Sleepiness in Narcolepsy

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KEYWORDS

• Excessive daytime sleepiness • Narcolepsy • Cataplexy • Multiple sleep latency test • Stimulant

KEY POINTS

- Excessive daytime sleepiness (EDS) is usually the first and the most disabling symptom in narcolepsy. Understanding the clinical characteristic of EDS in narcolepsy leads to an early diagnosis.
- EDS in narcolepsy varies in different aspects, such as onset age, severity, and clinical characteristics.
- The diagnosis of narcolepsy is based on the clarifying of EDS through history and polysomnography (PSG) followed by the multiple sleep latency test (MSLT). Cerebrospinal fluid (CSF) orexin measurement is helpful to classify type 1 and type 2 narcolepsy.
- The therapeutic goal is to optimize control of EDS through wake-promoting medications and nonpharmacological treatments.

INTRODUCTION

EDS, or hypersomnia, defined as the inability to stay awake and alert during the major waking episodes of the day, resulting in unintended lapses into drowsiness or sleep,[1] and has been well recognized by medical professionals and the public. The problem is common; it is estimated to affect up 9% of the general population[2] and 15% to 30% of patients suffering from sleep disorders. EDS is one of the most common complaints of patients seeking help in sleep clinics. EDS has critical implications for human productivity and safety, because EDS can result in reduced quality of life, impaired mood and cognitive function, and increased risk for motor vehicle accidents. The diagnosis and treatment of sleep disorders with EDS were major triggers of the development of modern sleep medicine. Factors influencing sleep quality and/or quantity may cause EDS. Narcolepsy represents the best understood hypersomnia, due in large part to the elucidation of the role of hypocretin (orexins) in the pathophysiology of animals and human narcolepsy cataplexy decades ago.[3–6] According to the *International Classification of Sleep Disorders, Third Edition* (*ICSD-3*), narcolepsy is classified as type 1 and type 2. Specifically, type 1 narcolepsy became defined as either documented low CSF hypocretin-1, even if it does not manifest cataplexy or clear cataplexy and a positive MSLT; cases without cataplexy but with a positive MSLT were called type 2 narcolepsy.

EPIDEMIOLOGY OF EXCESSIVE DAYTIME SLEEPINESS AND NARCOLEPSY

Narcolepsy affects 0.03% to 0.16% of the general population in various ethnic groups.[7–10] The prevalence of narcolepsy with cataplexy falls between 25 and 50 per 100,000 people.[11] Little is known about the epidemiology of type 2 narcolepsy. Two groups independently examined the population prevalence of a positive MSLT result with mean sleep latencies less than or equal to 8 minutes plus greater than or equal to 2 sleep-onset rapid eye movement (REM) periods (SOREMPs). In 1 sample of 539 subjects, 2.5% of subjects met MSLT criteria for narcolepsy.[12] A separate cohort study of 556 subjects found a surprisingly

Disclosure Statement: No conflict of interest declared.
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Sleep Med Clin ■ (2017) ■–■
http://dx.doi.org/10.1016/j.jsmc.2017.03.008

high prevalence of positive MSLTs; 4.1% men and 0.4% women met the criteria for narcolepsy and subjective sleepiness (Epworth Sleepiness Scale [ESS] score >10).[13]

Most cases of human narcolepsy are sporadic. Up to 5% are familial cases, and the risk of a first-degree relative developing narcolepsy cataplexy is 1% to 2%, which is 10 times to 40 times higher than in the general population.[14] Higher prevalence of EDS was found in relatives of patients with narcolepsy. In 1 study, including 378 parents of children with type 1 narcolepsy-cataplexy, MSLT testing found that 27% of parents had MSL less than or equal to 8 minutes; further analysis indicated 0.8% of parents have hypocretin deficiency with cataplexy and 2.4% parents are without cataplexy but with MSLT results consistent with narcolepsy, although a large portion of subjects did not report subjective daytime sleepiness or other ancillary symptoms (Yan H and Han F, unpublished data, 2017).

