RIVIEW ARTICLE

NARCOLEPSY

NARKOLEPSJA

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ABSTRACT
Narcolepsy is a life-long neurological, rapid eye movement (REM) sleep disorder. Most frequent symptoms involve excessive daytime sleepiness, cataplexy, hypnagogic hallucinations, sleep paralysis, and disrupted night-time sleep. The estimated prevalence of narcolepsy is 0.05%. Initial symptoms usually start in childhood and young adults. Diagnosis of narcolepsy is often problematic, and it can take up to 20 years between the first observed excessive sleepiness and a fully developed disorder. Both genetic and environmental contribute to narcolepsy onset. A very strong association was observed in the case of human leukocyte DQ antigens, especially DQB1_0602. We distinguish narcolepsy type 1 and 2. Diagnosis of both types is based on the patient's history, confirmed by multiple sleep latency test (MLST) with preceding polysomnography (PSG). Highly specific findings in these examinations are SOREMPs – occurrence of REM period within 15 minutes after falling asleep. In narcolepsy type 1 cataplexy is present, and CSF hypocretin-1 concentration is undetectable as opposed to narcolepsy type 2. Early diagnosis and implemented treatment can significantly improve the quality of life of patients with narcolepsy. Non-pharmacological treatment such as good sleep habits and daytime naps play an important role in better symptom control. Pharmacological treatment helps to overcome hypersomnia and cataplexy. This review includes the most important clinical features of narcolepsy.

Keywords: sleep, cataplexy, excessive daytime sleepiness, MSLT, narcolepsy

STRESZCZENIE
Narkolepsja to trwające całe życie neurologiczne zaburzenie snu związane z szybkimi ruchami gałek ocznych (REM). Najczęstsze objawy obejmują nadmierną senność w ciągu dnia, kataplepsję, halucynacje hipnagogiczne, paraliż senny i zaburzenia snu w nocy. Szacunkowa częstość występowania narkolepsji wynosi 0.05%. Początkowe objawy zwykle pojawiają się w dzieciństwie i młodych dorosłych. Rozpoznanie narkolepsji jest często problematyczne, a od pierwszej zaobserwowanej nadmiernej senności do w pełni rozwiniętego zaburzenia może minąć nawet 20 lat. Do wystąpienia narkolepsji przyczyniają się zarówno czynniki genetyczne, jak i środowiskowe. Bardzo silny związek zaobserwowano w przypadku antygenów DQ leukocytów ludzkich, zwłaszcza DQB1_0602. Wyróżniamy narkolepsję typu 1 i 2. Rozpoznanie obu typów opiera się na historii choroby pacjenta, potwierdzonej testem wielu latencji snu (MLST) z poprzedzającą polisomnografią (PSG). Wysoce specyficznymi wynikami

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tych badań są SOREMP – wystąpienie fazy REM w ciągu 15 minut po zaśnięciu. W narkolepsji typu 1 występuje katapleksja, a stężenie hipokretyny-1 w płynie mózgowo-rdzeniowym jest niewykrywalne w przeciwieństwie do narkolepsji typu 2. Wczesne rozpoznanie i wdrożone leczenie może znacząco poprawić jakość życia pacjentów z narkolepsją. Leczenie niefarmakologiczne, takie jak dobre nawyki dotyczące snu i drzemki w ciągu dnia, odgrywa ważną rolę w lepszej kontroli objawów. Leczenie farmakologiczne pomaga przezwyciężyć hipersomnię i katapleksję. Przegląd opisuje najważniejsze kliniczne cechy narkolepsji.

Słowa kluczowe: sen, katapleksja, nadmierna senność w ciągu dnia, MSLT, narkolepsja

Introduction

In 1880, the French Physician Jean-Baptiste-Edouard Gélineau (1828–1906) described a 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' (Gélineau, 1880). In 1934 Daniels published a review in which he emphasized main symptoms, currently called 'the clinical tetrad' (Daniels, 1934). Thirty years later, 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 (Vogel, 1960).

