The Epidemiology of Narcolepsy

W.T. Longstreth, Jr., MD, MPH1,2; Thomas D. Koepsell, MD, MPH1,3,4; Thanh G. Ton, PhD1,5; Audrey F. Hendrickson, MPH1,2; Gerald van Belle, PhD1,5,6

1The Neuroepidemiology Research Group at the University of Washington, 2Department of Neurology, School of Medicine, and Departments of 3Epidemiology, 4Health Services, 5Biostatistics, and 6Environmental and Occupational Health Sciences, School of Public Health and Community Medicine, Seattle, WA

Abstract: Much has been learned about the pathophysiology of narcolepsy over the last several decades. It is likely that hypocretin-producing cells in the lateral hypothalamus are selectively destroyed in genetically susceptible individuals carrying 1 or more alleles of HLA DQB1*0602. Despite advances, the causes of narcolepsy and how to prevent it remain elusive. Classic epidemiology aims not only to enumerate occurrence of disease in populations, but also to identify etiologic risk factors. This review details what the application of classic epidemiology has taught us so far about narcolepsy and suggests directions for future studies to clarify its etiology. The prevalence of narcolepsy with cataplexy has been examined in many studies and falls between 25 and 50 per 100,000 people. Information on incidence is limited, with 1 study finding the incidence of narcolepsy with cataplexy to be 0.74 per 100,000 person-years. The search for etiologic risk factors has yet to yield important associations. Factors most thoroughly examined include body mass index, immune responses, and stressful life events. Such associations may reflect a consequence rather than a cause of disease. As with other diseases characterized by selective cell loss, such as Parkinson disease or type 1 diabetes mellitus, narcolepsy is likely caused by environmental exposures before the age of onset in genetically susceptible individuals. Matching efforts in these other diseases and using large well-designed epidemiologic studies of narcolepsy, investigators must intensify the search for these exposures, focusing on the first 2 decades of life. Identification of modifiable risk factors will help to prevent this disease.

Keywords: Narcolepsy, epidemiology, prevalence, incidence, etiologic factors, risk factors

Citation: Longstreth WT Jr; Koepsell TD; Ton TG et al. The epidemiology of narcolepsy. SLEEP 2007;30(1):13-26.

INTRODUCTION

THIS REVIEW CONCERNS THE EPIDEMIOLOGY OF NARCOLEPSY. AFTER SOME BRIEF INTRODUCTORY COMMENTS, WE WILL SUMMARIZE WHAT IS KNOWN FROM DESCRIPTIVE STUDIES ABOUT MEASURES OF DISEASE FREQUENCY IN VARIOUS POPULATIONS. WE WILL THEN TURN TO ANALYTIC STUDIES THAT ATTEMPT TO IDENTIFY RISK FACTORS FOR NARCOLEPSY. FINALLY, WE WILL REVIEW THE TYPES OF ANALYTIC EPIDEMIOLOGIC STUDIES THAT COULD BE CONSIDERED IN EXPLORING FURTHER HYPOTHESES ABOUT THE CAUSE OF NARCOLEPSY.

History

In 1880, Gélineau applied the term narcolepsy to a sleep disorder characterized by excessive daytime sleepiness and episodic weakness triggered by strong emotions.1 Subsequently, the term cataplexy was adopted to describe the episodic weakness.2,3 Diagnostic criteria evolved emphasizing the clinical tetrad of excessive daytime sleepiness, cataplexy, sleep paralysis, and hypnagogic hallucinations.4 In the 1950s and 1960s, the duality of sleep with rapid eye movement (REM) and non-REM sleep was recognized in normal people,5 and sleep-onset REM was described in patients with narcolepsy.6 In the 1970s, the multiple sleep latency test (MSLT) was added to the polysomnogram as a way to document sleepiness and episodes of sleep-onset REM periods (SOREMPs).7 The recognition that obstructive sleep apnea syndrome was a common treatable cause of sleepiness and that diagnostic tests were reimbursable led to a proliferation of sleep medicine centers with expertise in diagnosing sleep-related conditions including narcolepsy.3

Diagnosis

Key to the diagnosis of narcolepsy is the combination of a common symptom, excessive daytime sleepiness, and an uncommon symptom, cataplexy. Formal sleep studies with polysomnography and the MSLT can be used to document the sleepiness and SOREMPs. Caution must be exercised in making a diagnosis of narcolepsy in the absence of cataplexy because formal sleep studies fall short of 100% sensitivity or specificity.7-9 Diagnostic criteria have been recently updated to define narcolepsy with cataplexy, narcolepsy without cataplexy, and narcolepsy due to another underlying medical condition (Table 1).10 Criteria for narcolepsy with cataplexy have changed little since the first recognition of the disease. Although encouraged, formal sleep studies are not required for a diagnosis of narcolepsy with cataplexy.

The new classification scheme also incorporates knowledge about genetics and hypocretins (orexins) to create clinical and pathophysiologic subtypes of narcolepsy. These aspects of the disease have been extensively reviewed.11 The association of narcolepsy with HLA, especially HLA DQB1*0602, has been recognized for decades.12 Because of studies in twins and families, this HLA type is not thought sufficient in itself for the development...
of the disease. Most people with this HLA DQB1*0602 do not have and will never develop narcolepsy. Familial forms of narcolepsy are known but represent a distinct minority. The frequency of HLA DQB1*0602 in patients with narcolepsy depends upon how the disease is defined but is highest among those who have cataplexy.

More recently, a remarkable series of studies have suggested that narcolepsy results from the selective loss of cells in the lateral hypothalamus that secrete a neurotransmitter called hypocretin or orexin. Hypocretin-1 (orexin A) can be measured in the cerebrospinal fluid (CSF) and has been found to be low in most patients diagnosed with narcolepsy with cataplexy, especially those with HLA DQB1*0602 positivity.13-16 The sensitivity is around 90%, with specificity even higher.17 Nonetheless, about 10% of patients with typical narcolepsy with cataplexy will have normal levels, and, conversely, some patients with narcolepsy without cataplexy will have low levels. Heterogeneity of the disease is further suggested by DQB1*0602 positive monozygotic twin pairs. One pair concordant for narcolepsy with cataplexy had normal levels in both twins,18 whereas another pair discordant for narcolepsy had low levels only in the twin with narcolepsy.19 Experiments in animals suggest that symptoms of narcolepsy may not appear until a critical number of hypocretin-producing cells are lost and that the remaining cells may increase their output to compensate for the loss.20,21