EXCESSIVE DAYTIME SLEEPINESS AS THE CARDINAL SYMPTOM OF NARCOLEPSY

EDS, cataplexy, sleep paralysis, and hypnagogic hallucinations are the classic tetrad of symptoms for narcolepsy. Only approximately one-third of patients, however, have all 4 of these symptoms on initial evaluation in a sleep laboratory.[15] EDS and cataplexy are considered the 2 primary symptoms of narcolepsy. Cataplexy typically presents as an abrupt and reversible decrease or loss of muscle tone usually elicited by strong emotions and is the only truly specific feature of narcolepsy, but it occurs in only 65% to 75% of individuals with confirmed narcolepsy and may improve or even completely disappear during the disease course.[10,16,17] It presents as the first symptom in less than 10% of the patients and appears usually months to years after the onset of EDS. In contrast, presence of objective EDS is considered the cardinal diagnostic criterion for narcolepsy; 100% of the narcoleptic subjects present with chronic sleepiness, and it often abates with time but never phases out completely. Clinically, type 1 and type 2 narcolepsy do not differ qualitatively and qualitatively in regard to daytime sleepiness. In a Japanese series, the mean ESS (14.9 $\pm$ 3.5) in 62 patients with type 2 was similar to the mean ESS (14.6 $\pm$ 3.7) of 52 patients with type 1 narcolepsy.[18] A similar finding was observed in a French series (ESS 19 $\pm$ 3.3 in 54 patients with type 1 vs 17.5 $\pm$ 2.7 in 46 patients with type 2).[19] In summary, EDS is often the most frequent cause for consultation in sleep clinics and the first clue to the diagnosis of narcolepsy type 1 and type 2. Given the average diagnostic delay of more than 10 years,[15] understanding the clinical characteristic of EDS in narcolepsy leads an early diagnosis of the disorder.

PRESENTATIONS OF EXCESSIVE DAYTIME SLEEPINESS IN NARCOLEPSY

Onset of Excessive Daytime Sleepiness in Narcolepsy

EDS and irresistible sleep episodes are usually the first and the most disabling symptoms in patients with narcolepsy. Narcolepsy onset is variable and may appear as either progressive or sudden. A majority of the narcoleptic patients begin to show symptoms, mostly sleepiness, in the second decade of life, with a bimodal distribution, including a large peak around puberty and a smaller peak between 35 years and 45 years.[20] This was confirmed in a US white population and a European Narcolepsy Network study,[21] with mean EDS onset age at 22.7 years old. Emerging evidences indicates that narcolepsy and EDS symptom onset seems different across various ethnic populations. EDS occurred in an earlier age in Chinese narcoleptics.[22] Childhood narcolepsy cases were first reported in a group of Northern Chinese[23] and confirmed in a follow-up study.[22] In a series of 2000 narcolepsy–cataplexy patients seen over 15 years in the same sleep laboratory, two-thirds had onset of symptoms at age 8.5 years, more than 15% with onset prior to 6 years. A major onset peak at approximately 10 years old to 11 years old was observed in Southern Han Chinese,[24,25] and childhood narcoleptics were often seen in Taiwan,[26] a place with mixed Chinese population from both South China and North China. Childhood narcolepsy is considered rare in whites, however. Only in recent years has the number of childhood diagnosis of narcolepsy increased, probably due to the higher disease awareness in the context of the possible association with H1N1 pandemic and vaccination.[27,28] Further comparison between patients in 2 large databases from Beijing University and Stanford University also revealed that age of onset for EDS was younger in Chinese patients versus whites, 2.5 years younger in children less than 18 years, and 6.7 years younger in all patients.[22]

Clinical Characteristics of Excessive Daytime Sleepiness in Narcolepsy

EDS in narcolepsy generally presents as a background of baseline sleepiness that easily leads to sleep episodes of a strong, sometimes overwhelming, desire for sleep not only under conducive circumstances, such as monotonous,