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Narcolepsy in the light of modern diagnostic, clinical and therapeutic concepts

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Abstract

Narcolepsy is a chronic neurological disease classified as hypersomnia of central origin. Core symptoms of the disease (hypersomnia and cataplexy) are particularly burdensome for patients. The etiology of the disease is not fully understood. There are several theories explaining the essence of the disease. One of the possible causes is the disruption of the autoimmune system leading to the disappearance of hypocretin-releasing neurons. Currently, multicenter studies on synthesizing hypocretin-like proteins that may be the basis of causal narcolepsy treatment are conducted. As yet pharmacotherapy contributes only to reduce the symptoms of the disease. Commonly used medications are amphetamine derivatives, modafinil, pitolisant and γ-hydroxybutyric acid sodium salt (GHB).

Keywords: narcolepsy • cataplexy • hypersomnia • hypocretins • orexins • HLA-DQB1*0602 • treatment of narcolepsy

1. Introduction

A healthy human sleeps on average 1/3 of his life. Sleep is a fully reversible physiological state, which consists of losing contact with the environment, reduction of the reactivity to external stimuli and cessation of physical activity. [1] It is indispensable in our lives, and its disorders significantly deteriorate the quality of life and negatively affect the state of our health. Despite the intensive development of science, we cannot fully explain its physiological and pathophysiological aspects. Perhaps this is why the phenomenon of narcolepsy appears in movies as a mysterious and intriguing, in the strict sense oneiric and related to life perturbations. As examples, "My Own Idaho" by Gus Van Sant (1991) or the Polish film by Magdalena Piekorz titled "Drowsiness" (2008), can be called here.

Sleep disturbances are frequent complaints reported to family doctors, neurologists and psychiatrists. Psychiatry has long recognized the relationship of sleep disorders with mental disorders (they accompany depression, herald exacerbation of mental illness). [2] Sleep disorders are generally divided into two groups: dyssomnias (abnormal sleep course) and parasomnias (abnormal episodic phenomena during awakening or transitioning between sleep stages). One of the types of dyssomnia is excessive drowsiness (hypersomnolence), which includes narcolepsy. This disease is characterized by excessive daytime sleepiness, which may be accompanied by episodes of sudden loss of muscle tone (cataplexy) and other symptoms associated with the REM sleep phase, such as sleep paralysis or hypnagogic and hypnopompic hallucinations. [3] These symptoms are referred to as so-called narcoleptic tetrad.

2. Historical outline

The first case report of a patient with narcoleptic symptoms was documented in 1877 by a German psychiatrist and neurologist Carl Westphal. [4] Three years later, the French doctor Gélineau, while documenting the next case of this disease, for the first time used the term *narcolepsie* from the Greek words *narkē* (light-headedness, stupefaction) and *lepsis* (attack, assault). [5,6,7] Despite the early description of this disease, only the discovery in 1998 of neuropeptides called hypocretin-1 (orexin-A) and hypocretin-2 (orexin-B) in the central nervous system has brought significant progress in the study of possible pathophysiology of narcolepsy. [8]

3. Etiology

The causes of the disease have not been hitherto clearly explained. The collected accumulated evidence indicate that narcolepsy, or at least the classic form with cataplexy, is based on irregularities in the hypocretin system in the brain, stemming from the destruction of the group of neurons in the hypothalamus, which release the neurotransmitter hypocretin (orexin). [9,10] This compound stabilizes the rhythm of sleep and wakefulness and influences the appetite and pleasure.