Narcolepsy is a life-long neurological, rapid eye movement (REM) sleep disorder characterized by excessive daytime sleepiness and abnormal sleep-wake cycle regulation. Classic clinical tetrad includes excessive daytime sleepiness, cataplexy, hypnagogic hallucinations, and sleep paralysis. Historical classification distinguished narcolepsy with and without cataplexy. Thanks to increasing understanding of narcolepsy in the International Classification of Sleep Disorders, third edition (ICSD-3) classification has changed. Currently, we recognized narcolepsy types 1 and 2. In both types there are daytime sleepiness and REM sleep phenomena such as hypnagogic or hypnopompic hallucinations and sleep paralysis. Hallmarks of narcolepsy type 1 are decreased level of hypocretin-1 (orexin-A) in cerebrospinal fluid and the presence of cataplexy. In narcolepsy type 2 cataplexy is not present, and hypocretin-1 concentration cannot meet the narcolepsy type 1 criterion (Sateia, 2014, 2014). Cases of narcolepsy 2 (without cataplexy) are estimated to be 10–50% of all cases of narcolepsy (Ohayon *et al.*, 2005).

Epidemiology

Narcolepsy is not an uncommon disorder but is under-recognized. It has an estimated prevalence of 0.047% based on a representative sample of five European countries in the general population using the minimal set of criteria proposed by the ICSD-2 (Ohayon *et al.*, 2002). There are differences in the prevalence of narcolepsy between nationalities and ethnicities. According to previous studies, the prevalence varies from 0.02% to 0.067% in North America (Dement *et al.*, 1972, Silber *et al.*, 2002, Longstreth *et al.*, 2009, Longstreth *et al.*, 2007) and Western Europe – Italian cohort at 0.03% (Franceschi *et al.*, 1982), Finnish twin cohort at 0.026% (Hublin *et al.*, 1994) and Norway cohort at 0.022% (Heier *et al.*, 2009). The highest prevalence, from 0.16% to 0.59% was observed in Japan (Honda, 1979, Tashiro *et al.*, 1992). There is no significant difference in prevalence in men and women (Dye *et al.*, 2018).

After the AH1N1 pandemic in 2009 increased narcolepsy incidence was noticed in children. A higher annual incidence of narcolepsy in children and adolescents was noted in Finland (17-fold increase), Sweden (25-fold), the USA (2–3-fold), and Germany (3.6-fold). On the other hand, in Italy, the Netherlands and South Korea there were no more cases of narcolepsy. Many studies

associate increased incidence of narcolepsy with exposure to one particular type of AH1N1 vaccination (AS03 adjuvanted pandemic A(H1N1)pdm09 vaccine) (Wijnans *et al.*, 2013, Nohynek *et al.*, 2012).

Diagnosis of narcolepsy is often problematic, and it can take up to 20 years between the first observed excessive sleepiness and a fully developed disorder. Initial symptoms usually start in childhood and young adults. Therefore, it's crucial to consider narcolepsy in the differential diagnosis of hypersomnia in younger patients [8, 30]. A clinic-based study of narcoleptics in Quebec and France suggested a bimodal pattern of the age of onset with a larger peak in the second decade and a smaller peak in the fourth decade (Dauvilliers *et al.*, 2001).

The importance of genetic factors in narcolepsy has been addressed for more than 60 years (Krabbe and Magnussen, 1942). The risk of narcolepsy in first-degree relatives is 1–2%, compared to 0.02–0.18% in the general population (Baraitser and Parkes, 1978, Billiard *et al.*, 1994, Hayduk *et al.*, 1997, Guilleminault *et al.*, 1989, Nevsimalova *et al.*, 1997). Nevertheless, genetics are only a partial influence because even among monozygotic twins in which one has narcolepsy, the second twin is affected only approximately 25–31% of the time (Maret and Tafti, 2005, Mignot, 1997, Honda *et al.*, 2001, Partinen *et al.*, 1994, Pollmacher *et al.*, 1990). Both genetics and environmental factors may be involved in the development of narcolepsy. The contribution of environmental factors in the development of narcolepsy has been well documented (Guilleminault *et al.*, 1989, Billiard *et al.*, 1994).