Table 1—Diagnostic Criteria for Narcolepsy

<table>
<thead>
<tr>
<th>Narcolepsy With Cataplexy</th>
<th>Narcolepsy Without Cataplexy</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Excessive daytime sleepiness</td>
<td>A. Excessive daytime sleepiness</td>
</tr>
<tr>
<td>B. Definite history of cataplexy</td>
<td>B. Typical cataplexy is not present</td>
</tr>
<tr>
<td>C. MSLT optional but advised</td>
<td>C. Abnormal MSLT required</td>
</tr>
<tr>
<td>D. Hypersomnia not better explained by another disorder</td>
<td>D. Hypersomnia not better explained by another disorder</td>
</tr>
</tbody>
</table>


Epidemiology

Epidemiology comprises the study of distribution, determinants, and outcomes of illness in human populations with the goal of improving people’s health.22 Epidemiology can be divided into 2 broad areas of study, classic and clinical.23 Classic epidemiology begins with descriptions of the occurrence and distribution of disease in a population, through descriptive studies. But the power of its methods lies in the attempt to discover determinants of disease, through analytic studies. The identification of etiologic risk factors opens the possibility of preventing disease by controlling modifiable risk factors. Importantly, prevention is possible even when the pathophysiology of disease is unknown, and, conversely, prevention does not always follow as the pathophysiology or pathomechanism of disease starts to be clarified. Clinical epidemiology uses the techniques of classic epidemiology but applies them to populations of patients rather than populations of healthy people. The key question is not who will develop disease but who will experience a particular outcome from disease. Here the drive is to identify modifiable prognostic factors whose control through interventions improves outcomes. This review is limited to the classic epidemiology of narcolepsy and starts with descriptive studies measuring prevalence, which is the proportion of people with narcolepsy in a population at a particular time, and incidence, which is the rate at which people in a population develop narcolepsy over time.

Descriptive Studies

Prevalence

Putting aside case reports, which characterized much of the earliest literature, the beginnings of epidemiologic research on narcolepsy can be tracked to large case series, especially reports from physicians at the Mayo Clinic detailing their experience with the disease. The first patient given this diagnosis was seen at the Mayo Clinic in 1919; 35 patients, all with cataplexy, were seen between 1919 and 192824 and 33 patients were seen just in 1931.25 Although interesting for the increasing numbers seen at a single referral center, these studies do not provide useful estimates of the prevalence of narcolepsy in any defined population or time period. Given the different study designs, disease definitions, age groups and geographic regions used in investigations on the prevalence of narcolepsy—not surprisingly—estimates of prevalence have differed. Studies are summarized in the excellent work by Partinen and Hublin26 and in Table 2A, which is broken into sections that attempt to explain some of the differences in estimates.

Some of the highest estimates of prevalence come from studies in which subjects report having been diagnosed with narcolepsy, ranging in four studies from 168 to 799 per 100,000, with broad and overlapping 95% confidence intervals (Table 2A).27-30 The results strain credibility given how often participants had never heard of narcolepsy in a 1997 survey of 1001 adults in the United States conducted by the Gallup Organization.29 Only 53% had heard of narcolepsy, and only 28% of those participants felt they knew what it was.

Estimates are also high from studies based solely on an initial symptom screen without more in-depth evaluations (Table 2A). If the initial screen has a low threshold, which may enhance sensitivity but can compromise specificity, the number who screen positive can be inflated by many false positives. In several such surveys, prevalence has ranged from 10% to 30%.31-34 In one of these studies,34 10% of customers in Swiss pharmacies met criteria for narcolepsy based on their responses on the Stanford Sleep Disorders Questionnaire.35 When more strict screening criteria are used, estimates are lower, ranging from 160 to 660 per 100,000 people (Table 2A).36-41

Estimates from other studies are lower still. For some, the exact methods used to derive the estimate are unclear or involve many assumptions (Table 2A).42-46 For others, the methods are clearer, and the estimates are fairly consistent, except for those from the

SLEEP, Vol. 30, No. 1, 2007
<table>
<thead>
<tr>
<th>Study year</th>
<th>Location and population</th>
<th>Diagnosis</th>
<th>Number diagnosed/number screened</th>
<th>Prevalence per 100,000 (95% CI)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1992</td>
<td>Tampere, Finland Random stratified sample of adults</td>
<td>Questionnaire</td>
<td>2/1,190</td>
<td>168 (20 - 606)</td>
<td></td>
</tr>
<tr>
<td>1993</td>
<td>Wisconsin, United States Random sample of state employees aged 30-60 y</td>
<td>Questionnaire physician-diagnosis of narcolepsy</td>
<td>13/4,931</td>
<td>264 (140 - 450)</td>
<td>Investigators provided additional information to allow estimates to be calculated</td>
</tr>
<tr>
<td>1997</td>
<td>United States National sample aged 18 y and older</td>
<td>Telephone survey with physician diagnosis of narcolepsy</td>
<td>8/1,001</td>
<td>799 (346 - 1569)</td>
<td>Gallup Organization provided additional information to allow estimates to be calculated.</td>
</tr>
<tr>
<td>2000</td>
<td>Switzerland Postal clerks aged 19-65 y</td>
<td>Questionnaire</td>
<td>3/668</td>
<td>449 (93 - 1,307)</td>
<td></td>
</tr>
</tbody>
</table>