The level of hypocretin is reduced when 85-90% of neurons are lost. [11] Most patients suffering from narcolepsy with cataplexy have an undetectable level of orexin in the cerebrospinal fluid. [9,12] The most likely cause of neuronal atrophy are autoimmune processes, which begin already in puberty, due to the presence of the HLA DQB1 * 0602 antigen typical of narcolepsy type 1. Almost 95% of patients with narcolepsy with cataplexy have HLA DQB1 * 0602 antigen, and prevalence of this antigen in persons without cataplexy ~~it~~ is similar to that in the general population of 12 - 38%.[11,13] In patients who are homozygous carriers of the DQB1 * 0602 allele, the risk of narcolepsy is 2 - 4 times higher than in heterozygotes. [15] The relationship occurs between the number of DQB1 * 0602 alleles and the severity of disease symptoms. DQB1 * 0602 is more specific to the black breed. [18]

Results of the studies indicate the relationship between narcolepsy and upper respiratory tract infections caused by streptococci (Streptococcus pyogenes). [16,19] In 65% of narcoleptic patients tested within one year ~~of~~ after the onset of disease symptoms, the presence of immunological markers of streptococcal infection i.e. ASO and anti-DNase B was detected, while these markers were found in 26% of control subjects of the same age. Epidemiological studies also show that in people who suffered from streptococcal pharyngitis and were passive smokers in childhood, the risk of developing narcolepsy rises more than 5 times. [21]

A number of recent studies have shown the onset of narcolepsy in relation to H1N1 influenza, especially in children and adolescents. An increase in disease frequency in Europe appears to be related to a special type of H1N1 (Pandemrix) vaccination while in China with influenza infection rather. Data from the Pediatric Working Group of the Sleep Research Network showed similar increases in early-onset narcolepsy in the United States. [11,19]

Most patients with vaccine-associated narcolepsy develop symptoms at younger than normally age, and typical is sudden onset of cataplexy, shortly after vaccination (mean duration of 7 weeks). [21]

In addition to spontaneous narcolepsy, which usually occurs with cataplexy and is associated with hypocretin deficiency, there is also secondary narcolepsy (symptomatic), with or without cataplexy. The cause of secondary narcolepsy could be congenital disorders, tumors (mainly located in the hypothalamus) and head injuries; rarely multiple sclerosis, inflammation of the brain and spinal cord or cerebrovascular changes in the brain. [20,22] Secondary narcolepsy with cataplexy is more common in children (20-30%) than in adults, and is mainly caused by tumors (most commonly pituitary tumor) and congenital malformations (Niemann-Pick type C disease and Prader-Willi syndrome). [14,22]

4. Epidemiology

Studies on the occurrence of narcolepsy have been conducted in many countries and among various ethnic groups. Due to the lack of typical, unambiguous symptoms of the disease, it is difficult to find people with narcolepsy in standard epidemiological studies, especially in

children. The disease rate in the USA is about 1/2000 (0.05%).[11,18,23] A European study involving five countries (Great Britain, Portugal, Spain, Germany and Italy) estimated the prevalence at 0.047%.[11,18] The rate of occurrence of the disorder in Caucasian and in the group of African Americans is 0.02 - 0.06%, while in Japanese it is 10 times higher (based on research conducted in 1979 - 0.16%, and in 1995 - 0.18%), and it is 10 times smaller in the Israelis (on the basis of research from 1987 - 0.002%).[24]

Narcolepsy occurs in both men and women. [24] It can emerge at any age, but is rarely diagnosed under 5 years of age. Two disease peaks can be seen - the first between 15 and 25 years of age, and another, smaller, around 40 years of age. [17,24] Most cases of the disease occurs sporadically and family narcolepsy is scarce. [20,22,25] The available epidemiological data show that the risk of narcolepsy with cataplexy in a first degree relative is 1-2% ~~it~~ and is 10-40 times higher than in the general population. [5,26]