The most robust of these genetic factors are specific human leukocyte antigens (HLAs). Narcolepsy has the highest HLA association among all medical diseases, with the association of haplotype DRB1*1501, DQA1*0102, DQB1*0602 being the most prominent. More than 90% of patients with narcolepsy type 1 carried DQB1*0602 haplotype according to an analysis performed in European and Asian cohorts. In contrast, in general populations only 15–25% carries this haplotype. Among patients with narcolepsy type 2 30 to 50% carried DQB1*0602 haplotype. In the case of narcolepsy type 2 genetic associations require further research (Miyagawa and Tokunaga, 2019).

Clinical features of narcolepsy

Narcolepsy is related to dysregulation of rapid-eye-movement (REM) sleep. In healthy individuals REM sleep appears only during usual sleep period. This sleep stage has unique features: high brain activity, irregular breathing dreams, and paralysis of skeletal muscles. Similar symptoms in patients with narcolepsy has been observed (Scammell, 2015). The classic tetrad of narcolepsy consists of excessive daytime sleepiness, cataplexy, hypnagogic hallucinations, and sleep paralysis. Symptoms of the disease usually appear gradually over time. Typically, hypersomnia is the initial symptom, followed by other months to years later (Vendrame *et al.*, 2008, Wise and Lynch, 2001, Peterson and Husain, 2008, Okun *et al.*, 2002, Silber *et al.*, 2002, Benca, 2007, Wise, 2004). Sneaky beginning of narcolepsy is responsible for delayed diagnosis, especially in children (Maski *et al.*, 2017). Mean time between first symptom and final diagnosis exceeds 10 years (Morrish *et al.*, 2004).

Hypersomnia, characterized by excessive daytime sleepiness and unintentional naps, results in difficulty in staying awake during normal daytime activities (Okun *et al.*, 2002, Silber *et al.*, 2002). During the daytime, with 'REM sleep intrusion', patients can suddenly feel overwhelmingly tired and appear transiently 'unaware' of their surroundings (Vendrame *et al.*, 2008, 2005). The intensity of sleepiness varies among patients – from difficulty getting out of bed in the morning to often and sudden sleep attacks (Peterson and Husain, 2008). Patients usually report dream content during these short naps (Peterson and Husain, 2008). The duration of the episode may vary from a few minutes to over an hour (Guilleminault and Pelayo, 2000). Despite chronic daytime sleepiness, patients

with narcolepsy sleep similar amount of time compared to healthy people during a 24-hour period (Broughton *et al.*, 1988). Such sleep attacks are refreshing on awakening (Kothare and Kaleyias, 2008). Daytime naps, which are normal in younger children, compound the difficulty in recognizing the excessive daytime sleepiness in the pediatric population. Such naps should cease by age 3–4 years, after which time persistence or reappearance of napping is significant (Stores, 2006).

Cataplexy is a unique feature of narcolepsy (Serra *et al.*, 2008, Kothare and Kaleyias, 2008, Wise and Lynch, 2001). Cataplexy is characterized by sudden and transient muscle weakness. These episodes arise in response to strong emotions particularly joking, laughter, or anger (Guilleminault and Pelayo, 2000, Nevsimalova, 2009, Scammell, 2003). During the episode patient is fully conscious unlike during atonic seizures (Overeem *et al.*, 2011). More commonly, attacks of cataplexy are partial, affecting only certain muscle groups, namely the arms, neck or face (Thorpy, 2006). During partial cataplexy attacks, the jaw may sag, the head may drop forward, and speech becomes garbled (Overeem *et al.*, 2001). Severe episodes produce bilateral, generalized weakness sufficient to cause a fall, although usually without injury (Scammell, 2003). Cataplexy may involve an only certain group of muscles or the entire voluntary musculature (Kothare and Kaleyias, 2008). Patient with narcolepsy may experience only partial attacks, only complete or both. Although the usual attack lasts less than a minute, long, more than 15 minutes of episodes were observed. Generally partial attacks are shorter than complete weakness (Overeem *et al.*, 2011). Most commonly, cataplexy is caused by laughter or humorous experiences. The most frequent trigger is laughing but telling or hearing a joke can provoke cataplexy easily as well (Dahl *et al.*, 1994, Guilleminault and Pelayo, 2000, Thorpy, 2006, Krahn *et al.*, 2005, Anic-Labat *et al.*, 1999, Overeem *et al.*, 2011). Other emotions can also trigger cataplexy, including anger, embarrassment, surprise, or

