Narcolepsy with Cataplexy: What we know about it in 2021

White Paper

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Abstract

Narcolepsy is a model disease for many sleep-wake disorders, a dyssomnia. Diagnostically important is the so-called "narcoleptic tetrad": Daytime sleepiness, cataplexy, sleep paralysis, and hypnagogic hallucinations. Common differential diagnoses are epilepsy, psychoses, pharmacological influences and sleep disorders. The correct diagnosis is often made too late. Often, negative psychosocial consequences of narcolepsy have already occurred for the patients in the meantime, which can be prevented by an early diagnosis. Therefore, the objective of this White Paper is to raise more awareness in the medical community.

Introduction

In 1880, Gélineau described a patient with cataplexies, daytime sleepiness with imperative attacks of falling asleep, and gave this syndrome its initial name, "narcolepsy" (Greek: "seized by sleepiness"). The clinical differentiation from epilepsy, syncope, and other "sleep disorders" is to his credit. Westphal and Löwenfeld were the first to define narcolepsy as a disease entity. Vogel succeeded in 1960 in demonstrating premature dream sleep "sleep onset REM" (Rapid Eye Movement) in narcolepsy patients. The introduction of the multiple sleep latency test and the discovery of the close association between HLA DR2 (HLA, human leukocyte antigen) and narcolepsy allowed an improved classification of the disease. In 1957, Yoss and Daly established the criteria for the diagnosis of primary narcolepsy based on 241 cases and defined the hallmark symptoms as such: daytime sleepiness, cataplexy, sleep paralysis, automatic behavior, weight gain and hypnagogic hallucinations.[1,2]

Symptoms and course

Daytime sleepiness is the most common symptom at the onset of narcolepsy. It develops into a chronic condition to which patients become accustomed, so that some of them are often not even fully aware of their daytime sleepiness before the disease progresses further. This symptom is subject to circadian rhythms, is dependent on situational monotonicity stress, and can seamlessly transition into daytime sleep episodes. These imperative episodes of falling asleep are frequent and are most common triggered by short monotone situations like reading, watching TV, and dangerous activities like driving a car in a stressless environment. These attacks can be massively imperative in nature and occur multiple times a day for seconds to hours. Most patients often feel crushed after these episodes. Work under stress, physical labor and tension reduce the tendency to fall asleep in about 30% of patients, however EEG tests show that their level of alertness drops by 25%-45% nevertheless during these “stealth attacks”. Narcolepsy sufferers not only have difficulty staying awake during the day, but also cannot sleep through the night. This may sound surprising at first, but it has been known for decades. The disturbed night sleep in more than two thirds of narcolepsy patients often begins with premature REM sleep, is usually light, shows increased alternation of sleep stages, frequent waking reactions and sometimes long periods of lying awake. Increased body movements, in part due to association with other dyssomnias, such as periodic movements during sleep and sleep apnea, occur in just under half of all narcolepsy sufferers. Parasomnias, such as behavioral disturbance during REM sleep are found in just over 27%.[2-6]

Automatic behavior characterizes the continuation of automated activities in a state of drowsiness for a few seconds to 30 minutes. In this state, perception and memory are impaired, speech and movements may be stereotyped and out of context. Accidents at home and on the road, severe burning wounds in smokers may result. Automatic behavior is a nonspecific consequence of increased daytime sleepiness that occurs in approximately 80% of all narcolepsy patients, usually in somewhat monotonous situations, and cannot be overcome completely through activity.[1-6,22]

Cataplexy and other syndromic symptoms

REM-associated cataplexies (Greek: "to knock over with fear") have the highest significance for the diagnosis of narcolepsy. They are more clinically significant than evidence of two premature REM sleep episodes or daytime sleepiness. Cataplexy is defined as a sudden loss of holding muscle tone, triggered by intense sensations, but also occurring as a purely subjective feeling of muscle weakness. Clouding of consciousness (severe brain fog) excludes cataplexy unless it progresses to a sleep attack and/or hypnagogic hallucination. The mimic musculature is often involved; smooth muscle, respiratory, and tongue-gullet muscles are never involved. Many patients try to avoid situations that trigger cataplexy. If only a few muscle groups are affected, cataplexies may be barely noticed by others. The frequency of cataplexies varies considerably from day to day; the reason for this is still not clear. Cataplexies are usually brief (between 2 and 30 seconds), but can last up to 30 minutes or longer. "Status cataplectic" lasting for hours to days occurs predominantly after sudden discontinuation of anticataplectic medications. They always end abruptly to rapidly. During withdrawal of tricyclic antidepressants, "rebound cataplexies" can still occur up to 14 days after discontinuation. In cases of falls, epileptic seizures or, in elderly patients, circulatory disturbances in the vertebrobasilar stromal area are often suspected. Because of their triggerability by affective stimuli, cataplexies are occasionally misclassified as a dissociative symptom and patients are sent to psychological treatment, which is unnecessary in every respect. Cataplexies are associated with inhibition of the mono-synaptic H-reflex and polysynaptic tendon reflexes. Sleep paralysis is the temporary inability to perform movements or speak at the transition from waking to sleeping (hypnagog) or from sleeping to waking (hypnopomp). Isolated sleep paralysis may occur sporadically (in approximately 4% of the population at least once in their lifetime) or with familial clustering in the absence of narcolepsy. Hypnagogic hallucinations occur at the transition from sleep to wakefulness. They may impress as very vivid visual experiences involving the environment, but also as frightening visual hallucinations.[24-26]

