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Diagnosing narcolepsy: validity and reliability of new diagnostic criteria

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Abstract

Background and purpose: No gold standard currently exists for the diagnosis of narcolepsy. Conventional diagnostic criteria are unwieldy and arbitrary. Clearly defined criteria for case selection are needed to compare the results of different studies.

Methods: We developed new clinical and neurophysiologic criteria for narcolepsy using four categories, based on the degree of diagnostic certainty. Category A is Definite Narcolepsy, Category B is Probable Narcolepsy (Laboratory Supported; two subgroups B1 and B2) and Category C is Probable Narcolepsy (Clinical). We assessed the charts of 69 new or established patients with narcolepsy seen consecutively in the Mayo Sleep Disorders Center and classified them according to our system. The human leucocyte antigen (HLA) DQB1*0602 status was determined for each patient as an indirect measure of validity. Two investigators independently assessed 30 charts to assess interrater reliability. We assessed additional 337 charts of patients with other hypersomnolence states to assess the specificity of our definitions.

Results: Seventy-four percent were positive for HLA DQB1*0602 (including 85% of those with cataplexy). Only 33% of those without cataplexy were HLA DQB1*0602 positive. The two investigators agreed on the classification of 29/30 patients (0.97 reliability). None of the 337 additional patients fulfilled criteria for narcolepsy, and specifically not for cataplexy.

Conclusions: We conclude that our new research diagnostic criteria for narcolepsy possess high interrater reliability and appear valid descriptors of the syndrome, based on HLA typing. They may be useful in providing consistent criteria to compare different research studies.

Keywords: Narcolepsy; Cataplexy; Diagnostic criteria; Validity; Reliability; HLA typing; Rapid eye movement sleep

1. Introduction

The diagnosis of narcolepsy poses several unique problems. Excessive daytime sleepiness, the most consistent symptom, is non-specific and is more commonly caused by other conditions such as insufficient sleep or sleep disordered breathing. Cataplexy is usually diagnosed on history alone and may be difficult to differentiate from non-specific autonomic and behavioral responses to emotional stimuli. In addition, about 25% of patients with sleepiness associated with premature onset of rapid eye movement (REM) sleep do not have cataplexy at the time of presentation [1]. The classic neurophysiologic marker of two or more sleep onset rapid eye movement (SOREM) periods on a multiple sleep latency test (MSLT) is not seen in 17–26% of patients with sleepiness and cataplexy [1,2] and may also be seen in other conditions such as obstructive sleep apnea (OSA) syndrome [2]. Despite a high sensitivity, the immune marker for narcolepsy (HLA DQB1*0602) has a low specificity (approximately 20% frequency in controls) [3,4]. While low cerebrospinal fluid (CSF) hypocretin-1 concentration in the CSF may with time provide a biochemical marker for the disease, an initial study has shown that 2/9 narcoleptic patients had normal CSF hypocretin concentrations [5]. Thus, there is currently no 'gold standard' for the clinical diagnosis of narcolepsy.

These difficulties result in the potential for imprecise diagnosis of narcolepsy and are a potentially serious problem for research studies. As research into the role of hypocretins in the pathogenesis of narcolepsy expands, it will be especially important that the inclusion criteria for patients are comparable from study to study. The current most accepted diagnostic criteria for narcolepsy are those of the International Classification of Sleep Disorders (ICSD), published by the American Academy of Sleep Medicine [6]. These criteria are complex, somewhat unclear (especially

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with regard to associated features), and have not been validated. Diagnostic and Statistical Manual of Mental Disorders-IV criteria [7] are entirely clinical and have also not been validated. With this background in mind, we developed a new set of research diagnostic criteria for narcolepsy and tested their validity and interrater reliability.

2. Methods

2.1. Diagnostic criteria

We developed four categories, designed to reflect increasing diagnostic certainty. We used both clinical and neurophysiologic data, whenever these were available. Table 1 lists the criteria and Table 2 provides a simple summary. Category A (Definite Narcolepsy) includes patients with the greatest clinical and laboratory probability of having narcolepsy. They all have objectively confirmed sleepiness, an absence of other disorders that could explain sleepiness, a history of cataplexy and two or more SOREM periods. Category B (Probable Narcolepsy–Laboratory Confirmation) includes patients with objectively confirmed sleepiness, an absence of other disorders that could explain sleepiness, and either a history of cataplexy but fewer than two SOREM periods (Category B1) or two or more SOREM periods but an absence of cataplexy (Category B2). All Category A and B patients underwent a polysomnogram (PSG) and a MSLT under standardized conditions, with exclusion of other possible causes of sleepiness including sleep disordered breathing, sleep deprivation and the effects of medications. Category C (Probable Narcolepsy–Clinical) includes patients with histories of daytime sleepiness and cataplexy, but no or inadequate sleep studies performed. Patients with both narcolepsy and OSA syndrome were included in Category A if they fulfilled the criteria for Category A on a repeat PSG and MSLT after adequate treatment of OSA. If a repeat study was not performed, but a clear history of cataplexy was obtained, they were included in Category C.