**Initial symptom screen without follow up testing**

<table>
<thead>
<tr>
<th>Study year</th>
<th>Location and population</th>
<th>Diagnosis</th>
<th>Number diagnosed/number screened</th>
<th>Prevalence per 100,000 (95% CI)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001</td>
<td>Kuwaiti adolescents aged 14 to 18 y</td>
<td>Symptoms from questionnaire</td>
<td>336/2,574</td>
<td>13,054 (11,775 - 14,417)</td>
<td>Sudden attacks of irresistible sleep</td>
</tr>
<tr>
<td>2003</td>
<td>Wisconsin, United States Random sample of state employees aged 30-60 y</td>
<td>Symptoms from questionnaire</td>
<td>790/3,023</td>
<td>26,133 (24,574 - 27,738)</td>
<td>At least 1 of the major symptoms of narcolepsy besides excessive daytime sleepiness.</td>
</tr>
<tr>
<td>2005</td>
<td>Sivas, Turkey Random sample of adults</td>
<td>Interview using standard questionnaire</td>
<td>1,633/5,339</td>
<td>30,586 (29,352 - 31,842)</td>
<td>Answering “yes” to 3 of 14 questions related to narcolepsy</td>
</tr>
<tr>
<td>2006</td>
<td>Customers at Swiss pharmacies</td>
<td>Stanford Sleep Disorders Questionnaire</td>
<td>493/4,901</td>
<td>10,059 (9,231 - 10,935)</td>
<td>Using published cut-off values</td>
</tr>
<tr>
<td>1979</td>
<td>Fujisawa City, Japan aged 12-16 y</td>
<td>Screening questionnaire</td>
<td>20/12,469</td>
<td>160 (98 - 248)</td>
<td>“Symptoms indicating narcolepsy”</td>
</tr>
<tr>
<td>1982</td>
<td>Finland Male military recruits with mean age 20 y Aged 17-59 y</td>
<td>Questionnaires</td>
<td>8/2,537</td>
<td>315 (136 - 620)</td>
<td>Answered yes to excessive daytime sleepiness and cataplexy</td>
</tr>
<tr>
<td>1992</td>
<td>Japan</td>
<td>Questionnaire</td>
<td>27/4,559</td>
<td>592 (390 - 860)</td>
<td>Using prespecified cut-off on Ullanlinna Narcolepsy Scale</td>
</tr>
<tr>
<td>1994</td>
<td>Finland White twins aged 33 – 60 y</td>
<td>Screen</td>
<td>75/11,354</td>
<td>660 (520 - 827)</td>
<td>Using prespecified cut-off on Ullanlinna Narcolepsy Scale</td>
</tr>
<tr>
<td>1998</td>
<td>Population in south of France 15 years and older</td>
<td>Questionnaire screen</td>
<td>29/14,195</td>
<td>204 (137 - 293)</td>
<td>Questionnaires displayed and distributed in waiting rooms of physicians.</td>
</tr>
<tr>
<td>2002</td>
<td>China, Hong Kong Chinese residents aged 18-65 y</td>
<td>Phone screen, interview</td>
<td>28/9,851</td>
<td>284 (188 - 410)</td>
<td>Chinese version of the Ullanlinna Narcolepsy Scale</td>
</tr>
</tbody>
</table>

**Studies with many or unknown assumptions**

<table>
<thead>
<tr>
<th>Study year</th>
<th>Location and population</th>
<th>Diagnosis</th>
<th>Number diagnosed/number screened</th>
<th>Prevalence per 100,000 (95% CI)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1972</td>
<td>San Francisco Bay Area, United States Uncertain age</td>
<td>Newspaper advertisements and phone interviews All with cataplexy</td>
<td>?</td>
<td>50 (?)</td>
<td>Many assumptions and estimates</td>
</tr>
<tr>
<td>1973</td>
<td>Los Angeles area, United States Uncertain age</td>
<td>Television show</td>
<td>?</td>
<td>67 (?)</td>
<td>Many assumptions and estimates</td>
</tr>
</tbody>
</table>
Middle East and a single study from Singapore. Unknown is whether the low prevalence in these studies reflects differences in methods, genetic susceptibility, exposure to etiologic risk factors, or some combination. For example, in Israel, only 6.8% of 252 healthy controls had DQB1*0602, suggesting that this population, compared with others, has fewer individuals who are genetically susceptible to developing narcolepsy.

Of the remaining studies, the oldest and perhaps most problematic concerns young African American military recruits screened by a neuropsychiatric interview at Camp Lejeune, North Carolina. When cataplexy was required, the prevalence was 20 per 100,000. Details are not provided about screening results on white military recruits, in which the prevalence is given as 3 per 100,000. The remaining studies all concern patients seen in more recent times and provide estimates from 26 to 79 per 100,000 with broad and overlapping confidence intervals.

Table 2a—continued

<table>
<thead>
<tr>
<th>Year</th>
<th>Country</th>
<th>Methodology</th>
<th>Prevalence</th>
<th>Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>1987</td>
<td>Israel</td>
<td>Sleep study, HLA, and cataplexy</td>
<td>6/4,300,000</td>
<td>0.14 (0.05 - 0.30)</td>
</tr>
<tr>
<td>1993</td>
<td>Thugbah, Saudi Arabia</td>
<td>Door-to-door survey with neurologist evaluation</td>
<td>1/22,630</td>
<td>4 (0.1 - 25)</td>
</tr>
<tr>
<td>2005</td>
<td>Singapore</td>
<td>Survey of providers and pharmacies</td>
<td>454,160,000</td>
<td>1.08 (0.79 - 1.45)</td>
</tr>
<tr>
<td>1945</td>
<td>United States</td>
<td>Neuro-psychiatric interview</td>
<td>2/10,000</td>
<td>20 (2 - 72)</td>
</tr>
<tr>
<td>1982</td>
<td>Finland</td>
<td>Questionnaire and clinic evaluation in subset</td>
<td>2/2,537</td>
<td>79 (10 - 284)</td>
</tr>
<tr>
<td>1982</td>
<td>Italy</td>
<td>Questionnaire and sleep study</td>
<td>1/2,518</td>
<td>40 (1 - 221)</td>
</tr>
<tr>
<td>1996</td>
<td>United Kingdom</td>
<td>Telephone system</td>
<td>2/4,972</td>
<td>40 (5 - 145)</td>
</tr>
<tr>
<td>2002</td>
<td>Five European countries</td>
<td>Telephone system</td>
<td>9/18,980</td>
<td>47 (22 - 90)</td>
</tr>
<tr>
<td>1998</td>
<td>Population in south of France aged 15 y and older</td>
<td>Questionnaire screen followed by phone interview</td>
<td>3/14,195</td>
<td>21 (4 - 62)</td>
</tr>
<tr>
<td>1994</td>
<td>Finland</td>
<td>Screen, sleep study, HLA typing</td>
<td>3/11,354</td>
<td>26 (5 - 77)</td>
</tr>
<tr>
<td>2002</td>
<td>Hong Kong, China</td>
<td>Phone screen, interview, sleep study, HLA</td>
<td>3/9,851</td>
<td>30 (6 - 89)</td>
</tr>
<tr>
<td>2002</td>
<td>Minnesota, United States</td>
<td>Medical records</td>
<td>35/97,667</td>
<td>36 (25 - 50)</td>
</tr>
</tbody>
</table>

The superscripted number refers to the reference number.

Point estimate and exact binomial confidence intervals (CI) per 100,000.
studies begin with a screen of symptoms followed up by more detailed testing, with the exception being the study from Mayo Clinic investigators. 6 Although other studies suggesting that many patients with narcolepsy do not come to medical attention or that narcolepsy is not diagnosed if they do,39,57 the estimates from Olmsted County are remarkably similar to those based on multistaged screening of particular populations. Perhaps residents of Olmsted County differ from those living elsewhere in their access to medical care and likelihood of their narcolepsy being diagnosed. One advantage of such studies includes identifying a larger number of people with narcolepsy, with the resulting estimate of prevalence having narrower 95% confidence intervals than in studies with multistaged screening of a population. The most methodologically sound studies seem consistent with the findings from Olmsted County,66 suggesting that the prevalence of narcolepsy with cataplexy is in the range of 25 to 50 per 100,000.

