HLA DR15 (DR2) and DQB1*0602 typing studies in 188 narcoleptic patients with cataplexy

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Journal Title: Neurology
Volume: Volume 48, Number 6
Publisher: American Academy of Neurology (AAN) | 1997-06-01, Pages 1550-1556
Type of Work: Article | Final Publisher PDF
Permanent URL: https://pid.emory.edu/ark:/25593/rmwv4

Final published version: http://www.neurology.org/content/48/6/1550.short

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Accessed March 17, 2019 7:42 PM EDT
Narcolepsy is a disorder characterized by excessive daytime sleepiness, sudden losses of voluntary muscle tone in response to strong emotion (cataplexy), and other pathologic manifestations of disassociated REM sleep. Although the familial aspects of this disorder have long been recognized,1,2 a genetic marker for narcolepsy was only identified in the early 1980s when Honda and his colleagues3 reported a tight association of narcolepsy with HLA class II antigens. These results confirm the importance of DQB1*0602 typing rather than DR15 (DR2) typing in Black narcoleptic patients and demonstrate that the presence of clear-cut cataplexy is a better predictor for DQB1*0602 positivity than the presence of abnormal MSLT results.

**NEUROLOGY 1997;48:1550-1556**
association (100%) between human leukocyte antigen (HLA) DR2 and narcolepsy among Japanese patients. These findings were quickly confirmed in Caucasian populations in Australia, Europe, and North America. In these populations, DR2 frequency ranges from 20 to 30% but almost all narcoleptic patients tested were DR2 positive. Some of these earliest reports, which focused on DR2, also mentioned that the frequency of second antigen, HLA-DQ1, was significantly higher in narcoleptic patients than in normal Japanese and Caucasian control subjects. The high frequency of DQ1 in control subjects, 60 to 80%, however, greatly diminished the specificity of DQ1 as a marker for narcolepsy.

The discovery of several cases of DR2-negative narcolepsy during the mid-1980s triggered a flurry of questions. For example, did these patients really have narcolepsy or could these DR2-negative cases be attributed to differences in the criteria used to diagnose narcolepsy? Or, could there be ethnic differences in linkage disequilibrium between DR2 and a putative narcolepsy-susceptibility gene? In one of these early reports, Neely et al. only included Black narcoleptic patients and 67% were DR2 positive. Although Nezu et al. described one Japanese non-DR2 case where the diagnosis of narcolepsy was quite questionable, other DR2-negative patients, mostly Caucasians, had a substantial history that was supportive of the diagnosis of narcolepsy-cataplexy. In 1987, Matsuki et al. reported that DR2 frequencies varied between 92 and 100% depending on the criteria used for diagnosis of narcolepsy (e.g., excessive daily sleepiness [EDS] present for more than 6 months, EDS with cataplexy, EDS with cataplexy plus two sleep-onset REM periods). The conclusion of the Japanese group, based on a large sample of Japanese patients (n = 227), was that presence of cataplexy was the best determinant for DR2 positivity, and that earlier reports on non-DR2 narcoleptic patients were likely the result of differences in diagnostic approaches. This position can be best exemplified as in Honda and Matsuki, “Most of the reports on DR2-negative narcolepsy lack precise clinical definition of cataplexy, and therefore might have included nonnarcoleptic patients owing to a difference in clinical judgment.”

Since these earlier reports, HLA class II typing techniques have become increasingly sophisticated. This first led to the subtyping of DR2 into DR15 and DR16 subtypes, with all narcoleptic patients found to be DR15-positive. As DR15 is the most common subtype of DR2 in most ethnic groups, this serologic splitting of DR2 did not improve the value of HLA typing for diagnostic purposes. More recently, subtyping was made possible at the genomic level, thus leading to the identification of more than 15 subtypes of DR2 and 30 subtypes of DQ1. Among those subtypes, DRB1*1501 (DR2) together with DQB1*0602 (DQ1) were identified in all Caucasian and Japanese narcoleptic patients with DR2, DQ1. In black Americans, genomic typing in 28 patients with cataplexy and abnormal Multiple Sleep Latency Test (MSLT) revealed the presence of DRB1*1501 in only three subjects, with many patients carrying a new variant of DR15 called DRB1*1503 (19 subjects) and all but one subject being positive for DQB1*0602. DQB1*0602 is thus now considered as the best HLA marker across all ethnic groups and this result likely explains the substantially lower DR2 frequency previously reported in black Americans.