Table 2
Summary of diagnostic criteria

Category	Cataplexy	Laboratory confirmation of sleepiness	SOREM periods
A	Yes	Yes	Yes
B1	Yes	Yes	No
B2	No	Yes	Yes
C	Yes	No	No

2.2. Subjects and study design

We identified 69 consecutive new or established patients with narcolepsy seen at the Sleep Disorders Center at Mayo Clinic, Rochester, MN between December 30, 1998 and May 5, 2000. Each chart was reviewed by one of the investigators (all are diplomates of the American Board of Sleep Medicine) and each patient was classified according to our new criteria. To assess interrater reliability, 30 of these patients were independently classified by two of us (MHS and EJO) and the results compared. Without a 'gold standard', it is not

Table 1
Diagnostic criteria

Category A. Definite narcolepsy
History of excessive daytime sleepiness
History of cataplexy, defined as definite bilateral weakness of brief duration brought on by emotion
Mean initial sleep latency of <8 min on MSLT[a]
Two or more SOREMP on MSLT[a], or 1 SOREMP on MSLT[a] and 1 SOREMP on the preceding nocturnal PSG
Apnea–hypopnea index (AHI) <10 per hour on nocturnal PSG preceding the MSLT[a]
(The last three criteria can be replaced by cataplexy witnessed by a physician with documented recoverable areflexia, or cataplexy recorded by PSG and video recording)
Category B. Probable narcolepsy (laboratory confirmation)
Subgroup B1
History of excessive daytime sleepiness
A history of cataplexy, defined as definite bilateral weakness of brief duration brought on by emotion
Mean initial sleep latency of <8 min on MSLT[a]
One or fewer SOREMP on MSLT[a] or on the preceding nocturnal PSG
AHI <10 per hour on the nocturnal PSG preceding the MSLT[a]
Subgroup B2
History of excessive daytime sleepiness
No history of cataplexy
Mean initial sleep latency of <8 min on MSLT[a]
Two or more SOREMP on MSLT or one SOREMP on the MSLT[a] and one SOREMP on the preceding nocturnal PSG
AHI <10 per hour on the nocturnal PSG preceding the MSLT[a]
Category C. Probable narcolepsy (clinical)
History of excessive daytime sleepiness
History of cataplexy, defined as definite bilateral weakness of brief duration brought on by emotion
No or inadequate sleep studies performed

[a] MSLT performed under standard conditions, including a total sleep time of ≥6 h on the preceding night PSG [17].

possible to assess validity directly. However, our criteria do not utilize the patients' HLA DQB1*0602 status, and thus we used the percentage of patients positive for this haplotype as an indirect measure of validity, comparing it to published data using other diagnostic criteria. To assess the specificity of our definition of cataplexy, one of the investigators (EJO) reviewed the charts of an additional 377 patients seen at Mayo Clinic with International Classification of Disease Version 9 diagnostic codes corresponding to a range of other hypersomnolence states. These included: sleepiness, hypersomnia or hypersomnolence, not otherwise specified; disorder of excessive somnolence; sleepiness, cause specified; psychophysiological hypersomnia; sleep drunkenness; sleep paralysis; and Kleine–Levin syndrome.

3. Results

3.1. General results

All but three patients were Caucasian. One was of Hispanic, one Native American and one Asian ethnicity. Thirty-five were female; 34 male. The mean time between onset of sleepiness and onset of cataplexy in Category A, B1 and C patients was 6.1 years. The mean duration of sleepiness in Category B2 patients was 17.7 years.

3.2. Interrater reliability

The two reviewers identically classified 29 of the 30 patients, giving an interrater reliability of 0.97

3.3. Validity

Table 3 shows the results of the classification of the 69 patients and the results of HLA typing. Seventy-eight percent of patients had cataplexy. Seventy-four percent were positive for HLA DQB1*0602 (including 85% of those with cataplexy). Only 33% of those without cataplexy were HLA DQB1*0602 positive.

3.4. Specificity

None of the 337 additional cases reviewed met our criteria for narcolepsy, and in particular, none met the criteria for cataplexy.

Table 3
HLA data in narcolepsy subtypes

Subtype	Number (%)	DQB1*0602 positive (%)
A	38 (55)	33 (87)
B1	6 (9)	3 (50)
B2	15 (22)	5 (33)
C	10 (14)	10 (100)
Cataplexy positive (A + B1 + C)	54 (78)	46 (85)
Total	69 (100)	51 (74)