5. Clinical symptoms and diagnostics

Excessive sleepiness during the day is usually the first manifestation of the disease, which may precede the occurrence of other characteristic symptoms even for many months or years. Drowsiness in narcolepsy involves repeated naps or sudden falling asleep during the daytime. Narcolepsy is usually accompanied by cataplexy, which is characterized by a sudden loss of muscle tone, caused most often by laughter, and in younger children is associated with the expectation of reward. Negative emotions (anger, fear) may be less likely to cause a seizure. [10] The muscles most often affected by cataplexy are that of the neck, face, upper and lower limbs or the whole body in some patients. In children, the seizure may manifest itself in a generalized or partial (limited to the face) reduction in muscle tone, eyelid sagging, open mouth, tongue protrusion (cataplectic facies). The frequency of seizures varies - from a few within a year to a dozen or so during the day! The duration of a single episode usually does not exceed 2 minutes, although there are cases of prolonged cataplexic states lasting half an hour. Patient's awareness during the attacks is completely preserved and the event itself is not covered by oblivion. [25] Cataplexy attacks in children are often generalized, which leads to falls. These phenomena are often mistaken with epileptic seizures. [26]

The narcolepsy tetrad also includes paralysis and sleep hallucinations. Hallucinations, most often visual ones, accompany processes of falling asleep (hypnagogic) and waking up (hypnopompic). [2,3] They usually contain unpleasant content for the patient and often cause fear. Children affected by narcolepsy often report the presence of vivid and colorful dreams that appear even during short naps. Sleep paralysis makes it impossible to perform targeted movements. [3] All muscles are affected except for those with extraocular and respiratory (the patient can only move his/her eyes and breathe quickly, which sometimes makes it easier to wake up). Sleep paralysis is thought to be the result of muscular atony and is physiologically found in the REM phase when falling asleep and waking up. Episodes of paralysis can last up to several minutes and can be interrupted by external stimuli (sound, touch). [11] A characteristic and frequently occurring symptom is also the fragmentation of nocturnal sleep. [26]

In the international classification of sleep disorders (ICSD-3) narcolepsy has been assigned to the group of hypersomnias of central origin. Hypersomnia (excessive daytime sleepiness) according to ICSD is defined as the inability to maintain an adequate level of waking during the day, regardless of the length of night sleep. The ICSD classification divides narcolepsy into type 1 (narcolepsy with cataplexy) and type 2 (narcolepsy without cataplexy). [25]

The American Psychiatric Association, in the latest version of the classification of mental disorders, DSM-5, divides narcolepsy into several subtypes [25]:

• Narcolepsy without cataplexy, but with hypocretin deficiency

• Narcolepsy with cataplexy, but without hypocretin deficiency

• Autosomal dominant cerebellar ataxia, deafness and narcolepsy

• Autosomal dominant narcolepsy, obesity and type 2 diabetes

• Secondary narcolepsy for another general medical condition.

In these diagnostic criteria, the level of <110 pg/ml in the cerebrospinal fluid or <1/3 of the normal value is considered to be a decreased concentration of hypocretin.

Additionally to physical and subjective examination, different scales and questionnaires are used in the diagnosis of narcolepsy. However, the golden standard of diagnosis are polysomnography (PSG) and the multiple sleep latency test (MSLT). During PSG, many parameters are assessed including electroencephalogram (EEG), electrocardiogram (ECG), electromyogram (EMG), electrooculogram (EOG), as well as airflow in the airways and saturation. The MSLT test is used to assess the time of falling asleep during the day. On the day of the examination, every 2 hours the patient gets the opportunity to fall asleep in a quiet and dark room. Each of the 4-5 trials lasts 20 minutes. At this time, apart from the assessment of the electrical activity of the brain, eyeballs and muscle tone, the time to sleep and the possible occurrence of REM sleep are measured. [1,23,26] If the average time of falling sleep (sleep latency) is below 8 min, one of the diagnostic criteria for pathological sleepiness is met. [23]