Most of the known HLA DR- or DQ-associated disorders (e.g., multiple sclerosis, insulin-dependent diabetes mellitus) are autoimmune in nature and several investigators have suggested a similar pathologic mechanism for narcolepsy. To date, however, there is no evidence for a direct involvement of the immune system in this sleep disorder. Human narcolepsy is not associated with any detectable circulating autoantibodies, CSF oligoclonal bands, increased sedimentation rate, C-reactive protein at the onset of the disease, or changes in CD4/CD8 lymphocytes subsets usually found in other autoimmune disorders. Pathologic studies have also shown that the CNS of human patients with narcolepsy does not contain sites of lymphocytic infiltrations. HLA DR15 or DQB1*0602 may thus be only linkage markers and not the actual susceptibility genes for narcolepsy. Recent studies do not, however, favor the linkage marker hypothesis. First, the onset of narcolepsy is associated with increased microglial class II expression in a canine model of the disorder. Second, detailed HLA haplotyping studies in human narcoleptic patients indicate that susceptibility to narcolepsy narrowly maps to the coding region of the DQB1*0602 and associated DQA1*0102 genes and not in the region flanking these alleles. These results suggest that the HLA DQ molecules themselves are involved in disease predisposition.

Whether or not narcolepsy is autoimmune, DQB1*0602 is neither necessary nor sufficient for the development of the disorder. This DQB1 allele is present in 12 to 38% of the general population in various ethnic groups, with only 0.02 to 0.16% affected with narcolepsy-cataplexy. DQB1*0602 sequence is identical in control and narcoleptic subjects. A few patients with typical narcolepsy-cataplexy are negative for DQB1*0602 and family members frequently share the same HLA haplotype with the proband and never develop narcolepsy. Even monozygotic twins can be discordant for the development of narcolepsy; only 25 to 31% of the monozygotic twins reported to date are concordant for narcolepsy. Overall, the data suggest that narcolepsy-cataplexy, like many other HLA-associated disorders, is a complex disorder that involves both genetic predisposition and environmental triggering factors.

Increasingly sophisticated techniques are being developed for identifying the genetic causes of disease, but without careful subject selection, valuable...
Table 1 Clinical subgroups of patients with narcolepsy

<table>
<thead>
<tr>
<th>Group</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (n = 132)</td>
<td>Clear-cut cataplexy and EDS, MSLT with mean sleep latency ≤8 min and two or more SOREMPs</td>
</tr>
<tr>
<td>B (n = 6)</td>
<td>Clear-cut cataplexy and EDS, MSLT with a mean sleep latency of ≤8 min and only one SOREM observed</td>
</tr>
<tr>
<td>C (n = 10)</td>
<td>Clear-cut cataplexy and EDS, polysomnographic test other than MSLT (or MSLT without preceding nocturnal polysomnogram) showing EDS and SOREMPs</td>
</tr>
<tr>
<td>D (n = 6)</td>
<td>Clear-cut cataplexy and EDS, MSLT with mean sleep latency ≤8 min without any SOREMPs or mean sleep latency &gt;8 min with two or more SOREMPs</td>
</tr>
<tr>
<td>E (n = 3)</td>
<td>Clear-cut cataplexy, MSLT with mean sleep latency &gt;8 min and one or no SOREMPs; patients with clear-cut cataplexy but no complaints of EDS</td>
</tr>
<tr>
<td>F (n = 17)</td>
<td>Clear-cut cataplexy and EDS, but no polysomnographic tests performed</td>
</tr>
<tr>
<td>G (n = 14)</td>
<td>Atypical cataplexy with positive polysomnographic tests (G1) Doubtful cataplexy with positive polysomnographic tests (G2) Atypical or doubtful cataplexy with inconclusive polysomnographic tests (G3)</td>
</tr>
</tbody>
</table>

EDS = excessive daily sleepiness; MSLT = Multiple Sleep Latency Test; SOREMP = sleep-onset REM period.