The prevalence of narcolepsy is higher when cataplexy is not required: 56 per 100,000 with the 95% confidence interval 42 to 73 in the study from Olmsted County.6 In the community-based Wisconsin Sleep Study, nocturnal polysomnograms and MSLTs were performed in 556 people.9 Criteria for narcolepsy without cataplexy (Table 1) were met in 13 (2.3%), of whom 5 (0.9%) were also positive for HLA DQB1*0602. These findings suggest that current criteria for narcolepsy without cataplexy (Table 1) will identify many false positives, that many more people are affected by narcolepsy than would be suggested by considering only those symptomatic with typical cataplexy, or that a combination of these explanations is present.9

Incidence

Investigators at the Mayo Clinic also used the records-linkage system of the Rochester Epidemiology Project to estimate the incidence of narcolepsy. The average incidence between 1960 and 1989 was 0.74 per 100,000 person-years for narcolepsy with cataplexy and 1.37 per 100,000 person-years for narcolepsy with or without cataplexy (Table 2b),66 putting it in the range of what has been described for multiple sclerosis and motor neuron disease. If the incidence and time course of illness remain stable over time, prevalence should approximately equal incidence times duration of illness.22 Applying this relation with results from Olmsted County suggests that the estimated duration of narcolepsy with or without cataplexy would be about 48.6 years (36/0.74).

Demographics

Sex, race, ethnicity, and geographic distribution have not been studied beyond what has already been described in the studies of prevalence and incidence. In Olmsted County, narcolepsy was more common in men than women,66 as suggested in an early case series from the Mayo Clinic.23 Considering all patients with narcolepsy, the relative risk was 1.6:1, and prevalence ratio was 1.8:1. Considering patients with narcolepsy with cataplexy, the relative risk was 1.2:1, and prevalence ratio was 1.4:1. These findings and those from the Wisconsin Sleep Cohort Study6 suggest that the sex difference is greater in those without cataplexy. Although a case series had suggested a bimodal distribution of onset with 1 peak around age 15 and a second peak around age 35,68 the Mayo Clinic study did not.69 In Olmsted County, the median age of onset was 16 years old with a range from 4 to 56. The 25th percentile for onset was 12.5 years; the 75th percentile, 25.7 years; and the 90th percentile, 33.4 years. Onset did not differ by sex or HLA type.

Analytic Studies

Several etiologic hypotheses for narcolepsy have been suggested. Over a decade ago, Guilleminault wrote,60 “Clearly, at this time, one must conclude that some combination of genetic and environmental factors is probably involved in the development of human narcolepsy.” We now summarize findings on studies examining a number of factors possibly related with the risk of narcolepsy.

Lifestyle

Little has been reported about lifestyle and behavioral risk factors such as exercise, alcohol use, tobacco use, or illicit drug abuse. One study suggested that excessive alcohol use may be more common in patients with narcolepsy.51

Obesity

Many studies have indicated an association between narcolepsy and obesity (Table 3), as was suggested in early case series.24,25 In small studies from the 1970s, narcoleptic cases reported eating more snacks than controls,62-64 but, in a subsequent study, were found to consume fewer kilojoules of food per day than controls.65 The early studies also demonstrated that narcoleptic cases were more likely to be overweight than were controls.62-64 An observation subsequently confirmed by others.14,66-71 Using oral glucose tolerance tests, Honda and associates identified definite non–insulin-dependent diabetes mellitus in 6 of 48 (12.5%) patients with narcolepsy in Japan and argued that this prevalence was higher than reported in other populations in Japan.66

<table>
<thead>
<tr>
<th>Table 2b—Studies on the Incidence of Narcolepsy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study year</strong></td>
</tr>
<tr>
<td>200266</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

*The superscripted number refers to the reference number. 
*Point estimate and exact binomial confidence intervals (CI) per 100,000.

SLEEP, Vol. 30, No. 1, 2007
### Table 3—Studies of Factors Potentially Associated With Narcolepsy

<table>
<thead>
<tr>
<th>Study Year</th>
<th>Number of Cases</th>
<th>Diagnosis of Narcolepsy</th>
<th>Number of controls</th>
<th>Source</th>
<th>Factors examined</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>197562</td>
<td>24</td>
<td>Unknown cataplexy</td>
<td>14</td>
<td>Community</td>
<td>Eating habits</td>
<td>Cases more likely overweight and more snacks than controls</td>
</tr>
<tr>
<td>197663,64</td>
<td>42</td>
<td>Unknown cataplexy</td>
<td>16</td>
<td>Unknown</td>
<td>Eating habits</td>
<td>Cases more likely overweight and more snacks than controls</td>
</tr>
<tr>
<td>199665</td>
<td>12</td>
<td>All with cataplexy</td>
<td>12</td>
<td>Matched on sex and social class</td>
<td>Spontaneous food choice</td>
<td>Cases consumed fewer kilojoules of food per day than controls</td>
</tr>
<tr>
<td>198666</td>
<td>197</td>
<td>All with cataplexy</td>
<td>96</td>
<td>General psychiatry patients</td>
<td>Weight</td>
<td>Obesity more common in cases than controls</td>
</tr>
<tr>
<td>200148</td>
<td>132</td>
<td>All but 3 with cataplexy</td>
<td>5,236</td>
<td>Sample of general Swiss and German population</td>
<td>BMI</td>
<td>Greater in cases than controls</td>
</tr>
<tr>
<td>200148</td>
<td>132</td>
<td>All but 3 with cataplexy</td>
<td>104</td>
<td>Psychiatric inpatients</td>
<td>BMI</td>
<td>Greater in cases than controls</td>
</tr>
<tr>
<td>200144</td>
<td>38</td>
<td>All with cataplexy</td>
<td>34</td>
<td>Healthy and neurologic controls</td>
<td>BMI and CSF leptin</td>
<td>BMI greater in cases than controls. CSF leptin higher in cases than controls</td>
</tr>
<tr>
<td>200370</td>
<td>138</td>
<td>With and without cataplexy</td>
<td>10,696</td>
<td>Sample of general Dutch population</td>
<td>BMI and waist circumference</td>
<td>Obesity and excess body fat more common in cases than controls</td>
</tr>
<tr>
<td>200370</td>
<td>138</td>
<td>With and without cataplexy</td>
<td>33</td>
<td>Patients with idiopathic hypersomia</td>
<td>BMI and waist circumference</td>
<td>Obesity and excess body fat more common in cases than controls</td>
</tr>
<tr>
<td>200371</td>
<td>124</td>
<td>Newly diagnosed</td>
<td>120</td>
<td>Newly diagnosed with other conditions</td>
<td>BMI</td>
<td>Greater in cases than controls</td>
</tr>
<tr>
<td>200472</td>
<td>31</td>
<td>Children</td>
<td>31</td>
<td>Age and gender matched</td>
<td>BMI</td>
<td>Greater in cases than controls</td>
</tr>
<tr>
<td>200573</td>
<td>157</td>
<td>75% with cataplexy</td>
<td>164</td>
<td>Spouses of patients with sleep disorders</td>
<td>BMI</td>
<td>Greater in cases than controls even controlling for age and gender</td>
</tr>
<tr>
<td>200074</td>
<td>15</td>
<td>All with cataplexy</td>
<td>30</td>
<td>Psychiatric and neurologic patients matched on age, sex, and BMI</td>
<td>Serum and CSF leptin</td>
<td>Serum levels lower in cases than controls</td>
</tr>
<tr>
<td>200275</td>
<td>6</td>
<td>All with cataplexy, HLA DQB1*0602, and low CSF hypocretin 1</td>
<td>6</td>
<td>Matched on age, sex, BMI</td>
<td>Plasma leptin levels</td>
<td>Decreased in cases compared to controls</td>
</tr>
</tbody>
</table>

