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Review Article

Delayed diagnosis of narcolepsy: characterization and impact

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ABSTRACT

Narcolepsy, a chronic neurologic condition resulting from dysregulation of the sleep–wake cycle, usually has an onset at an early age. However, a long delay until diagnosis has been consistently reported in the literature across countries and several publications have focused on characterizing this delay. Most studies report a mean delay to diagnosis of up to 15 years, with individual cases of >60 years, although a trend over time toward a shorter diagnostic delay has been suggested. While variables associated with this delay have been identified, a lack of symptom recognition resulting in misdiagnosis prior to reaching the narcolepsy diagnosis is the likely underlying reason. This lack of symptom recognition is especially relevant considering the high comorbidity burden that has been shown in patients with narcolepsy as some disorders manifest with symptoms that overlap with narcolepsy. A consequence of delayed diagnosis is delayed treatment, which affects the burden of disease. Substantial detrimental effects on healthcare resource utilization, employment, and quality of life have been described after narcolepsy onset and prior to the diagnosis of narcolepsy. This review highlights the importance of closing the diagnostic gap by expanding awareness of narcolepsy and its symptoms.

1. Introduction

Narcolepsy is a chronic neurologic condition resulting from dysregulation of the sleep–wake cycle [1]. Evidence indicates an autoimmune component linked to specific genotypes including human leukocyte antigen (HLA *DQB1*06:02*) and T-cell receptor alpha variants associated with loss of orexin (hypocretin)-producing neurons [2–4]. However, not all cases are associated with loss of hypocretin neurons. Narcolepsy can also be precipitated by seasonal *Streptococcus* infections, H1N1 influenza, and H1N1 vaccination in genetically predisposed individuals [5].

The estimated prevalence of narcolepsy is 0.05% in the United States [6] and 0.02–0.067% worldwide [7], and it is associated with a substantial socioeconomic burden. This burden results from increased health care resource utilization; reductions in patient function, quality of life, and productivity; and an adverse impact on the patient's partner and family [8–13]. Reduced employment and income can be present before diagnosis [11], and an early diagnosis leading to appropriate treatment may lessen the burden.

Narcolepsy is characterized by excessive daytime sleepiness (EDS), cataplexy, hypnagogic or hypnopompic hallucinations, and sleep paralysis, although not all symptoms are present in all patients. Recognition of disturbed nocturnal sleep (DNS) as a patient-reported symptom and as a polysomnography (PSG)-characterized feature suggests that DNS can be added to the other symptoms to form a symptom pentad [14].

While narcolepsy onset can occur in children <10 years of age [15–17], symptom onset typically peaks during the second decade of life [15], with a main peak at approximately 15 years of age and possibly a lesser secondary peak at approximately 35 years [18]. However, evidence suggests that few patients are diagnosed within the first 10 years as indicated by the disproportionate number of patients who report onset prior to 20 years of age relative to those who have been diagnosed (Fig. 1) [19].

Numerous publications have reported the discordance between narcolepsy onset and its diagnosis. Because such a diagnostic gap results in delay of treatment and increases the disease burden, it is important to characterize this gap and identify factors that may potentially reduce it. Therefore, the purpose of this article is to provide an overview of the diagnostic delay between symptom onset and diagnosis, including discussion of the potential reasons and implications of this delay.

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2. Methods

Articles reporting on the diagnostic delay were identified from several sources. Although the primary source was the authors' knowledge of the narcolepsy literature, searches were also performed in PubMed. The PubMed searches, with no publication date limits and for English language articles, used the search term "narcolepsy" in combination with "delayed diagnosis," "diagnostic delay," and "diagnosis delay." The PubMed searches returned 39 unique citations, of which 10 were relevant for inclusion in this review; relevancy was determined based on quantitative report of a delay between symptom onset and diagnosis, or discussion of factors and/or implications related to a diagnostic delay. Additionally, the Introduction and Discussion sections of articles initially identified for inclusion were further hand searched to identify other studies that stated the duration of the diagnostic delay or provided relevant analyses or discussion related to characterizing the delay. A backward search was also performed based on articles that cited previous articles in order to identify the earliest description of the diagnostic delay. Although the current article does not represent an exhaustive systematic review, it consolidates available information to impart recognition of an issue that has mainly been noted in passing as part of specific studies and in general reviews of narcolepsy.

