Sys Rev Pharm 2022; 13(6): 696-698
A multifaceted review journal in the field of pharmacy
E-ISSN 0976-2779 P-ISSN 0975-8453 / DOI: 10.31858/0975-8453.13.6.696-698

Research Article

Regularly Missed Symptoms in Primary and Secondary Narcolepsy

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Article History: *Submitted: 01.06.2022* *Accepted: 23.06.2022* *Published: 30.06.2022*

ABSTRACT

Based on an analysis of anonymized medical records from four hospitals in Asia and Africa, we succeeded in identifying symptoms typical for narcolepsy (with cataplexy) that are regularly overlooked because they are masked by the two severe leading symptoms. Our results do not differ between primary and secondary cases of narcolepsy. We have succeeded in uncovering strong indications that the current description of narcolepsy in textbooks and other information publications is just as inadequate as the knowledge of most physicians who treat patients with narcolepsy.

Keywords: Narcolepsy, Cataplexy, Symptoms, Cognitive function, Sleep, Seizures

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INTRODUCTION

Narcolepsy is an illness of the brain, incurable and severely debilitating for most patients. Recent research shows that there is less hypocretin (also known as orexin) in the brains of narcolepsy patients than in healthy individuals, in both the primary and secondary forms (due to an underlying brain-organic disease). In narcolepsy patients, it is thought that an immune defect destroys the cells that produce the neurotransmitter hypocretin. Without hypocretin, humans cannot follow normal sleep and wake rhythms. Accordingly, in people with narcolepsy, the normal sleep-wake rhythm is disturbed and symptoms occur (Mahoney CE, *et al*., 2019; Bassetti CL, *et al*., 2019).

Men and women are affected equally often. In the primary form, the first symptoms appear mainly between the ages of 15 and 30; the secondary form is independent of age and often more progressive. The most striking feature of narcolepsy is daytime sleepiness, which is manifested by attacks of falling asleep at any time of day and in the most unusual situations. In addition, there are spontaneous muscle relaxations, called cataplexy. Narcolepsy disease does not affect life expectancy, but leads to significant disabilities with considerable extent in terms of the limitations it causes. The quality of life of many sufferers significantly reduced. Narcolepsy is a purely organic disease. That is, it has a physical cause and is in no way psychological (Thorpy MJ, 2006; Bassetti CL, *et al*., 2019).

Patients increasingly lose the ability to resist imperative sleep attacks. Suddenly falling asleep is therefore not a sign of lack of interest, indifference or even laziness, but rather due to illness. As a rule, narcolepsy manifests itself through sleep attacks in monotonous situations in which concentration is easily reduced even in healthy people, for example when reading a long text, as a passenger in a car or while watching television (Bassetti CL, *et al*., 2019; Bassetti C and Aldrich MS, 1996; Han F, 2012; Yoss RE, 1957).

However, individuals suffering from narcolepsy not only fall asleep quickly during monotonous situations, but also suddenly and involuntarily in situations such as during meals or while driving a car on an empty road without much external stimulation (Bassetti C and Aldrich MS, 1996; Han F, 2012; Yoss RE, 1957; Lima FC, *et al*., 2019).

There is also the very dangerous (due to accidents) symptom of cataplexy which makes the patient's muscles fail, such as facial muscle slackening or a person's complete physical slump, often triggered by the biological correlates to emotions (catecholamine storm). Because the symptoms of cataplexy are very clear and a clear sign of the presence of narcolepsy, they greatly contribute to the diagnostic process. Nevertheless, the diagnosis is most often complicated or delayed because patients often perceive mild cataplexies as normal and assume that other people also experience brief moments of muscle failure. Accordingly, they do not tell their doctor that their jaw occasionally drops, for example. Still other sufferers do not talk about their symptoms for fear of suffering from a serious illness, such as a brain tumor. Fears of being mentally ill also cause patients not to see a neurologist. Because narcolepsy is a rare disease, doctors sometimes have quite some problems making the right diagnosis. It may be that the doctor himself has never seen or treated a narcolepsy patient before. If this is the case, the doctor may refer the affected person to a specialist in neurology or sleep medicine (Sullivan SS, 2010; Zhang J and Han F, 2017).