**Migraine**

<table>
<thead>
<tr>
<th>Study Year</th>
<th>Number of Cases</th>
<th>Diagnosis of Narcolepsy</th>
<th>Number of controls</th>
<th>Source</th>
<th>Factors examined</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>200370</td>
<td>96</td>
<td>From approved sleep clinics With and without cataplexy</td>
<td>96</td>
<td>Matched on age and sex</td>
<td>Formal evaluation for headache</td>
<td>Migraine not more common (OR 1.13; 95% CI 0.56-2.27) but other types of headaches were (OR 2.23, 95% CI 1.38-3.61)</td>
</tr>
</tbody>
</table>

**Genetic issues**

<table>
<thead>
<tr>
<th>Study Year</th>
<th>Number of Cases</th>
<th>Diagnosis of Narcolepsy</th>
<th>Number of controls</th>
<th>Source</th>
<th>Factors examined</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>200177</td>
<td>420</td>
<td>All with cataplexy in 3 ethnic groups</td>
<td>1,087</td>
<td>Unknown in 3 ethnic groups</td>
<td>Other HLA class II alleles</td>
<td>Six increased and three decreased risk. Also increased risk with DQB1*0602 homozygosity</td>
</tr>
<tr>
<td>200177</td>
<td>149</td>
<td>All DQB1*0602 positive</td>
<td>83</td>
<td>All DQB1*0602 positive</td>
<td>TNF and its receptor-2 genes</td>
<td>Increased risk with the combination of both. Also Decreased risk with DRB1*1501</td>
</tr>
<tr>
<td>200689</td>
<td>370</td>
<td>All with cataplexy and DQB1*0602 positive</td>
<td>735</td>
<td>DQB1*0602 positive in 125</td>
<td>Genomewide search with 23,244 microsatellite markers</td>
<td>In series of case-control studies, new resistance gene found on chromosome 21</td>
</tr>
</tbody>
</table>
Table 3—continued

<table>
<thead>
<tr>
<th>Year</th>
<th>Cataplexy</th>
<th>Sleep Apnea</th>
<th>Serologic reactions to bacterial and viral agents</th>
<th>Cases with significantly more elevated antibodies to streptolysin O, 42% vs. 2% Elevated in both groups, 23% in cases and 33% in controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>1989</td>
<td>52</td>
<td>49</td>
<td>Unknown</td>
<td>Serologic reactions to bacterial and viral agents</td>
</tr>
<tr>
<td>1989</td>
<td>31</td>
<td>18</td>
<td>Idiopathic hypersomnia</td>
<td>Antibodies to streptolysin O</td>
</tr>
<tr>
<td>1990</td>
<td>100</td>
<td>107</td>
<td>Unknown</td>
<td>Antibodies to streptolysin O</td>
</tr>
<tr>
<td>2005</td>
<td>63</td>
<td>63</td>
<td>Unknown</td>
<td>Infectious diseases</td>
</tr>
<tr>
<td>1988</td>
<td>11</td>
<td>10</td>
<td>Sleep apnea</td>
<td>Many autoimmune screens</td>
</tr>
<tr>
<td>2002</td>
<td>41</td>
<td>0</td>
<td>Multiple autoantibodies</td>
<td>No support for autoimmune hypothesis</td>
</tr>
<tr>
<td>2003</td>
<td>28</td>
<td>0</td>
<td>Antiganglioside antibodies</td>
<td>No support for autoimmune hypothesis</td>
</tr>
<tr>
<td>2004</td>
<td>39</td>
<td>40</td>
<td>Family and friends</td>
<td>All elevated in cases</td>
</tr>
<tr>
<td>2005</td>
<td>41</td>
<td>55</td>
<td>Patient with OSA</td>
<td>IgG reactive to prepro-hypocretin, hypocretin-1 &amp; 2</td>
</tr>
<tr>
<td>1989</td>
<td>9</td>
<td>13</td>
<td>Patients undergoing lumbar punctures</td>
<td>IgG reactive to prepro-hypocretin, hypocretin-1 &amp; 2</td>
</tr>
<tr>
<td>2005</td>
<td>34</td>
<td>49</td>
<td>Patients with OSA and psychiatric problems</td>
<td>Various hypocretin antibodies</td>
</tr>
<tr>
<td>2005</td>
<td>45</td>
<td>57</td>
<td>Unknown</td>
<td>Serum tests seeking reactivity to rat hypothalamic extract</td>
</tr>
<tr>
<td>2005</td>
<td>76</td>
<td>111</td>
<td>Unknown</td>
<td>Autoantibodies against human lateral hypothalamic neurons</td>
</tr>
<tr>
<td>2006</td>
<td>76</td>
<td>63</td>
<td>Without any medical condition</td>
<td>Autoantibodies against human lateral hypothalamic neurons</td>
</tr>
<tr>
<td>2006</td>
<td>181</td>
<td>101</td>
<td>Healthy controls and 10 with other hypersomnias</td>
<td>Serum autoantibodies against hypocretin and its 2 receptors</td>
</tr>
<tr>
<td>2004</td>
<td>9</td>
<td>9</td>
<td>Unknown</td>
<td>Functional autoantibodies enhancing postganglionic cholinergic neurotransmission</td>
</tr>
<tr>
<td>2005</td>
<td>20</td>
<td>20</td>
<td>Unknown</td>
<td>IgG in CSF reactive to rat hypothalamic protein extract</td>
</tr>
<tr>
<td>Stress</td>
<td>1994</td>
<td>50</td>
<td>Matched</td>
<td>Life-stress events in year before onset</td>
</tr>
<tr>
<td>2005</td>
<td>63</td>
<td>63</td>
<td>Unrelated family and community members</td>
<td>Psychological stressors</td>
</tr>
</tbody>
</table>