even arousal (Krahn *et al.*, 2005, Anic-Labat *et al.*, 1999). Most patients experience warning signs previewing cataplexy attack and they can predict coming episodes. They can take precautions before attack such as sitting down to avoid injuries (Overeem *et al.*, 2011). The frequency of cataplexy is highly variable, ranging from a few times a year to several per day (Peterson and Husain, 2008). Many patients report better and worse periods in terms of the frequency of attacks (Overeem *et al.*, 2011).

In childhood cataplexy often differs from the classical presentation. Mainly generalized hypotonia and motor activity are observed. Over time clinical presentation changes to usual brief muscle weakness attacks (Pizza *et al.*, 2013). In early childhood, cataplexy attacks are more often the complete fall type. Attacks of cataplexy may be confused with atonic seizures ('drop attacks'), especially in children under the age of 5 years (Guilleminault and Pelayo, 2000, Kothare and Kaleyias, 2008). In rare cases, an isolated appearance of cataplexy preceding excessive daytime sleepiness may pose a diagnostic problem as it can be misdiagnosed for Doose syndrome: astatic myoclonic epileptic seizures (Ohayon *et al.*, 2002, Guilleminault and Pelayo, 2000, Hayes, 2006).

Hypnagogic and hypnopompic hallucinations occur in approximately 60% of patients with narcolepsy (Thorpy, 2001, Sturzenegger and Bassetti, 2004) and in up to 36% of healthy controls (Dahmen *et al.*, 2002). These are typically very vivid visual, auditory dreams or out-of-body experiences and are usually frightening (Stores, 2006, Overeem *et al.*, 2001). These hallucinations are usually visual, consisting of simple forms (colored circles, parts of objects and so forth) which are constant or changing in size sometimes with reports of seeing people or animals (Scammell, 2003, Guilleminault *et al.*, 1989). Auditory hallucinations are also common and can range from a simple sound to an elaborate melody (Guilleminault *et al.*, 1989). Though they may occur with any disorder in which there is significant

sleep disruption, when these hallucinations occur during short daytime naps, narcolepsy should be strongly suspected (Peterson and Husain, 2008).

The prevalence of sleep paralysis in narcoleptic patients is around 25% (from 17% to 66%) (Kales *et al.*, 1982, Yoss and Daly, 1957, Goode, 1962). Sleep paralyzes are brief episodes of an inability to move, generally occurring during awakening or upon falling asleep in contrast to cataplexy attacks triggered by strong emotions (Kothare and Kaleyias, 2008, Guilleminault and Pelayo, 2000). Usually the entire body is involved, but invariably respiratory and extraocular muscles are spared. Sleep paralysis occurs due to the persistence of REM atonia after awakening (Peterson and Husain, 2008). The patient is fully aware of this state and able to recall the event which usually lasts seconds to minutes and ends spontaneously or after sensory or touching stimulation (Peterson and Husain, 2008, Goode, 1962). During episodes of sleep paralysis, the patient may have extreme anxiety associated with a fear of dying (Guilleminault and Pelayo, 2000). Fifty percent of the episodes can be associated with hypnagogic/hypnopompic hallucinations (Goode, 1962). Children are often reluctant to talk about these events (Guilleminault and Pelayo, 1998).