Methods. Subjects. A total of 188 subjects was obtained from a database of 777 narcoleptic subjects and relatives whose HLA typing has been done at Stanford University. Subjects in the database were recruited using six possible protocols: (1) “random” narcoleptic patients from various ethnic groups (n = 291); these subjects were referred to the center because they had narcolepsy-cataplexy or were diagnosed at the Stanford Sleep Disorder Clinic; (2) parents or relatives of random narcoleptic patients for haplotype relative risk studies or HLA haplotype segregation analysis (n = 98 relatives); (3) relatives and narcoleptic patients of multiplex families (n = 342 subjects in 48 families)34,35; (4) narcoleptic subjects recruited because they were found to be non-DR2 positive at another sleep center (n = 41)34,35; (5) subjects and parents with essential hypersomnia (n = 4); (6) posttraumatic narcolepsy cases (n = 6).

In this study, only available “random” narcoleptic subjects with a complete clinical file and an established diagnosis of narcolepsy-cataplexy were included in the analysis. Subjects recruited because of DR2 negativity, posttraumatic narcolepsy, or as part of recruitment effort aiming at gathering multiplex family study were thus not included in the analysis. A clinical file was established for every subject. The file contained photocopies of clinical notes obtained from the medical file(s) of the patient, notes made by direct interview of the patient by the Center For Narcolepsy staff (mostly by phone), and results of polysomnographic studies (e.g., MSLT and nocturnal polysomnography), if any. The Stanford Center for Narcolepsy Sleep Inventory, a 146-item questionnaire requesting details and specific examples for all narcolepsy symptoms experienced, with special emphasis on cataplexy, was also completed and included in the file (108 of 188 patients). Final diagnosis/category was made by one of us (C.G.) after a review of the clinical data file and without any knowledge of the HLA testing, name of the patient, or the patient’s geographic origin. Table 1 shows how subjects were categorized based on their clinical history and polysomnographic studies.

Ninety-four of the 291 “random” subjects were excluded either because the patient’s diagnosis of narcolepsy-cataplexy could not be confirmed or because the clinical file was not complete at the time of the submission of this manuscript. Subjects reporting a mixed ethnic background, e.g., Asian-Caucasian, black-Caucasian were also excluded due to their small number (n = 9). Our final...
Table 2 Chi-square analysis of DRB1*15 and DQB1*0602 by patient characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients positive for DRB1*15</th>
<th>Percent positive for DRB1*15</th>
<th>$df$</th>
<th>Chi-square statistic</th>
<th>$p$ Value</th>
<th>Patients positive for DQB1*0602</th>
<th>Percent positive for DQB1*0602</th>
<th>$df$</th>
<th>Chi-square statistic</th>
<th>$p$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>84/105</td>
<td>80.0</td>
<td>1</td>
<td>0.68</td>
<td>0.41</td>
<td>91/104</td>
<td>87.5</td>
<td>1</td>
<td>0.00</td>
<td>1.000</td>
</tr>
<tr>
<td>Male</td>
<td>68/82</td>
<td>82.9</td>
<td></td>
<td></td>
<td></td>
<td>70/80</td>
<td>87.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>23/24</td>
<td>95.8</td>
<td>2</td>
<td>11.4</td>
<td>0.003</td>
<td>21/23</td>
<td>91.3</td>
<td>2</td>
<td>0.53</td>
<td>0.765</td>
</tr>
<tr>
<td>Black</td>
<td>41/61</td>
<td>67.2</td>
<td></td>
<td></td>
<td></td>
<td>54/61</td>
<td>88.5</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Caucasian</td>
<td>87/103</td>
<td>84.5</td>
<td></td>
<td></td>
<td></td>
<td>87/102</td>
<td>86.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cataplexy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Clear-cut</td>
<td>144/174</td>
<td>82.8</td>
<td>1</td>
<td>8.80</td>
<td>0.003</td>
<td>154/171</td>
<td>90.1</td>
<td>1</td>
<td>12.88</td>
<td>0.001</td>
</tr>
<tr>
<td>Atypical/doubtful</td>
<td>7/14</td>
<td>50.0</td>
<td></td>
<td></td>
<td></td>
<td>8/14</td>
<td>57.1</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>MSLT findings</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>113/144</td>
<td>78.5</td>
<td>2</td>
<td>2.38</td>
<td>0.30</td>
<td>125/143</td>
<td>87.4</td>
<td>2</td>
<td>0.97</td>
<td>0.617</td>
</tr>
<tr>
<td>Ambiguous</td>
<td>22/27</td>
<td>81.5</td>
<td></td>
<td></td>
<td></td>
<td>21/25</td>
<td>84.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never performed</td>
<td>16/17</td>
<td>94.1</td>
<td></td>
<td></td>
<td></td>
<td>16/17</td>
<td>94.1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