Another diagnostic method, SOREMP (sleep onset REM periods), identifies occurrence of REM sleep within 15 minutes after falling asleep.[23] Positive test result indicates narcolepsy, however, it cannot be considered pathognomonic as it may occur in healthy people in consequence of sleep-deprivation. Additional test employed in the diagnosis of excessive drowsiness is the maintenance of wakefulness test (MWT). It measures the quality of wakefulness during the day. [26] This method evaluates the ability to maintain wakefulness in conditions conducive to falling asleep. Diagnosis of excessive drowsiness can be made when the patient falls asleep during the examination. Among the laboratory tests utilized in the diagnosis of narcolepsy, the level of hypocretin-1 in the cerebrospinal fluid (CSF hcrt-1) and human leukocyte antigens (HLA) are listed. The first one is recommended when MSLT

examination is impossible or difficult to perform (e.g. in children under 8 years of age, patients with other psychiatric and neurological diseases and in subjects treated with ~~on~~ psychotropic or anti-epileptic medications). The HLA determination is recommended in patients presumed of narcolepsy with cataplexy. The positive result of the DQB1 * 0602 haplotype can confirm the accuracy of the diagnosis. [9,26] However, the absence of the DQB1 * 0602 haplotype cannot rule out the possibility of the disease.

6. Treatment

The non-pharmacological methods of therapy are mainly recommended for improving the quality of life of people struggling with narcolepsy. Regular lifestyle and proper sleep hygiene are essential. Reduction of the incidence of paroxysmal sleep can be achieved ~~by~~ through scheduling naps during the day and avoiding overly emotional or monotonous situations. [27]

Although the causal treatment of this disease is not fully understood, it is assumed that the disappearance of hypocretin neurons in the brain may influence the occurrence of narcolepsy. Other attitudes acknowledge the role of genetic predisposition, hormonal disorders or the impact of autoimmune reactions. [20] Therefore, two types of therapy have been proposed to reduce the symptoms of narcolepsy: immunomodulatory treatment and hypocretin replacement therapy. [28] However, symptomatic treatment of narcolepsy consists ~~in~~ of pharmacological therapy with medications affecting monoaminergic transmission.

The first of these aims to limit the degeneration of hypocretin neurons. The efforts to limit the degeneration of hypocretin neurons were based on plasmapheresis and the administration of immunomodulatory drugs (prednisone and intravenous immunoglobulins), but they have not produced satisfactory results. [29,30]

Hypocretin replacement therapy is expected to increase the central transmission of hypocretin. Research centers carry out research aimed at the synthesis of modified hypocretin molecules and its analogues with good blood-brain barrier permeability. These studies give high hopes for synthesizing compounds that will be agonists of hypocretin receptors. [31]

Widely recognized and much better understood is the method of treatment dedicated to combat the symptoms associated with narcolepsy. Nevertheless, before the start of treatment, the patient's opinion on which of the narcoleptic symptoms is most disruptive to him/her is especially important. This allows to choose the right treatment scheme. Monotherapy usually does not bring the desired effects. In practice, at least two drugs should be introduced to suppress unpleasant symptoms of the disease. The flow chart for drug is shown in Figure 1. [32]