Narcolepsy can occur at almost any age, both as primary narcolepsy (a disease in its own right) or as secondary narcolepsy (as a symptom of a brain disease such as Parkinson's, multiple sclerosis, H63D syndrome, or post-stroke conditions), with the main misdiagnoses being epilepsy and hyperkinetic syndrome. Children tend to hide their narcolepsy symptoms or compensate for their sleepiness with hyperactivity, which is why they and adolescents are sometimes misdiagnosed with hyperkinetic syndrome. In late manifestation, the latency period between onset of daytime sleepiness and cataplexy can be particularly long, up to three decades. Narcolepsy with late manifestation is clinically sometimes less severe than that with an early manifestations; however it is always an incurable slowly progressive disorder. Many narcolepsy patients suffer from their disability; chronic rumination, self-doubt, and depression may be the psychological consequence. The patients often develop avoidance strategies with social withdrawal, more problems in marriage and family and frequent accidents. Many (about 90%) can no longer practice their profession. Due to daytime sleepiness, they also have a reduced attention capacity.[21-24]

Causes

The risk of developing narcolepsy in first-degree relatives is 1%-2% (as compared to 0.03% to 0.17% percent in the general population). The risk for single symptoms is approximately 5%. Narcolepsy has the highest HLA association of all disorders. 98% of all European narcolepsy patients have an association with the allele HLA DR15 (formerly DR2), whereas only 60% of African-American narcolepsy patients do. The haplotype of all DR-15-positive narcolepsy patients with DR15/DQ6 serologic specificity is DRB1*1501, DQA1*0102, DQB1*0602. The relative risk (factor of excessively elevated risk of trait carriers) is less than 10 for most HLA-associated disorders, but more than 200 for narcolepsy. Because the association with haplotype DQB1*0602 and DQA1*0102 is strongest in narcolepsy patients of all ethnic groups, this haplotype is thought to contain the "narcolepsy gene" on the short arm of chromosome 6. Hcrtr knockout mice have been found to have an abnormality of REM sleep control and states of weakness comparable to cataplexy. The Hcrtr-2 gene is located on chromosome 12 in dogs. This region is homologous to the short arm of human chromosome 6. Hypocretin- (also called orexin-) producing cells are localized predominantly in the thalamus and have extensive axonal projections to brain regions significant for REM sleep regulation. Additional projections exist to the amygdala, which may be directly involved in the emotional triggering of cataplexies. The hypocretin system thus includes the neuronal structures that can be held responsible for the development of the two leading symptoms of narcolepsy, namely cataplexies and daytime sleepiness. The concept of narcolepsy as an auto-immune disorder is still being discussed.[5,8,12,14]

Neurochemical models suggest the following for **primary narcolepsy**:

- There is an increase in noradrenergic and serotonergic turn-over in brain areas receiving innervations from the locus coeruleus and raphe dorsalis (increased activity of REM off cells).
- There is increased activity of REM-Off cells, which suppresses the activity of cholinergic pedunculopontine REM-On cells. This results in increased cholinergic sensitivity. Dopaminergic neurons can modulate the noradrenergic systems and activate noradrenergic REM-On cells.

Secondary narcolepsy has the same symptoms but is caused by damages to the brain due to a variety of conditions.[11,13,20,21]

Treatments

Non-drug treatment includes adherence to the individually required amount of sleep, stress reduction, a balanced diet, consumption of stimulating beverages, abstinence from alcohol, physical training, practice of specific coping patterns, and protective measures against injury. Because of the lifelong course of the disease, the immense social impairments, and the difficulty of a drug treatment, constant medical care should be provided by a physician experienced with the disease.

Medications for narcolepsy symptoms exist, but can only be used on an individual basis. Amphetamine-like substances are preparations that release catecholamines, and to a lesser extent serotonin, in the CNS and periphery. They have side effects to varying degrees, affecting the cardiovascular system, the psyche, and the vegetative system. The most common side effects are hyperexcitability, palpitations, headache, gastrointestinal discomfort, inappetence, sweating, insomnia, irritability, overconfidence, hypertension, angina, cardiac arrhythmias, tremor, dizziness. Some stimulants are problematic because of their addictive potential, as tolerance development occurs in about 40% of all narcolepsy patients taking amphetamines. In this case, "drug vacations" and choice of an optimal substitute drug under inpatient conditions are recommended. Antidepressants are the drugs of choice for REM-associated symptoms. The tricyclic antidepressants have the strongest anticataplectic effect, and are therefore still first-line agents for refractory cataplexy, although some of them have significant side effects. The number of studies with common antidepressants is small, long-term results are not available, and in practice therapy failure is experienced in a good half of the cases. The drug therapy of secondary narcolepsy always depends on the underlying disease. Since these conditions are usually accompanied by structural brain damage, these patients often remain without any prospect of a drug therapy.
Narcolepsy, both primary and secondary, is a very serious disorder with significant potential for injury, destruction of social life and occupational ability, as well as the ability to participate in life normally. Driving should be avoided unless the patient has learned with total certainty to reliably recognize relevant early warning signs of an oncoming seizure. The household should be organized in such a way that no water or fire damage can occur; frequent severe cataplexies may necessitate aids such as orthoses, crutches or the use of a wheelchair.[1-6,17,18,26,27]

Conclusions

Narcolepsy with and without cataplexy is a chronic progressive neurological disorder with a high symptom burden that frequently leads to severe disability. Secondary cataplexy differs from primary cataplexy only in that it is the consequence (a symptom) of another disease of the brain. The clinical presentation and the course are largely identical in both forms.[1-7,11,27]

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Conflicts of interest

None.

Ethical standards and patient's rights

This article is about scientific facts based on research literature. It is not reporting on a clinical trial, especially not a prospective one. Our research work is always conducted in accordance with the Declaration of Helsinki.

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