MSLT = Multiple Sleep Latency Test.

The sample included 107 females and 80 males (1 unknown) recruited from Asia ($n = 14$), Europe ($n = 3$), and North America ($n = 171$). Twenty-four subjects (12.8%) were Asian, 61 (32.4%) were black, and 103 (54.8%) were Caucasian. Four (2.1%) of the 188 subjects recruited as “random” narcoleptic patients were later found to have another family member with documented narcolepsy-cataplexy.

HLA typing. The presence or absence of DQB1*0602 and DRB1*15 was determined either using polymerase chain reaction sequence specific oligonucleotide (PCR-SSO) as previously described or using Innotype reverse dot blot kits according to manufacturer recommendation (Robbins Scientific, Sunnyvale, CA). All non-DR15 and/or non-DQB1*0602-positive subjects were fully HLA DR and DQ high resolution PCR SSO typed as described in Kimura et al.

Subject categorizations. Group assignments (A–G) were then used to categorize subjects by their history of cataplexy and MSLT results. Subjects who reported recurrent brief episodes of weakness in the knees, jaw, face, or neck triggered by laughter, amusement, happiness, game playing, or anger were considered to have clear-cut history of cataplexy (Groups A–F). Subjects who reported atypical symptoms (e.g., unilateral weakness in one arm or cataplexy mostly induced by stress or by other less typical emotions, unusually long episodes, etc.) or extremely mild symptoms (e.g., feeling of weakness that does not result in detectable changes in body position or report of a single or a few attacks in the past) were considered to have a “possible” history of cataplexy (Group G).

MSLT data were then analyzed on all subjects. When subjects had a mean sleep latency of ≤8 minutes and at least two sleep onset REM periods (SOREMPs) their MSLT findings were considered positive (Groups A, G1, G2). Polygraphic results were considered ambiguous when the mean sleep latency was either >8 minutes, or when there were less than two SOREMPs during the MSLT (Groups B, D, G3) or when polygraphic tests other than MSLTs were performed and suggested a possible abnormality (Group C). A third category, no sleep studies performed, was created for subjects who had well-documented history of EDS and clear-cut cataplexy but who had never undergone any diagnostic studies (Group F). Ethnicity and gender were determined from information provided by the subjects.