*Superscripted numbers refer to the reference numbers.
BMI refers to body mass index; CSF, cerebrospinal fluid; TNF, tumor necrosis factor; IL, interleukin; OSA, obstructive sleep apnea; IgG, immunoglobulin G.
In a comprehensive study, Kok and associates compared anthropometric data in 138 patients with narcolepsy to similar measurements made in a population survey of 10,696 people and to a group of 33 patients with idiopathic hypersomnia. Excess body mass index and excess body fat, as reflected in waist circumference, were more common in case patients with narcolepsy than those in the 2 control groups. The findings did not seem to depend upon the drugs used by the patients with narcolepsy, an observation also made by others. The differences with patients affected by idiopathic hypersomnia suggested that the findings did not simply reflect sleepiness and inactivity but, rather, reflected hypocretin levels, which was documented in the CSF of a subgroup of the patients with narcolepsy and idiopathic hypersomnia. In another study, body mass index was higher in narcoleptic patients with lower CSF hypocretin-1 levels, compared with those with higher CSF hypocretin-1 levels. Although 1 study documented higher CSF leptin levels in cases than controls, another study did not. Two studies showed serum leptin levels lower in cases than in controls. Whether a problem with leptin production, resistance, or some combination plays a role in narcolepsy and obesity is unresolved by these studies.

Although obesity seems to be present from the early stages of the disease, even in disease with onset in childhood, whether it predates the onset of symptoms of narcolepsy is unknown. Obesity in patients with narcolepsy may be related to some other substance produced by hypocretin-containing cells in that mice lacking these cells have obesity whereas those lacking just hypocretin do not. Whether obesity provides clues about etiology or is simply a manifestation of narcolepsy cannot be resolved by these case-control studies, none of which examined weight before the onset of disease, for example, at birth.

**Associated Diseases**

Given these considerations about obesity, patients with narcolepsy may be at greater risk than the general population for conditions that can complicate abdominal obesity, including type 2 diabetes mellitus and cardiovascular disease. Given that HLA-DQB1*0602 is protective for type 1 diabetes mellitus, one would expect fewer narcoleptics to be affected with type 1 as opposed to type 2 diabetes mellitus, but such studies are yet to be done.

A high prevalence of migraine in patients with narcolepsy was suggested by initial case series: 54% of 68 patients in 1 study and 37% of 100 patients in another. In a follow-up case-control study including 96 patients with narcolepsy and 96 healthy matched controls, a significant association was not found with migraine but was found with other types of headaches, which in all but 2 subjects met criteria for tension-type headaches. The investigators suspected that these headaches were most likely a consequence of the sleep disorder or its treatment. Narcolepsy is also said to be associated with other sleep disorders, which may reflect in part the bias of being cared for by sleep medicine specialists.

**Timing of Birth**

A preliminary study on narcolepsy from France suggested peaks for births of patients destined to develop narcolepsy in March and August, with a valley in November. An increase in March and a decrease in September was described in a study from the United States and in a larger overlapping study with patients from France, Canada, and the United States. An increase in the first half of year, especially in the spring, and a decrease in the second half of the year, especially in September, was described in a German study. Using data from the randomized trial of modafinil, investigators found an overall excess of births in March and deficit in September in patients with narcolepsy with cataplexy. The differences were not significant except in the subgroup whose cataplexy was moderate or severe. Such studies suggest that an exposure in utero may increase risk of disease, in which case concordance in monozygotic and dizygotic twins would be expected to be greater than has been described. Alternatively, an infection in the first few months following birth could affect subsequent risk of narcolepsy.

**Genetics**

Although the association of narcolepsy with HLA-DQB1*0602 is well established and will not be reviewed further, investigators have attempted to define other genetic contributors to disease risk. In a large case-control study involving 420 case patients with narcolepsy and cataplexy and 1,087 control subjects, investigators examined the risk associated with other HLA class II alleles. They found 6 alleles increased and 3 alleles decreased the risk. Also, risk was increased with DQB1*0602 homozygosity. In another case-control study—in which all subjects, cases and controls, were HLA-DQB1*0602 positive—investigators looked at tumor necrosis factor and its receptor-2 genes in 149 cases and 83 controls. Results showed associations with certain combinations of tumor necrosis factor and its receptor-2 genes. Finally, in a series of recent case-control studies, investigators used genome-wide association studies starting with 23,244 microsatellite markers to identify a novel resistance gene on chromosome 21. They proposed the name narcolepsy candidate-region gene (NLC1-A) and found it to be expressed in the human brain, including the hypothalamus. Confirmation of these findings and investigations of other regions is pending.

**Immune Considerations**

Given that genetic susceptibility to narcolepsy is linked to a specific HLA type, many investigators have suspected an immunologic basis for the disease, either by an autoimmune mechanism or in response to some external antigen, possibly an infectious agent. Two studies have suggested a role for streptococcal infections. Streptococcal disease has long been associated with brain dysfunction thought to be based on an immunologic response, such as with Sydenham chorea and, more recently, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS). Unfortunately, results from these initial studies could not be confirmed in a subsequent large study. Infections in general were addressed in another case-control study, in which 63 patients with narcolepsy with cataplexy were recruited from the Stanford Center for Narcolepsy. An equal number of controls frequency matched on age were recruited from unrelated family members of cases and local community members. Using a mailed self-administered questionnaire, information was collected about events prior to age 20 years old. Flu infections (odds ratio 1.8, p < .05) and unexplained fevers (odds ratio 3.9, p < .05) were more common in cases than in controls.

Several case-control studies have examined a variety of labora-
ory tests that could support an immunologic basis for narcolepsy. In an early study, investigators looked for markers of autoimmune process but found none, including rheumatoid factor, antinuclear antibodies, antibodies to rodent brain and primate brain stem, and neurotoxic antibodies. In case series without controls, investigators studied blood and CSF but found little support for an immune-mediated etiology. In another study, tumor necrosis factor-α and interleukin-6 and human growth hormone were found to be higher in narcoleptics (n = 39) than in controls (n = 40), who were nonnarcoleptic family members and friends. Nonetheless, multiple other efforts have failed to find differences between cases with narcolepsy and controls in a variety of measures, as detailed in Table 3.

Some studies have provided support for an immune-mediated etiology. Comparing 9 cases and 9 controls, investigators identified functional autoantibodies in immunoglobulin G fraction of patients with narcolepsy but not controls. The autoantibodies enhanced postganglionic cholinergic neurotransmission. Other investigators have found significant differences when they compared CSF of 20 patients with narcolepsy and 20 controls. The patients with narcolepsy all had cataplexy, carried HLA DQB1*0602, and had low CSF hypocretin-1 concentrations. The narcoleptic patients but not the controls had immunoglobulin G in their CSF that reacted to a rat hypothalamic protein extract, presumably containing hypocretin-secreting cells. Difficult in all of these studies is knowing if positive findings represent a cause or effect of the disease.