4. Discussion

4.1. Choice of criteria

A number of considerations underlay our choice of criteria. The lack of a single definitive test led itself to a hierarchical approach to diagnosis with levels of increasing certainty. This approach has been used in generating research criteria for multiple sclerosis [8], another disorder with difficulties in clinical diagnosis. Criteria have been suggested for the diagnosis of cataplexy [9] and a decision tree has been suggested for optimal definition [10]. Our relatively simple definition of cataplexy was similar to those used by other investigators [2,11] and was precise enough to result in almost complete agreement between two experienced clinicians. In addition, all ten of our Group C patients in whom the diagnosis of narcolepsy depended entirely on the clinical delineation of cataplexy were positive for HLA DQB1*0602. We reviewed the charts of 337 additional patients who were diagnosed with a range of other states of hypersomnolence, and found none who met our criteria for cataplexy. We allowed the objective observation of cataplexy, either by demonstration of transient areflexia [12] or polygraphy with video recording [13], to replace PSG and MSLT in Category A, because definite cataplexy with subjective sleepiness is considered pathognomonic of the disorder. We realize that few patients will be diagnosed in this way and emphasize that demonstration of transient areflexia is essential for the clinical diagnosis of cataplexy; without this sign, it is impossible to differentiate cataplexy from a psychogenic spell. We did not include hypnagogic or hypnopompic hallucinations in our criteria, because of their lifetime occurrence in 37 and 13% of the population [14] and in 43% of patients with idiopathic hypersomnia [15]. Similarly, we did not include sleep paralysis, a phenomenon reported in 6% of normals [16] and in 40% of patients with idiopathic hypersomnia [15]. The precise mean initial sleep latency on the MSLT separating normality from excessive sleepiness is not known. Accepted criteria [17] state that latencies below 5 min represent definite sleepiness, while those between 5 and 10 min are a 'diagnostic gray area ' of uncertain significance. ICSD criteria for narcolepsy include a mean latency of <5 min [7]. Eight minutes as a cutoff has been suggested as most appropriate in order to optimize sensitivity and specificity [18], and has been used in other studies [2,11]. We deliberately did not use the presence of periodic limb movements of sleep as an exclusion criterion because PLMS are common in narcolepsy [19] and there is no correlation between MSLT latencies and PLM indices in a population of sleepy patients [20].

4.2. Narcolepsy without cataplexy

SOREM periods are non-specific and can be seen in other disorders, such as OSA syndrome [2]. However, when other

disorders are excluded, there remains a group of sleepy patients with SOREM periods but no cataplexy. In a series of 295 sleepy patients with other causes ruled out and two or more SOREMS on MSLT, 73 (25%) did not have cataplexy [1]. This is similar to the 27% found in two large multicenter studies of 509 patients with narcolepsy [11] and close to the 22% found in our study. The nosologic status of this condition remains uncertain. It differs from narcolepsy with cataplexy in several respects, including a lower prevalence of hypnagogic hallucinations and sleep paralysis [15,18], more efficient sleep [18], and less sleepiness on MSLT [18]. The prevalence of HLA DQB1*0602 is about 40% [11] which is lower than in the cataplexy group, but higher than in the general population. It is possible that these patients include a subgroup of true narcoleptics (perhaps with cataplexy not yet manifesting in some) [21] and another group with a condition closer resembling idiopathic hypersomnia. Alternatively, all these patients may have narcolepsy with the presence or absence of HLA DQB1*0602 having a direct effect on the clinical manifestations of the disorder [11]. It is possible that some of our Category B2 patients may not yet have developed cataplexy at the time of the study. However, the mean duration of sleepiness in this group was 17.7 years, compared with a much shorter mean interval between onset of sleepiness and onset of cataplexy in the Category A, B1 and C patients of 6.1 years. Until this problem is better resolved, these patients should generally be considered as having a form of narcolepsy.

4.3. Validity and interrater reliability

Without a 'gold standard' for diagnosis, true validation of diagnostic criteria is not possible. We used the percentage of patients in each group who carried the HLA DQB1*0602 haplotype as an indirect measure of validity. In two multicenter studies of 421 patients with narcolepsy and cataplexy, 312 (74%) were positive. When only those 155 patients with clear-cut cataplexy were included, the percentage positive rose to 84% [11]. In a single center study of 171 narcoleptics with clear-cut cataplexy, 154 (90%) were positive [22]. Our finding of 85% positivity in those with cataplexy falls well within this range. In particular, 87% of our Group A patients (definite narcolepsy) and all ten of our group C patients (clinical diagnosis only) were positive. Surprisingly, only 3/6 of our Group B1 patients (cataplexy, laboratory confirmed sleepiness, but no SOREMS) were positive, but this may be attributable to the small sample size. As regards narcolepsy without cataplexy, 36 of 88 (41%) patients in the multicenter trails were positive for HLA DQB1*0602, including 37% of 75 Caucasian American patients [11]. These figures are similar to the 33% positivity found in our 15 Group B2 patients, all of whom were Caucasian. In two studies of Caucasian controls, 22.8 and 18.4% were positive. Thus, the HLA data on our patients provide indirect validation of our diagnostic criteria. We did not use the HLA data to define the degree of diagnostic certainty, but rather to compare our results with previously published results using similar diagnostic categories. Thus, the lower percentage of patients with HLA DQB1*0602 in Category B2 than in Category C does not imply a lesser degree of diagnostic certainty in the former group, as we would not have expected narcoleptics without cataplexy to have a higher rate of HLA positivity. We found the interrater reliability between two experienced clinicians to be 0.97, suggesting that the criteria can be reliably used by different investigators.

4.4. Summary

In summary, we propose new research diagnostic criteria for narcolepsy, based on the degree of diagnostic certainty. We have demonstrated that these criteria possess high interrater reliability and appear valid descriptors of the syndrome, based on HLA typing. They may be useful in providing consistent criteria to compare different research studies.

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