [104]. This increased aminergic signaling may promote wakefulness through direct effects on the cortex or via activation of subcortical pathways [79]. Amphetamines also weakly inhibit monoamine oxidase (MAO) [132]. Due to its sympathomimetic effects, dextroamphetamine can also reduce the frequency of cataplexy [42]. The safety of dextroamphetamine in children below 6 years has not been established [42]. These therapeutic agents are not available in Poland.

Selegiline hydrochloride

Selegiline is an irreversible MAO-B inhibitor (in dosages of up to 20 mg/day) which is metabolized to amphetamine and methylamphetamine, however above this dosage, the drug starts to lose its selectivity [145]. Selegiline 10 ± 40 mg/day has produced statistically and clinically significant improvement in narcoleptic symptoms and polysomnographic measures in patients with narcolepsy [16, 146–148].

Modafinil and Armodafinil

Modafinil is regarded as the first-line medication for the treatment of excessive sleepiness in narcolepsy [132]. Modafinil is a unique, non-amphetamine wake-promoting drug that effectively treats sleepiness with a minimum of side effects [79].

Modafinil does not reduce cataplexy, and additional anticataplexy medications may be needed [79]. Starting dose of modafinil in adults is 100 mg in the morning, escalated as needed within a few days up to 200 mg [42]. Modafinil has an elimination half-life of 9–14 h, permitting once-daily administration for most patients [132]. Modafinil use has decreased sleep attacks in up to 71% of narcolepsy patients in clinical trials [149–152].

Armodafinil is a combination of R-modafinil and S-modafinil. R-modafinil is a longer acting isomer of modafinil with a half-life of 10–14 h, whereas S-modafinil has a half-life of 3–4 h. Armodafinil has a T_{max} of 2 h and a half-life of approximately 15 h. This drug has been shown to be effective and produces longer wakefulness than modafinil in patients with sleepiness due to acute sleep loss [132, 153, 154]. The modafinil group of drugs is not available in Poland.

Sodium Oxybate

Sodium oxybate is the sodium salt of gamma-hydroxybutyrate (GHB) [132]. Sodium oxybate induced sleep that closely resembled natural sleep and was initially used as an anaesthetic agent, as it induced a level of unconsciousness

that was acceptable for some surgical procedures [155–157]. The drug is only available in liquid form and must be taken twice a night to induce sleep [42, 104]. The administration of sodium oxybate at bedtime was found to reduce nocturnal awakenings, increase N3 (delta or slow wave) sleep and consolidate REM sleep [158, 159]. GHB reduced subjective daytime sleepiness and the number of hypnagogic hallucinations and daytime naps [160]. It is important to note that sodium oxybate improves both daytime sleepiness and cataplexy [42]. The exact mechanism by which sodium oxybate reduces cataplexy is unclear. This therapeutic agent is not available in Poland.

Cataplexy

While EDS can often be managed with stimulants, these medications often do not provide significant relief from cataplexy [132]. Most patients with narcolepsy do not require treatment of their cataplexy because it is mild or infrequent, but in some patients, cataplexy occurs several times each day, producing embarrassment or even injury [79]. In these patients, the additional medications with anticataplectic activity must be used to reduce the frequency and severity of cataplexy [132].

Tricyclic antidepressants (TCA), have been used successfully to treat cataplexy for many years, but more recently selective serotonin reuptake inhibitors (SSRI), have been used [75]. Tricyclic antidepressants form the first line of medication widely available for the treatment of cataplexy [161]. Clomipramine doses of 10–75 mg daily are generally effective for cataplexy [162, 163]. Because of their anticholinergic activity, antidepressants also tend to suppress hypnagogic hallucinations and sleep paralysis [42]. Serotonin-specific reuptake inhibitors are effective, but higher doses than those for tricyclic drugs are often needed [79, 81, 85, 164, 165]. The dual norepinephrine and serotonin reuptake inhibitor venlafaxine is also effective against cataplexy [164, 166, 167]. Recently, sodium oxybate was approved for use in the United States and Europe for consolidating sleep in patients with narcolepsy, and also improve cataplexy.