Apart from 'clinical tetrad', patients with narcolepsy have many different symptoms such as dysregulation of nighttime sleep, other sleep disorders, neuropsychiatric problems and eating disorders. Disrupted nighttime sleep is common in narcolepsy and may partially contribute to chronic sleepiness (Peterson and Husain, 2008). Narcoleptic patients with the greatest sleep disturbance have more severe daytime sleepiness, but even those with good nighttime sleep still have substantial daytime sleepiness (Harsh *et al.*, 2000). According to narcoleptic patients, disrupted nighttime sleep has a significant impact on their life (Maski *et al.*, 2017). Another common problem in narcolepsy is obesity (Okun *et al.*, 2002, Dahmen *et al.*, 2008). Putting on weight is caused by an irresistible craving for food

and changes in behavior such as snacking during nighttime (Bell, 1976). In childhood narcolepsy with cataplexy, obesity usually is accompanied by precocious puberty (Poli *et al.*, 2013). Because of the increased weight, obstructive sleep apnea is a frequent co-existing disorder with narcolepsy (Baker *et al.*, 1986, Harsh *et al.*, 2000).

Laboratory Findings

Diagnostic Criteria for Narcolepsy types 1 and 2 (ICSD-3)(2014):

1. Narcolepsy type 1 – criteria A and B must be met
   A. The patient has daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for at least three months.[1]
   B. The presence of one or both of the following:
      1. Cataplexy and a mean sleep latency of ≤ 8 minutes and two or more sleep-onset REM periods (SOREMPs) on an MSLT performed according to standard techniques. A SOREMP (within 15 min of sleep onset) on the preceding nocturnal polysomnogram may replace one of the SOREMPs on the MSLT.[2]
      2. CSF hypocretin-1 concentration, measured by immunoreactivity, is either ≤ 110 pg mL-1 or < 1/3 of mean values obtained in normal subjects with the same standardized assay.

Notes:
   1. In young children, narcolepsy may sometimes present as excessively long night sleep or as resumption of previously discontinued daytime napping.
   2. If narcolepsy type 1 is strongly suspected clinically but the MSLT criteria of B1 are not met, a possible strategy is to repeat MSLT.

2. Narcolepsy type 2 – criteria A–E must be met
   A. The patient has daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for at least 3 months.

B. A mean sleep latency of ≤ 8 min and two or more sleep-onset REM periods (SOREMPs) are found on a MSLT performed according to standard techniques. A SOREMP (within 15 min of sleep onset) on the preceding nocturnal polysomnogram may replace one of the SOREMPs on the MSLT.

C. Cataplexy is absent.[1]

D. Either CSF hypocretin-1 concentration has not been measured or CSF hypocretin-1 concentration measured by immunoreactivity is either > 110 pg/mL or > 1/3 of mean values obtained in normal subjects with the same standardized assay.[2]

E. The hypersomnolence and/or MSLT findings are not better explained by other causes such as insufficient sleep, obstructive sleep apnoea, delayed sleep phase disorder or the effect of medication or substances or their withdrawal.

Notes:

1. If cataplexy develops later, then the disorder should be reclassified as narcolepsy type 1.

2. If the CSF hypocretin-1 concentration is tested at a later stage and found to be either ≤ 110 pg/mL or < 1/3 of mean values obtained in normal subjects with the same assay, then the disorder should be reclassified as narcolepsy type 1.

Diagnosis of narcolepsy is based on the patient's history, confirmed by multiple sleep latency test (MLST) with preceding polysomnography (PSG) (Peterson and Husain, 2008, Littner *et al.*, 2005). Measurement of cerebrospinal fluid (CSF) hypocretin-1 concentration can be an alternative, but it is not routinely used (Mignot *et al.*, 1999, Kothare and Kaleyias, 2008).