Well-known symptoms of narcolepsy with cataplexy

The main symptom of narcolepsy is excessive daytime sleepiness, which occurs regardless of whether and how much the affected person has slept during the night. Other leading symptoms include cataplexy, disturbed nighttime sleep, hallucinations upon awakening from a seizure, and sleep paralysis. Thus, narcolepsy has not only one symptom, but is a symptom complex. The main symptom of narcolepsy is excessive daytime sleepiness, which is accompanied by involuntary falling asleep. It can be observed in almost all people suffering from narcolepsy. As a rule, the sleep attacks occur in the presence of low external stimulation (decrease in sympathetic nervous system activity). As long as the diagnosis of narcolepsy has not been made, those affected very often have to contend with prejudice, for example when they fall asleep at work or in the middle of a conversation. For those affected, staying awake is not a question of wanting to, they often simply cannot prevent falling asleep. Since outsiders often have no understanding, those affected withdraw and avoid activities with friends or family. People with narcolepsy are not only sometimes tired, but actually always and every day. A feeling like "really well rested" or "rested and fit" does not exist for people with narcolepsy (Antelmi E, *et al*., 2020; Sullivan SS, 2010; Feldman NT, 2003; Zhang J and

Han F, 2017).

Cataplexies are short-lasting bouts of muscle failure that can vary in severity. In milder cases, for example, cataplexy causes only facial muscles to go slack. In other patients, however, the knees go weak, and in more severe cases, the patients may completely slump and fall to the floor, often resulting in injuries of various degree. This is also called a loss of muscle tone. During cataplexy, the patient remains fully conscious. Cataplexy is not dangerous in itself, but its consequences (injuries) are significant (Thorpy MJ, 2006; Sullivan SS, 2010; Feldman NT, 2003). Usually the attacks most often last only a few seconds. However, many cases are mild cataplexies, such as failure of the muscles of a finger or articulation difficulties. Cataplexies may occur several times a day in some patients and only a few times a year in others (Bassetti CL, *et al*., 2019; Thorpy MJ, 2006; AC MP, *et al*., 2018; Bassetti C and Aldrich MS, 1996; Han F, 2012; Yoss RE, 1957).

About 80% of people with narcolepsy suffer from disturbed nighttime sleep. Compared to healthy people, night sleep is often not restful for people with narcolepsy. Sleep paralysis is a loss of muscle tone that occurs when falling asleep or waking up and is accompanied by a complete inability to move or paralysis. That is, one wakes up and cannot move. Sleep paralysis is not a definite sign of narcolepsy. They are seen in only 35% of patients with narcolepsy and also occur in 4% of the normal population (Bassetti CL, *et al*., 2019; Ohayon MM, *et al*., 2002; Sullivan SS, 2010).

Hypnagogic (when falling asleep) or hypnopompic (when waking up) hallucinations are vivid, realistic and mostly fearful dream or delusion perceptions. The affected person sees and hears things when falling asleep or waking up, which do not take place in reality. The sensory phenomena experienced by a person suffering from narcolepsy during a hallucination are often unpleasant and sometimes bizarre or frightening. Hallucinations occur in about 50% of people with narcolepsy while waking up from an attack (seizure) (Bassetti CL, *et al*., 2019; Thorpy MJ, 2006; AC MP, *et al*., 2018; Bassetti C and Aldrich MS, 1996; Han F, 2012; Yoss RE, 1957; Lima FC, *et al*., 2019; Zhang J and Han F, 2017; Mignot E and Black S, 2020; Bahammam AS, *et al*., 2020).

MATERIALS AND METHODS

In addition to these commonly known symptoms, we suspected other symptoms specific to narcolepsy based on anecdotal reports. We therefore screened 127 anonymized patient records from a total of five Western-standard clinics (two in Africa, three in Asia) for evidence suggesting clustering of identical symptoms. Potentially confounding comorbidities were considered.