Statistical analysis. Four variables were used to describe the population: gender, ethnicity (Asian, black, Caucasian), history of cataplexy (clear-cut, atypical/doubtful), and MSLT findings (abnormal, ambiguous, not performed). These variables were examined singly and in combination both for descriptive purposes and to evaluate their interrelationships. First, each variable was examined for its relationship with being positive for DRB1*15, and only those variables with a $p$ value of less than 0.10 were included in the multiple logistic regression modeling. Tests of association between each categorical predictor variable and DRB1*15 positivity were based on chi-square tests. Variables deemed to be significant, statistically and/or medically, were included in final model. The association between being positive for DQB1*0602 and the predictor variables gender, ethnicity, history of cataplexy, and MSLT results was tested in the same way.

Results. DRB1*15 as a marker for narcolepsy. Of the total sample, 19.7% ($n = 37$) of the subjects were negative for DR15 (DR2), and 80.3% ($n = 151$) of the subjects were positive. Univariate testing revealed that being positive for DR15 was not associated with gender or MSLT results (table 2). Therefore, only two covariates (history of cataplexy and ethnicity) were included in the final models tested (table 3). Two indicator variables were used to analyze the effect of ethnicity; Caucasian, which refers to a comparison of Caucasian and black subjects, and Asian, which compares Asian and black subjects. Additional statistical testing revealed that blacks were significantly dif-
frequent from Asians ($\chi^2 = 7.584, p = 0.005$) and Caucasians ($\chi^2 = 6.656, p = 0.009$), but there was no significant difference in Asians and Caucasians ($\chi^2 = 2.169, p = 0.140$). Although the first model tested (DRB1*15 #1, see table 3), using cataplexy alone, was significant ($p = 0.007$, and $p = 0.003$), it was neither sensitive nor specific. When cataplexy and ethnicity were combined in the second model (DRB1*15 #2, see table 3), both sensitivity and specificity were improved. Subjects with atypical/doubtful cataplexy were 3.9 times more likely than subjects with clear-cut cataplexy to be DR15-negative in this model. Black patients are 2.5 and 9.4 times more likely than Asian or Caucasian patients to be DR15-negative in this model.

**Table 3 Summary of model results for DRB1*15 and DQB1*0602**

<table>
<thead>
<tr>
<th>Model</th>
<th>Variable</th>
<th>Coefficient</th>
<th>Standard error</th>
<th>Wald chi-square</th>
<th>$p$ value</th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRB1*15 #1</td>
<td>Constant</td>
<td>$8.47 \times 10^{-10}$</td>
<td>0.5345</td>
<td>0.00</td>
<td>1.00</td>
<td>6.40</td>
</tr>
<tr>
<td></td>
<td>Cataplex</td>
<td>1.5686</td>
<td>0.5710</td>
<td>7.55</td>
<td>0.006</td>
<td>4.80</td>
</tr>
<tr>
<td>DRB1*15 #2</td>
<td>Constant</td>
<td>$-0.4675$</td>
<td>0.5833</td>
<td>0.64</td>
<td>0.42</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>Cataplex</td>
<td>1.3596</td>
<td>0.5881</td>
<td>5.34</td>
<td>0.02</td>
<td>3.90</td>
</tr>
<tr>
<td></td>
<td>Caucasian</td>
<td>0.9350</td>
<td>0.3930</td>
<td>5.66</td>
<td>0.02</td>
<td>2.55</td>
</tr>
<tr>
<td></td>
<td>Asian†</td>
<td>2.2434</td>
<td>1.0618</td>
<td>4.46</td>
<td>0.03</td>
<td>9.45</td>
</tr>
<tr>
<td>DQB1*0602</td>
<td>Constant</td>
<td>0.2877</td>
<td>0.5401</td>
<td>0.28</td>
<td>0.59</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>Cataplex</td>
<td>1.9161</td>
<td>0.5975</td>
<td>10.28</td>
<td>0.001</td>
<td>6.79</td>
</tr>
</tbody>
</table>

* Caucasians compared with blacks.
† Asians compared with blacks.

that a small but significant portion (10%) of non-DR15 patients may carry rare DQB1*0602-positive haplotypes without DR15. Typing for DQB1*0602 should thus ideally be performed in all patients instead of typing for DR2 or DR15.