The sleep history is a key feature enabling correct diagnosis. Detailed questions about sleep habits, duration and quality of nighttime sleep, overwhelming daily sleepiness and daily 'sleep attacks' are needed. Sleep logs give an estimate of the number, duration, and timing of daily episodes of nocturnal sleep, daytime naps, and wake periods. These can be used to evaluate sleep-wake habits over weeks to months, including weekdays and weekends (Martin and Eastman, 2002). The medical history should be supplemented by a physical and neurological examination seeking symptoms of cataplexy and hypnagogic or hypnopompic hallucinations.

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) (Hoddes *et al.*, 1973), Epworth Sleepiness Scale (ESS) (Johns, 1991), and Pediatric Daytime Sleepiness Scale (PDSS) (Drake *et al.*, 2003). SSS and ESS are two extensively used sleep scales used to assess sleepiness in adults. PDSS is a recently introduced validated measure for assessing sleepiness in children (Drake *et al.*, 2003).

Key features in narcolepsy diagnosis are nocturnal PSG and MLST performed a day after PSG. Two weeks before studies the patient should keep a sleep diary to evaluate the patient's circadian rhythm. Insufficient sleep, desynchronosis, shift work or another circadian sleep disorder can affect the MLST outcome. Medications capable of influencing results should be withdrawn for two weeks before examinations. This applies to all central nervous stimulants, sedative-hypnotics, and antidepressants [186]. It is worth to perform a urine drug screen before tests (ICSD-3).

Numerous diseases associated with sleep disturbances are characterized by similar symptoms to narcolepsy. Nocturnal PSG is obtained to rule out among others sleep-disorder breathing and periodic limb movements of sleep (Kothare and Kaleyias, 2008). Nocturnal PSG is the only diagnostic technique shown to quantify the ventilatory and sleep abnormalities associated with sleep-disordered breathing, along with an objective measure of adequate sleep efficiency above 75% (2002). Overnight polygraphic sleep records also exclude parasomnias as a cause of fragmented and non-restorative

nocturnal sleep and/or verified REM behavior disorder as one of the possible symptoms of narcolepsy (Nevsimalova *et al.*, 2007, Nevsimalova, 2009).

In recent years the new diagnostic possibility of nocturnal PSG was described. Very early occurrence of REM period during polysomnography seems to be highly specific to narcolepsy (Cairns and Bogan, 2015). SOREMP means the occurrence of REM period within 15 minutes after falling asleep. The presence of two SOREMPs on an MLST remains major feature in narcolepsy diagnosis from many years. In ICSD-3 nocturnal SOREMP has been taken into account – SOREMP during nocturnal polysomnography can replace one SOREMP on an MLST (ICSD-3). The usefulness of nocturnal SOREMP in narcolepsy diagnosis was confirmed with regard to the pediatric population also (Reiter *et al.*, 2015).

This overnight study with sleep efficiency over 75% is followed the next day by the multiple sleep latency test (MSLT). MSLT should be performed in the morning, beginning 1.5 to 3 hours after PSG. An examination is divided into 2 hours four or five intervals. In every interval patient has the opportunity to nap while the degree of sleepiness and timing of REM sleep onset is analyzed [186]. Details of the protocol have been described (Kothare and Kaleyias, 2008, Littner *et al.*, 2005). During the test patient should be isolated from stimulators – dark, quiet bedroom and comfortable room temperature is recommended [186]. During MSLT polygraphic recording is checking in order to find SOREMPs. The occurrence of two SOREMPs during the test is a required feature to diagnose both narcolepsy type 1 and type 2 (ICSD-3). The second measured parameter mean sleep latency (MSL) is the time between lights-out to falling asleep. MSL evaluates the degree of sleepiness (Kothare and Kaleyias, 2008). MSL scores under 8 minutes are generally considered to be in the pathological sleepiness range; those over 10 minutes are considered normal in adults (Guilleminault and Pelayo, 2000). Recent data have shown that

narcoleptic patients MSL is around 3.1 ± 2.9 minutes (ICSD-3). Usually, healthy adults have sleep latency between 10 and 15 minutes. After 20 minutes interval is discontinued if the patient does not fall asleep until then. In that case sleep latency is 20 minutes [186]. The reliability of MSLT for the diagnosis of narcolepsy was called into question by recent evidence that similar results can occur in up to 15% of the normal population (Arand *et al.*, 2005, Singh *et al.*, 2006, Aldrich *et al.*, 1997). 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 in adults (Littner *et al.*, 2005, Arand *et al.*, 2005, Kotagal *et al.*, 1990).