3. Review of delayed diagnosis

3.1. Delay duration

A delay between symptom onset and diagnosis was mentioned in the narcolepsy literature as early as 1976, with 5 years reported as the average time between symptom onset and a correct diagnosis [20]. Consistent with this duration, a 1995 study anecdotally reported survey results that stratified the delay between symptom onset and narcolepsy diagnosis at a single sleep disorders clinic in the UK by years of delay duration in 132 patients [21]. While the majority of patients (66%) were diagnosed within the first 5 years, there was a delay of >10 years in almost one-quarter (24%) of these patients. The results of the only published study characterizing this interval reported that the most commonly cited delay in the narcolepsy literature is 10–15 years [17]. That study, performed in the UK using a postal questionnaire based on self-report of patients with symptom onset from 1910 to 2000 ($n = 219$), reported a diagnostic delay of 1–61 years, with a median of 10.5 years and a mean of 15 years.

While no other published studies have specifically focused on characterizing this delay, a delay duration has sometimes been stated in clinical trials and other narcolepsy studies (Table 1), often reporting wide variability in the time between onset and diagnosis. Furthermore, delay sometimes can be imputed by the difference reported between age at symptom onset and age at diagnosis, often presented as part of a study's demographic data. For example, an evaluation of patients who were diagnosed with narcolepsy after the age of 40 reported that many of these patients had symptom onset in their teens or early 20 s [22], suggesting delays $\geqslant$20 years. In some studies, the reported interval exceeded 60 years [17,23,24], possibly reflecting the lack of narcolepsy knowledge during the time period in which these older patients first presented with symptoms.

A diagnostic delay appears to be consistently present across countries, including Austria, Canada, Denmark, France, Germany, Italy, New Zealand, Saudi Arabia, The Netherlands, Poland, Slovakia, Spain, Switzerland, the UK, and the United States [13,19,21–31]. In a study of nine European countries, delay duration significantly varied among the countries ($p < 0.0001$), with the shortest delay in France (11.9 ± 13.7 years) and the longest delay in Spain (21.1 ± 14.7 years) [24]. Although potential reasons for the differences among countries were not discussed, it was noted that the country with the shortest delay had the lowest age at diagnosis, and the one with the longest delay had the highest age at diagnosis.

Two studies that evaluated the diagnostic delay based on year of symptom onset suggested a trend over time toward a shorter diagnostic delay. In the first study, which combined data from narcolepsy patients at two study centers (one in France and one in Canada), the mean diagnostic delay was 52.5 years for patients who had symptom onset before 1940, with a linear decrease in delay duration over >50 years [26]. Estimates of the diagnostic delay by decade using linear regression revealed that this delay decreased to 3 years for the most recent evaluated interval of 1990–1998 (Fig. 2A). A similar trend toward a shorter delay during more recent decades of symptom onset was observed in the dataset of Morrish et al. [17] (Fig. 2B). Although both studies suggest a trend toward earlier diagnosis, they also show a large spread of the delay even for recent decades of symptom onset.

Despite these trends, the fact that a diagnostic delay continues to be reported suggests that there is still under-recognition of this

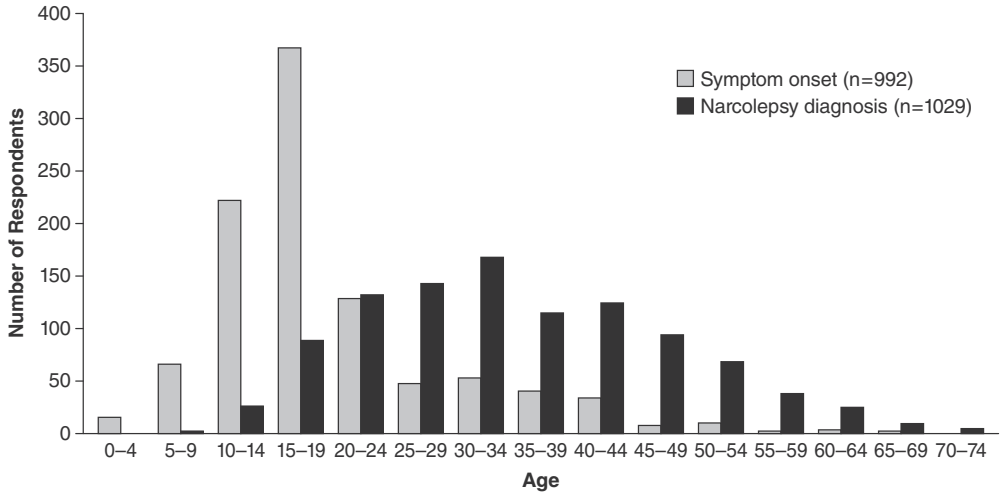

Fig. 1. Narcolepsy diagnosis relative to symptom onset. Numbers of patients denoted in the figure represent those from a population of 1035 individuals who provided information on the stated variable. The total population was derived from 501 patients in a narcolepsy database and 534 in a clinical trial. Data from Thorpy et al. [19].