Of the 127 patients, 71 were male and 56 were female. The age range was 19 to 52 years, the mean age was 42. Overall, 76% suffered from primary narcolepsy and 24% from secondary narcolepsy (with or without cataplexy). The data did not differ significantly between those with primary or secondary narcolepsy. The same is true for the sexes.

RESULTS AND DISCUSSION

Obviously, the paucity of well-funded research has meant that relevant symptoms of narcolepsy (primary and secondary) have not been adequately researched and some misconceptions have persisted in medical textbooks for decades (*Table 1*). Especially the supposed "refreshing" effect of a narcoleptic seizure seems more than questionable. The opposite appears to be the case. Aspects of cognitive decline, impairment of olfactory sense, and far-reaching dangers and hardships for people suffering from narcolepsy have also remained largely unnoticed. Our work shows the very clear tendency that narcolepsy is more than a sleeping disorder, but rather a complex neurological disease due to structural damage in the brain (cells and/or synapses). In particular, it is a highly significant finding that "narcolepsy without cataplexy" does not exist in our patients. Obviously, every narcolepsy is also accompanied by cataplexies, even if these are only minimally manifested. The risk of injury in people with narcolepsy has also apparently been completely underestimated up to now. Physicians worldwide are now also called upon to take a closer look at the concrete dangers to life and health of people with narcolepsy, as well as their social interaction issues, and to systematically investigate these risks.

Table 1: Data regarding missed symptoms in primary and secondary narcolepsy

Missed symptoms in primary and secondary narcolepsy	Values
Symptom clusters beyond the known pathology	103/127 (81%)
Increase in wakefulness clinically and/or in Electroencephalogram (EEG) between 21 and 03 hours (9:00 pm-3:00 am)	91/127 (72%)
Nocturnal hunger attacks	101/127 (80%)
Paralysis of digestive activity during sleep seizures	109/127 (86%)
Paralysis of digestive activity when sleep seizure is avoided by strong external stimulation	72/127 (57%)
Dream images or dreaming while awake (analogous to a hallucination)	48/127 (38%)
Occasional slurred speech as a symptom of cataplexy of the vocal organs	89/127 (70%)
Occasional balance problems	95/127 (75%)
A feeling of being shattered after a sleep seizures	112/127 (88%)
Impairment of the olfactory sense (permanent)	62/127 (49%)
Undesired weight gain	119/127 (94%)
Brain fog/cognitive challenges (more than one episode/day)	126/127 (99%)
Mini-cataplexies (in max. one muscle segment such as a finger) that results in injury	98/127 (77%)
Mini-cataplexies (in max. one muscle segment such as a finger)	127/127 (100%)
Diagnosed with "narcolepsy only" despite cataplectic symptoms	49/129 (39%)
Drop in measured Intelligence (IQ) by more than 20 percentage points	27/59 IQ data available from 59 patients only
Aversion to strong stimuli (bright light, crowds, etc)	68/127 (54%)
Impairment of normal social interaction due to cognitive issues	108/127 (85%)

CONCLUSION

We have succeeded in uncovering strong indications that the current description of narcolepsy in textbooks and other information publications is just as inadequate as the knowledge of most physicians who treat patients with narcolepsy. Now, a larger-scale study with a broader study design is urgently warranted.

LIMITATIONS

This study, like many others, has limitations. It is likely to be particularly relevant that patients were included only in the form of anonymized med-

ical records. However, the records were from renowned and specialized clinics where meticulous documentation can be assumed. The number of patients was also relatively small, but cannot be considered underpowered given the rarity of this condition. Therefore, we believe that our results provide sufficiently robust results despite the previously mentioned and other limitations.

ETHICAL STANDARDS AND PATIENT'S RIGHTS

This study is based on the anonymized medical records of 127 fully informed adult patients who gave their written consent to such participation. Our paper 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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