In children and adolescents mean sleep latency is longer. In prepubertal children mean sleep latency of 23.7 and 26.4 minutes was found (Gozal *et al.*, 2001, Palm *et al.*, 1989). For these reasons, 30-minute naps in MSLT in children have been proposed on a research basis (Fallone *et al.*, 2002). A sleep latency of 5 to 10 minutes indicates moderate daytime sleepiness, whereas lower than 5 minutes indicates severe sleepiness (Kothare and Kaleyias, 2008). In young children based on the observation that the sensitivity for the identification of ≥ 2 SOREMPs in patients is 70%, the AASM recommends repeating MSLT testing when the patient is suspected of having narcolepsy, but earlier MSLT evaluation did not provide polygraphic confirmation (Littner *et al.*, 2005). Recently a new study about narcolepsy type 1 diagnosis in the pediatric population was published. After analyzing 357 children below 18 years old It turned out that at least 2 SOREMPs or a mean sleep latency below 8.2 minutes on the MSLT are appropriate criteria in NT1 diagnosis in children and adolescents (Pizza *et al.*, 2019).

Laboratory tests such as human leukocyte antigen (HLA) typing and cerebrospinal fluid (CSF) hypocretin-1 analysis are useful as adjuncts but at present are not considered mandatory for a diagnosis of narcolepsy (Mignot *et al.*, 1999, Kothare and Kaleyias, 2008).

The common occurrence of specific HLA haplotypes and narcolepsy has been known for many years. The strongest association was observed in the case of human leukocyte DQ antigens, specifically DQB1_0602 and QA1_0102 (Mignot *et al.*, 1999). HLA-DQB1_0602 is highly suggestive for both NT1 and NT2 across all ethnicities, absence of this haplotype suggests other diagnose than narcolepsy (Capittini *et al.*, 2018). Twenty five percent of the normal population has a positive DQB1*0602 haplotype. Interestingly HLA DRB1*1301-DQB1*0603 haplotypes have a protective role in narcolepsy susceptibility (Hor *et al.*, 2010).

CSF hypocretin-1 concentration below 110 pg/mL or less than 1/3 of mean values is one of the NT1 diagnostic criteria (ICSD-3). It is not a routine test, useful in specific clinical situations such as a problem with conducting or interpreting MSLT or in children (Kothare and Kaleyias, 2008). Decreased CSF hypocretin-1 level is the most frequent in HLA DQB1_0602 positive patients (Bourgin *et al.*, 2008). Recent data suggest a value for measuring CSF hypocretin-1 concentration in patients with narcolepsy without cataplexy. Study of 171 patients with narcolepsy without cataplexy revealed that 24% of patients had low concentration (≤ 110 pg/mL, diagnostic criterion for NT1), 8% intermediate (110–200 pg/mL) and 68% normal level of CSF hypocretin-1 (> 200 pg/mL) (Andlauer *et al.*, 2012). Kanbayashi *et al.* [23] showed that the CSF level of Hcrt-1 remains stable from early infancy up to old age; hence, an undetectable level of Hcrt-1 in CSF is a very valuable diagnostic marker in children (Nevsimalova, 2009). CSF Hcrt-1 testing should be considered in the following situations: (1) equivocal MSLT results; (2) children younger than eight 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 (Peterson and Husain, 2008, Dauvilliers *et al.*, 2007).