FUTURE DIRECTIONS

Despite major advances in our understanding of the neurobiological basis of narcolepsy, current treatment protocols all respond to specific symptoms but are not effective enough against the disease as a whole [126].

The replacement therapy for hypocretin deficiency remains the most logical approach for treating narcolepsy [161]. Such manipulations are effective when administered centrally in hypocretin-deficient mouse models [168]. In humans, part of the problem is getting hypocretin into the brain [161]. The peripheral administration has been disappointing, since the peptides do not cross the blood brain-barrier [166,167]. An intranasal delivery method looks promising [169]. Hypocretin-based therapies such as direct use of hypocretin agonists are currently under investigation in animal models [126]. Cell transplantation [170–172] and gene therapy [168] have also been examined in animal models too.

Based on the autoimmune hypothesis of narcolepsy, treatments such as intravenous immunoglobulins and plasmapheresis have shown promising results in a few cases, which need to be confirmed in larger series [65, 66, 173]. Steroid and immunosuppressive treatment in dogs with narcolepsy more than doubled the time to cataplexy onset, and the time spent in cataplexy was reduced by more than 90% [62]. A limitation of immunosuppressive treatments, however, will be the need to intervene at disease onset [126]. In some studies, steroids, plasma exchange, and immunoglobulins have been given without clear benefit [63, 66, 173]. Immunoglobulins generated the most interest as some reported improvements in narcolepsy symptoms. Use of intravenous immunoglobulin (IVIg) in one series resulted in improvement of cataplexy especially in the three patients who had the shortest time from onset of symptoms but sleepiness persisted [65, 67]. However, the improvement was more transient than sustained [66]. Other medication groups like rituximab may be more effective in recent studies.

The histamine receptor has also been a target of different manipulations, as the drowsiness effects of antihistamine agents are well known [161]. Histamine 3 (H3) receptors regulate the release and synthesis of histamine. Stimulation of the H3 receptors causes sedation, whereas antagonism causes wakefulness [174]. H3 antagonists have been shown to be effective on sleepiness and cataplexy in canines and in mice with ablation of hypocretin neurons (orexin/ataxin-3) [175].

Thyrotrophin-releasing hormone (TRH) and TRH agonists have alerting properties [176, 177]. TRH is excitatory on neurons and enhances dopamine and adrenergic transmission, and may promote wakefulness by direct effect on thalamocortical pathways [176, 178]. TRH has been shown

to have anticataplectic activity in the narcoleptic canine [176]. Inhibition of the TRH-degrading enzyme inhibitor, metallopeptidase, may be a promising treatment in the future.

CONCLUSION

Despite significant advances in understanding the pathophysiology of narcolepsy, we do not have an ideal treatment regimen to completely restore full and sustained alertness across the day. Early recognition and institution of effective therapy are keys to improving quality of life especially in the early formative years. When evaluating children with hypersomnia, a thorough and detailed history is essential to elucidate signs that maybe associated with narcolepsy. Physicians should be aware that children may not experience the classic initial manifestations of narcolepsy, and young patients should be referred for a comprehensive sleep evaluation. Polysomnography followed by multiple sleep latency testing should be obtained, allowing for the definitive diagnosis of narcolepsy.

Currently, a number of different drug therapies are available for the treatment of the symptoms of narcolepsy. Modafinil and sodium oxybate have shown strong evidence of improvement in daytime alertness and their combination appears to offer additional benefits. Sodium oxybate has demonstrated additional efficacy for the treatment of cataplexy. Other agents such as antidepressants of the TCA and SSRI classes are often effective but must be used in combination with hypnotic and stimulant medications if insomnia and/or EDS are co-existent symptoms. Treatment approaches should be directed toward development of more effective and better tolerated therapies, and primary prevention.

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