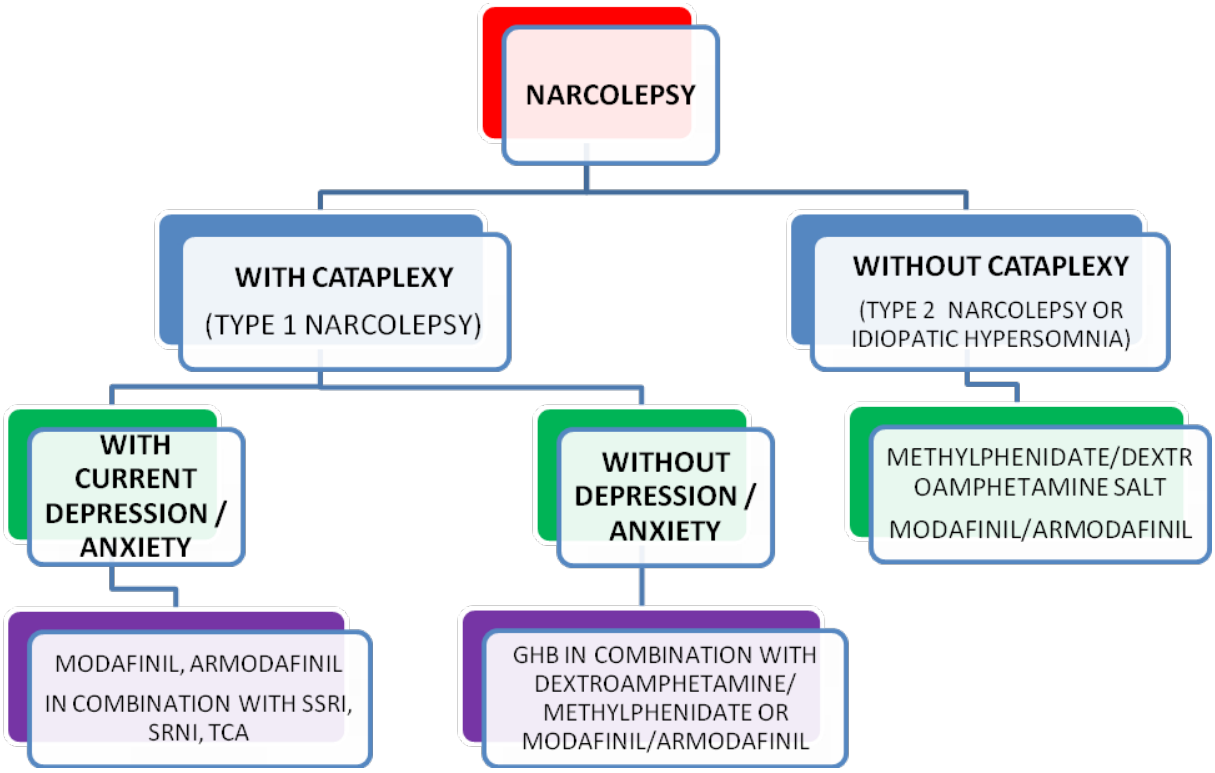

Fig. 1 The schedule of treatment of narcolepsy depending on the symptoms.

Symptomatic medications for narcolepsy could be divided into agents that suppress symptoms of drowsiness (psychostimulants) and those that endure the symptoms of cataplexy. Psychostimulants used for excessive drowsiness are derivatives of amphetamine, modafinil and armodafinil. The FDA (Food and Drugs Administration) have not approved any daytime sleepiness medication for children and adolescents. The use of these drugs in the pediatric population is therefore empirical, off label. Moreover, none of the psychostimulants available in Poland ~~is~~ have been registered in the treatment of narcolepsy. [32]

6.1 Amphetamine derivatives

Amphetamine and its derivatives (methylphenidate, dexamphetamine) increase the concentration of catecholamines in the synaptic cleft. Medications from this group increase the burst of noradrenaline (NA) and dopamine (DA) and limit their re-uptake through inhibition of both dopamine and noradrenaline transporter proteins. As a result, the intensification of dopaminergic and noradrenergic transmission occurs. [27,20]

Due to high addictive potential of amphetamine derivatives, only methylphenidate is accepted in Poland. It is one of the few medications available in Poland to treat narcolepsy. Methylphenidate is quickly absorbed from the gastrointestinal tract, and thanks to the high lipophilicity easily overcomes the blood-brain barrier. The biological half-life of methylphenidate is 2-2.5 hours and ~~it~~ is metabolized to ritalinic acid in kidneys. [27] The

commercial names of methylphenidate-containing formulations and the usual doses are shown in Table 1. As for dextroamphetamine, clinical observations suggest that, despite its prolonged half-life, this compound most effectively reduces the symptoms of drowsiness while administered twice a day. In Poland, it has not yet been registered for the treatment of narcolepsy.

Amphetamine derivatives, regardless of the proven high efficacy in the treatment of narcolepsy, cause side effects, i.e. tics, anorexia, headache, nervousness, insomnia and weight loss.

Psychostimulants could be used for children over 6 years of age. Preparations containing amphetamine derivatives are contraindicated in children with heart disease.