Although the percentage of blacks and Asians positive for these markers is similar to those reported in earlier studies, the percentage of Caucasian subjects positive for either DR15 (DR2) or DQB1*0602 is slightly lower than usually reported (i.e., 91–100%). We are aware of only two other studies reporting such a low percentage of Caucasian subjects with cataplexy who are positive for DRB1*15.

**Discussion.** Our finding that ethnicity influences the frequency of DRB1*15 among narcoleptic patients confirms previous studies that used much smaller sample sizes. Only 41 of our 61 (67.2%) black narcoleptic subjects were positive for this marker, compared with 84.5% (n = 87) of our Caucasian subjects and 95.8% (n = 23) of our Asian subjects (see table 2). In contrast, DQB1*0602 positivity was roughly equivalent in all ethnic groups, with values ranging from 86.1 to 91.3% (table 2). Typing for DQB1*0602, rather than for DRB1*15, thus increased diagnostic specificity in blacks but has little or no influence in Asians or Caucasians. In this last ethnic group, however, a recent study has shown that

In favor of this last hypothesis, the presence of "clear-cut" versus "possible" cataplexy was identified as a critical factor in predicting both DR15 and DQB1*0602 positivity. This contrasted with the poor predictive value of the MSLT findings in this group of patients with cataplexy (see table 2). Significantly more subjects with clear-cut cataplexy were positive for DRB1*15 than subjects whose symptoms were considered atypical or possible cataplexy (82.3% versus 50.0%, $\chi^2 = 8.80, p = 0.003$). Only 57.1% of subjects with possible cataplexy were positive for DQB1*0602 compared with 90.1% of those with clear-cut cataplexy. Cataplexy was a significant covariate in both models. Patients with history of cataplexy were more likely to be positive for DR15 and DQB1*0602 than patients with no history of
cataplexy. Clearly clinically defining cataplexy might thus be more important than the MSLT for the diagnosis of narcolepsy.

Even in patients with clear-cut cataplexy, HLA DQB1*0602 is neither sufficient nor necessary for the diagnosis of narcolepsy. Approximately 10% of patients with definite cataplexy (with or without MSLT findings) were DQB1*0602 negative in this large series. Genetic epidemiologic data also suggest that HLA-related genetic factors constitute only a small fraction of genetic predisposition to narcolepsy. Twelve to thirty-eight percent of the normal general population in various ethnic groups carry the HLA DQB1*0602 allele and only 0.02 to 0.06% of the population has narcolepsy-cataplexy. The gene has been sequenced in many control and narcoleptic subjects and found to be normal in all cases. Even if DQB1*0602 is the actual HLA narcolepsy susceptibility gene, it is thus a very low penetrance factor since more than 99.9% of individuals with the gene do not have narcolepsy. Family and twin studies also suggest the importance of environmental and non HLA genetic factors.

In spite of these limitations, HLA typing can be a useful diagnostic tool, especially in cases where cataplexy is doubtful, atypical, or not present. Samples described in the literature contain varying portions of “narcoleptic” subjects without cataplexy (8–42%), suggesting that this less-studied clinical subgroup might actually represent a substantial number of patients. The absence of DQB1*0602 in subjects without or with atypical cataplexy should lead the clinician to explore more thoroughly other possible causes for excessive daytime sleepiness (e.g., abnormal breathing or movements during sleep) and this may have therapeutic consequences. MSLT testing might also be more useful in this group of patients with “possible narcolepsy” than in patients with cataplexy. In our study, of the 157 patients with clear-cut cataplexy who had undergone an MSLT, only 132 (84%) had typical MSLT results (sleep latency ≤8 min and ≥2 SOREMPs). Thus, many genuinely narcoleptic patients would be excluded if positive MSLT findings were required for the diagnosis. In contrast, MSLT can be very useful to demonstrate sleepiness in patients with ill-defined fatigue, tiredness, or sleepiness, with or without sleep paralysis or other symptoms of abnormal REM sleep.

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