In differential diagnosis clinician should rule out the following disorders: chronic sleep deprivation with erratic sleep-wake schedule, idiopathic CNS hypersomnia, recurrent hypersomnia including Klein-Levin syndrome, primary sleep disorders, psychiatric disorder including depression, Medication side effects, drug or alcohol abuse, atonic drop attacks associated with childhood epilepsy syndromes like Lennox Gastaut syndrome and EDS associated with acute illness (Żarowski *et al.*, 2009).

Treatment

For most patients, chronic sleepiness is the most disabling symptom (Scammell, 2003). Once symptoms of narcolepsy are established, treatment is generally required (Wise, 2004). Current management of narcolepsy involves a combination of behavioral and pharmacologic therapies (Wise, 2004). Some non-pharmacological interventions can temporarily reduce sleepiness and improve alertness such as the combination of regular sleep wake schedules and planned 15-minute daytime naps (Nevsimalova, 2009, Peterson and Husain, 2008, Rogers *et al.*, 2001, Mullington and Broughton, 1993, Wise *et al.*, 2007).

Dietary modification can also help in maintaining wakefulness (Peterson and Husain, 2008). Foods high in refined sugars and carbohydrates tend to produce more EDS (Peterson and Husain, 2008). Caffeine in sodas and coffee can serve as a stimulant. Meals at scheduled times, avoidance of alcohol and certain types of food is also recommended (Husain *et al.*, 2004).

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 (Thorpy, 2007, Peterson and Husain, 2008).

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 (Thorpy, 2007).

Modafinil is a unique, non-amphetamine wake-promoting drug that effectively treats sleepiness with a minimum of side effects (Scammell, 2003). Modafinil is regarded as the first-line medication for the treatment of excessive sleepiness in narcolepsy (Thorpy, 2007). Starting dose of modafinil in adults is 100 mg in the morning, escalated as needed within a few days up to 200 mg (Peterson and Husain, 2008). Modafinil does not reduce cataplexy, and additional anticataplexy medications may be needed (Scammell, 2003). The modafinil group of drugs is not available in Poland.

Methylphenidate is a dopamine and catecholamine reuptake inhibitor, thereby increasing the amount of these neurotransmitters in the synaptic cleft (Peterson and Husain, 2008). There was a study showing significant improvement in dosages of 10, 30, and 60 mg/day compared with the baseline (Mitler *et al.*, 1986). Methylphenidate is not registered for treatment of narcolepsy in Poland, so must be used off label.

Sodium oxybate is the sodium salt of gamma-hydroxybutyrate (GHB) (Thorpy, 2007). The administration of sodium oxybate at bedtime was found to reduce nocturnal awakenings, increase N3 (slow wave) sleep and consolidate REM sleep (Broughton and Mamelak, 1980, Scrima *et al.*, 1990). It is important to note that sodium oxybate improves both daytime sleepiness and cataplexy (Peterson and Husain, 2008). The exact mechanism by which sodium oxybate reduces cataplexy is unclear. This therapeutic agent is not available in Poland.

While EDS can often be managed with stimulants, these medications often do not provide significant relief from cataplexy (Thorpy, 2007). Tricyclic antidepressants (TCA), have been used successfully to treat cataplexy for many years, but more recently selective serotonin reuptake inhibitors (SSRI), have been used (Wise, 2004). Serotonin-specific reuptake inhibitors are effective, but higher doses than those for tricyclic drugs are often needed (Dauvilliers *et al.*, 2003, Overeem *et al.*, 2001, Thorpy, 2006, Scammell, 2003, Langdon *et al.*, 1986). The dual norepinephrine and serotonin reuptake inhibitor venlafaxine is also effective against cataplexy (Dauvilliers *et al.*, 2003, Abad and Guilleminault, 2004, Mignot and Nishino, 2005).

Currently, a number of different drug therapies are available for the treatment of the symptoms of narcolepsy. Treatment approaches should be directed toward development of more effective and better tolerated therapies, and primary prevention.

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