**Stress**

Case series initially suggested a role for stress, and subsequently 2 case-control studies found associations with stressful events prior to the onset of disease. In the more recent case-control study, major changes in sleeping habits (odds ratio = 2.0, p < .01) and childbirth (odds ratio = 2.7, p < .05) were more common in cases than in controls. Total stressors before age 10 years old were also associated (odds ratio 1.2, p < .05). In a small case series of 9 patients, closed head injury was suggested as another possible stress. Such studies are challenging because patients with narcolepsy may be more motivated to recall stressful events than control subjects who lack a dramatic event such as the onset of a chronic disease.

**Hypothesis and Epidemiologic Study Designs**

**Hypothesis**

Analytic studies begin with an etiologic hypothesis or model. For narcolepsy, such a model might posit that genetically susceptible individuals, as defined by having 1 or more alleles of HLA DQB1*0602, are exposed to an environmental agent that selectively and irreversibly affects the neurotransmitter systems involved in REM-sleep regulation by destroying hypocretin-producing cells in the hypothalamus. The system either fails at the time of the exposure or at some later date, possibly following some event that brings the patient to medical attention, at which time symptoms may be recognized as due to narcolepsy (Figure 1). Given that most individuals have the onset of their symptoms of narcolepsy in late adolescence, the exposures responsible for most cases would need to have occurred during or before late adolescence. Lack of concordance of narcolepsy in twins makes less likely an exposure prior to birth, namely in utero.

Analytic studies use a variety of epidemiologic study designs to address an etiologic hypothesis, with the 2 main observational study designs being the case-control study and the cohort study. Each has its advantages and disadvantages. Regardless of which is used, design considerations should always include the number of subjects needed to ensure that important associations are not missed due to inadequate statistical power. Investigators must also be alert to the possibility of confounding and effect modification and accept that more than a strong association is needed to establish causality.

**Case-Control Studies**

For investigations of uncommon diseases like narcolepsy, case-control studies may have advantages, especially when hypotheses include gene-environment interactions. Investigators begin by identifying patients with narcolepsy. To reduce the risk of bias, ideally, patients with narcolepsy comprise all of the cases in a defined population, not just those seen at specialty clinics. Identification of control subjects is then simplified in that they are recruited from the same population. If gene-environment interactions are suspected and a marker for genetic susceptibility is known, the search for environmental risk factors is facilitated if cases and controls are chosen to be similar on this marker. Information on past exposures is then collected from cases and controls in an identical fashion, concentrating on exposures occurring before the onset of the disease, say for narcolepsy before the age of 20. To make sure that strong associations are not missed, analyses must consider the genetic marker and seek gene-environment interactions (Table 4).

**Cohort Studies**

Rather than starting with a group of cases with the disease, the investigator begins a cohort study by assembling a cohort of people who are free of the disease of interest. The exposures of interest are documented, and both exposed and nonexposed individuals are followed over time for the occurrence of disease. Study cohorts can be assembled prospectively or retrospectively. Although the cohort design is a powerful tool for epidemiologic investigations of etiology, prospective cohort studies may not be practical with uncommon diseases such as narcolepsy, and retrospective cohort studies depend on having good preexisting data on quite a large population. The study from Olmsted County.
would never be identified or included in such studies. Information on a particular risk factor was available on the entire incidence that are reported in Table 2a and b. To the extent that patients with narcolepsy were identified between 1960 and 1995 in Olmsted County using the record-linkage system of Minnesota, represents an example of a retrospective cohort study, in which patients with narcolepsy were identified and used to calculate prevalence and conclusion is not statistically significant.

A. Case-Patients Control-Subjects
Exposed 21 72
Not exposed 41 178
62 250
Odds ratio (21*178)/(41*72) = 1.3
(95% Confidence interval 0.7 - 2.4)

HLA DQB1*0602 alleles sought and found in 80% of cases and 20% of controls. Anticipating such a difference, investigators had recruited proportionately more controls than cases to obtain comparable numbers of cases and controls in the following analysis. Only those with 1 or more alleles are included in subsequent analyses and in Table B. The association is stronger. The 95% confidence interval does not include 1, and the association is statistically significant.

B. Case-Patients Control-Subjects
Exposed 17 6
Not exposed 33 44
50 50
Odds ratio (17*44)/(33*6) = 3.8
(95% Confidence interval 1.2 - 12.9)

In those without any HLA DQB1*0602 alleles, Table C shows no association with exposure.

C. Case-Patients Control-Subjects
Exposed 4 66
Not exposed 8 134
12 200
Odds ratio (4*134)/(8*66) = 1.0
(95% Confidence interval 0.2 - 3.9)

Conclusion: A gene-environment interaction is present. Exposure to the putative risk factor only confers risk in those who carry 1 or more HLA DQB1*0602 alleles.

Minnesotans, represents an example of a retrospective cohort study, in which patients with narcolepsy were identified between 1960 and 1995 in Olmsted County using the record-linkage system of the Rochester Epidemiology Project. A total of 72 patients with narcolepsy were identified and used to calculate prevalence and incidence that are reported in Table 2a and b. To the extent that information on a particular risk factor was available on the entire population in Olmsted County, it could be evaluated in this retrospective cohort study. Small numbers of patients with narcolepsy, especially those with cataplexy, would limit the statistical power of such studies. Also, without a screen of the entire population, some patients with narcolepsy, especially those without cataplexy, would never be identified or included in such studies.

Given the estimates on incidence and prevalence of narcolepsy, huge numbers of people would need to be screened for the diagnosis of narcolepsy in a prospective cohort study. In the classical cohort study design, information on potential etiologic risk factors would have to be collected on the entire cohort. Although such studies may seem impossible, they have been done for other chronic disabling diseases, such as multiple sclerosis and Parkinson disease, although not as a primary goal of the original study, which typically concerns more common diseases, such as vascular disease and cancer. An example would be the cohort study of multiple sclerosis in female registered nurses living in the United States. The investigation included combining results from 2 prospective studies, 1 recruiting 121,700 nurses in 1976, and the other, 116,671 nurses in 1989, for a total of 238,371 nurses. On follow-up, consisting of 2,349,356 person-years, 173 women were diagnosed with multiple sclerosis and were eligible for the study of vitamin D, which was found to be protective.