Drug name and chemical formula	Trade names	Doses
Metylofenidat	Medikinet Concerta Delmosart Difumenil	5–20 (up to 60) mg / day
Dextroamphetamine	Dexedrine	5–30 mg in two divided doses
Modafinil	Vigil	50–800 mg / day
GHB	Xyrem	4,5–9 g / night
Pitolisant	Wakix	9–36mg / day

Table 1. Commercially available methylphenidate-containing drugs and their usual doses

6.2 Modafinil and armodafinil

Since 1986, modafinil has been the first-line medication for the treatment of narcolepsy. Despite the unexplained mechanism of action, it effectively maintains the waking state. Recent research suggests that modafinil and its derivative affect the alpha1-adrenergic receptor. They also raise the level of hypothalamic catecholamines and histamine.

Armodafinil is a racemic derivative of modafinil. It is about twice as strong as modafinil. None of the drugs has been approved by the FDA for use under the age of 16, but off-label use is common in the pediatric population. They are contraindicated in pregnancy. Potential side effects of modafinil / armodafinil include headache and the occurrence of Stevens-Johnson syndrome.

Therapy with the above-mentioned drugs is quite expensive, therefore in the United States it is recommended to start pharmacological treatment with amphetamines and switch to modafinil or armodafinil if the previously used medication is ineffective or involves significant side effects. [33,34]

6.3 Pitolisant

Pitolisant belongs to a group of compounds that act on histamine receptors. It binds to the H3 receptor blocking the inhibitory effect of histamine on its own release. This leads to an increase in the secretion of histamine above the basal level. As a result, the activity of histaminergic neurons in the brain increases and this leads to maintaining the waking state. In addition, it increases the secretion of acetylcholine and dopamine by blocking the H3 receptor neurons. [35]

Comparative studies, carried out in 2013, showed that pitolisant suppresses daytime sleepiness with comparable strength to modafinil. In addition, the treatment showed fewer side effects. Among them were headache, nausea, anxiety and irritability. [36]

The safety of pitolisant in pregnant women and children has not been studied. Clinical trials give hope for higher safety compared to previously used drugs. Long-term observations are necessary to confirm it.

6.4 Anticataleptic drugs

Medications that suppress cataplexy attacks are tricyclic antidepressants (e.g. imipramine, desipramine, clomipramine), selective serotonin (5-HT) reuptake inhibitors (e.g. fluoxetine), norepinephrine and serotonin reuptake inhibitors (e.g. venlafaxine). The mechanism of anticataleptic action of antidepressants is not fully understood. It may be associated with inhibition the REM sleep phase. [20]

Selective serotonin reuptake inhibitors are less able to abolish cataplectic symptoms compared to tricyclic antidepressants. On the other hand, they show a better safety profile. Additionally, they can induce anorexia, which is beneficial for people with cataplexy who often struggle with overweight.

6.5 New treatment methods

Sodium γ-hydroxybutyric acid (GHB) is a metabolite of GABA, a natural neurotransmitter found in the organism. The mechanism of action of GHB, used to treat narcolepsy, is to stimulate the GHB receptor. This results in a longer NREM (slow-wave) sleep, stabilization

of the REM phase and prolongation of sleep latency. In addition, GHB sodium salt is used for shortening of the first phase of sleep and elongation of the third and fourth phase. The effectiveness of GHB treatment is related with reduction of the daytime sleepiness and the frequency of cataplexy attacks. The anticataleptic effect appears after about 2 weeks of application. [20]

There are many limitations in the use of GHB. Above all, numerous side effects like headaches, concentration disorders, nausea, vomiting, drowsiness, and urinary incontinence are problematic.

7. Summary

Effective treatment of narcolepsy remains a challenge for clinicians. An additional problem is the tolerance of pharmacological agents. On the other hand, non-pharmacological methods do not bring satisfactory results. The phenomenon of narcolepsy requires further research both neurobiological and neurophysiological as well as in the field of psychopharmacotherapy.

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