To date, etiologic questions in narcolepsy have not been addressed in such cohort studies. Even assuming that all participants with prevalent narcolepsy with cataplexy could be identified among the 238,371 nurses in this study and given the estimate above from Olmsted County of prevalence of narcolepsy with cataplexy of 36 per 100,000, investigators would anticipate finding only 86 nurses with prevalent narcolepsy. Also, the exposure of interest would have had to have been collected as part of the original study. Otherwise, information on the past exposure would need to be collected from everyone in the cohort. Alternatively, a nested case-control or case-cohort design could be used, getting exposure data on just a sample of noncases or a sample of the full cohort. Either design would offer major advantages in efficiency. One can even still estimate exposure-specific prevalences, albeit with somewhat wider confidence limits than if exposure data were available on everyone.

**DISCUSSION**

Compared with other chronic disabling diseases of the nervous system, relatively few epidemiologic studies of narcolepsy have been performed, especially analytic studies addressing etiologic hypotheses. The prevalence of narcolepsy with cataplexy lies between 25 and 50 per 100,000 people. In 1 study, the incidence of narcolepsy with cataplexy was estimated to be 0.74 per 100,000 person-years (95% confidence interval 0.47-1.16). With respect to risk factors, the association with HLA DQB1*0602 is well established and makes a gene-environment interaction likely to play a role in the etiology of narcolepsy with cataplexy. Studies showing associations with obesity are consistent but may reflect a consequence rather than a cause of the disease. Evidence to support an immune mechanism of disease has been sought but has not yet pointed to the inciting event, avoidance of which could prevent the disease.

Other diseases with selective cell loss may provide useful lessons for investigators seeking risk factors for narcolepsy. Parkinson disease results from a selective loss of dopamine-secreting cells in the substantia nigra. Parkinson disease is an example in which gene-environment interaction is strongly suspected but not yet been established despite substantially more effort than has been devoted to narcolepsy. Both diseases result from imbalances in neurotransmitter systems. Both are improved by medications that act through these systems to try to restore balance. Suspicions that neurotoxins could cause parkinsonism have been confirmed by observations in patients and animals exposed to certain chemicals, but especially to the meperidine derivative 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). This
toxin is very selective in irreversibly damaging a neurotransmitter system that employs dopamine. An intensive epidemiologic search continues to identify a xenobiotic that, in susceptible individuals, could act like MPTP to selectively injure neurotransmitter systems and result in Parkinson disease. Such an ecogenic hypothesis may explain other chronic nervous system diseases.

The selective cell loss need not be in the brain to carry potential lessons. Type 1 diabetes mellitus has some remarkable similarities to narcolepsy. Both involve selective loss of cells that secrete an essential chemical, in the case of type 1 diabetes, the beta cells in the pancreatic islets of Langerhans that secrete insulin.\(^\text{121,122}\) Like narcolepsy, the disease typically starts in childhood, in a genetically susceptible individual defined by certain HLA types. Figure 1 is actually modified from a figure included in a review of type 1 diabetes.\(^\text{122}\) Curiously, the HLA haplotype associated with susceptibility to narcolepsy is found to be protective in type 1 diabetes mellitus. An autoimmune disease is suspected, and autoantibodies have been identified to islet cells, insulin, and glutamic acid decarboxylase (GAD). Whether they are a cause or effect of the process that destroys islet cells is uncertain.

Much remains to be learned about the etiology of narcolepsy using the techniques of epidemiology, and the search for etiologic risk factors for narcolepsy should be intensified, as has occurred with many other diseases that affect the nervous system. One advantage with narcolepsy is that the genetic predisposition and the critical period of exposure in the environment are both well defined. Prospective cohort studies specifically about narcolepsy are not likely to be done for reasons discussed above. Retrospective cohort studies are possible, as the investigators from the Mayo Clinic have demonstrated, and should be used to seek etiologic risk factors. On the other hand, case-control studies may be the most efficient means to address etiologic hypotheses, especially those including a gene-environment interactions. Finally, case-control studies can be nested in cohort studies if cases can be identified within the cohort study and some assessment is needed, such as blood or CSF test, which would not be appropriate to perform on all members of the cohort. The case patients could be identified and matched to control subjects on factors such as demographics and HLA type and then assessed in a similar fashion. Information prospectively collected as part of the cohort study could be used, or new information could be collected. Such a nested design often requires fewer resources than the cohort design.

Given the similarities between narcolepsy and type 1 diabetes, a search for some of the risk factors suggested for type 1 diabetes, including viral infections, toxins, and certain foods.\(^\text{123}\) Although investigators have already begun the search for evidence to support an immunologic basis for narcolepsy, little has been done to investigate a neurotoxin as has also been suggested with Parkinson disease. Genetic susceptibility to a neurotoxin could be conferred in a number of ways.\(^\text{124}\) Whether an HLA gene or another in genetic disequilibrium with the HLA haplotype, the genetic factor could make the sleep-regulatory system or its development more susceptible to injury from a toxin. The genetic factor could also alter the way in which a potential toxin is metabolized, resulting in failure to break down a toxin or in excess production of a toxin from a pro-toxin.

With respect to neurotoxins, a chemical that has the potential to affect brain function seems most likely. Such a substance could include medications or illicit drugs. Exposure to environmental neurotoxins, such as heavy metals, pesticides, and solvents could happen with certain behaviors such as pica, with certain activities such as playing outdoor sports, or with certain hobbies such as those involving glues and paints. Although most work histories before adulthood will be limited, certain jobs likely done by children and adolescents such as gardening and lawn work could involve exposures to pesticides and fertilizers. Parents’ work history could also be important in this regard as a source for a potential neurotoxin.

The funding of epidemiologic studies of narcolepsy will remain a challenge. Given the relative scarcity of the disease, multisite collaborative efforts may be needed. Having narcolepsy advocacy groups involved in the design and implementation of such studies will be useful but in proportion to the strength of the group. Using lessons learned from other advocacy groups such as for type 1 diabetes mellitus may also be important. Perhaps partnerships would be useful for diseases whose etiologic pathways may be similar, such as is the case for narcolepsy and type 1 diabetes. The task of finding the etiology for narcolepsy will always depend on a partnership with the basic sciences, but epidemiologic studies can have an important role to play in elucidating how pathophysiologic mechanisms ultimately impact the public’s health.

ACKNOWLEDGMENT

This work was supported by a grant from the National Institute of Neurological Disorders and Stroke (NS038523).

REFERENCES


34. Bell IR, Hawley CD, Guilleminault C, Dement WC. Diet and symptoms of narcolepsy in two large populations of patients in France and Quebec. Neurology 2002;51:578-84.


85. Piccioni D, Mignot EJ, Harsh JR. The month-of-birth pattern in narcolepsy is moderated by cataplexy severity and may be independent of HLA-DQB1*0602. Sleep 2004;27:1471-5.


