NARCOLEPSY

Diagnoses Received by Narcolepsy Patients in the Year Prior to Diagnosis by a Sleep Specialist

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Study Objectives: Narcolepsy is a neurological disorder whose clinical features include excessive daytime sleepiness, hypnagogic hallucinations, cataplexy, sleep paralysis, and disrupted nocturnal sleep. It has been shown that there may be quite a long interval between the onset of symptoms, and the correct diagnosis. We tested the hypothesis that given their severe symptomatology, these patients would have been diagnosed more often with a variety of psychiatric and neurologic conditions than controls in the year prior to confirmation of their narcolepsy diagnosis.

Design: Using the Province of Manitoba Health database, we compared the diagnoses made in the year prior to initial sleep disorder center evaluation of 77 patients with narcolepsy (33 males, 44 females) and 1155 matched control subjects from the general population.

Setting: Sleep disorders center in University-based teaching hospital

Participants: N/A

Interventions: N/A

Measurements and Results: Patients were much more likely than controls to be diagnosed with mental disorders (Odds ratio (OR) = 4.0645; 95% confidence limit (CL) = 2.4671-6.6962; p<0.0001) and nervous system disorders (OR= 5.0495; CL = 3.0606 –8.3309; p<0.0001) and there was a trend towards more injuries in these patients (OR =1.6316; CL = 0.9857-2.7007; p=0.0514). We found that cases were statistically much more likely than controls to have received a diagnosis for neurotic disorders (17% of cases), depression (16%), personality disorders (3%) and adjustment reaction (4%). Although the cases had twice as many doctor visits as the controls (9.3±0.97 (sem) vs. 4.8±0.17 p<0.0001), only 38% of them had received a diagnosis of narcolepsy in the year prior to sleep specialist evaluation. Neurologists had the highest “success rate” for correct diagnosis: neurologists diagnosed narcolepsy in 55% of the cases they had seen. The other medical practitioners diagnosed narcolepsy in a much smaller percentage of the cases they had seen: 23.5% for internists (excluding neurologists), 21.9% for general practitioners, 11.1% for psychiatrists, and 0% for pediatricians.

Conclusions: In the year prior to documentation of narcolepsy in a sleep disorders center, patients with narcolepsy were diagnosed with a wide variety of mental and neurologic disorders. Our findings are supportive of either the coexistence of these disorders in narcolepsy patients or a high frequency of missed diagnosis by their clinicians. The latter may help explain the very long interval between onset of symptoms and correct diagnosis.

Key words: Narcolepsy; health care utilization; medical economics; mental disorders; depression

INTRODUCTION

NARCOLEPSY IS A NEUROLOGICAL DISORDER WHOSE CLINICAL FEATURES INCLUDE EXCESSIVE DAYTIME SLEEPINESS, HYPNAGOGIC HALLUCINATIONS, CATAPLEXY, SLEEP PARALYSIS, AND DISRUPTED NOCTURNAL SLEEP.1-3 Great strides have been made in the understanding of this still enigmatic disorder; reduced levels in the nervous system of the recently described neuropeptide, hypocretin 1;4 progress in the elucidation of the genetic control of hypocretin production;5 and, the association of this disorder with the HLA system, which had suggested that autoimmunity may play a role.6 Although in most cases the symptoms of narcolepsy begin during the teenage or young adult years, the disorder may first be evident in the very young,7-11 or in middle-aged adults. It has been shown that there may be quite a long interval between the onset of symptoms, and the current diagnosis.12This interval may be over a decade. Because of this long interval, and because misdiagnosis may occur,13,14 we wondered what patients who were ultimately diagnosed with narcolepsy had been diagnosed with prior to their being referred to a sleep disorders center for the first time. We hypothesized that given their severe symptomatology, these patients would have been diagnosed more often than controls with a variety of psychiatric and neurologic conditions. We compared diagnoses made during visits to doctors in a group of patients with narcolepsy and matched controls.

METHODS

This study was conducted in Manitoba, a Canadian province. All permanent residents have access to government funded health care services. These include physician visits, diagnostic procedures, therapeutic procedures, and hospitalizations. For each visit to a physician, a standardized claim form is submitted to a central government agency (Manitoba Health), which then renders payment. Manitoba Health maintains a detailed computer database, the Manitoba Health database (MHdb), which tracks all visits to physicians, hospitalizations, and associated diagnoses and costs for all residents of Manitoba. This database, described in greater detail elsewhere,15 allows us to track health care utilization of individuals and diagnoses over extended intervals.16-18 The database includes International Classification of Disease (ICD-9 CM) codes for each visit based on the diagnoses stated on individual physician claim cards submitted for each physician
We assessed diagnoses made by physicians (along with their respective ICD-9 codes in brackets) in the major disease categories: Infectious and parasitic diseases (001-139); Neoplasms (140-239); Endocrine, nutritional and metabolic diseases, and immunity disorders (240-279); Diseases of the blood and blood-forming organs (280-289); Mental disorders (290-319); Diseases of the nervous system and sense organs (320-389); Diseases of the circulatory system (390-459); Diseases of the respiratory system (460-519); Diseases of the digestive system (520-579); Diseases of the genitourinary system (580-629); Complications of pregnancy, childbirth and the puerperium (630-677); Diseases of the skin and subcutaneous tissue (680-709); Diseases of the musculoskeletal system and connective tissue (710-739); Congenital anomalies (740-759). We also examined other categories that could be placed on a claim card when the practitioner does not use a specific diagnostic category including: Symptoms, signs, and ill-defined conditions (780-799); Injury and poisoning (800-999); Supplementary classification of factors influencing health status and contact with health services (V codes V01-V82). These latter categories (especially 780-799) are used when a practitioner is unsure of a diagnosis and instead indicates a symptom.

Confidentiality of narcolepsy cases and controls (see below) was ensured by “encrypting” each person’s health insurance number and using the encrypted number as that person’s only unique identifier. This project was approved by the Human Ethics Committee of the University of Manitoba and the Access and Confidentiality Committee of Manitoba Health.

Selection of Cases

All the patients in our study were residents of Manitoba who had been referred by their doctors to our Sleep Disorders Centre. This center is one of two in the city; both are associated with university teaching hospitals. These two centers provide sleep medicine services for the entire province. One of the authors (MHK) evaluated the cases. Patients were studied with polysomnography and Multiple Sleep Latency Testing, if there was any ambiguity about their diagnosis, and were especially done to exclude sleep-breathing disorders. Polysomnography involved the recording of electroencephalogram, electro-oculogram, electromyogram, electrocardiogram, oxygen saturation, and end tidal carbon dioxide levels. Thoracic and abdominal movements were recorded using inductance plethysmography belts and we recorded activity in the anterior tibialis muscle. If patients met the criteria of sleep apnea, they were excluded.

We selected all patients who had a clinical diagnosis of narcolepsy using the guidelines of the International Classification of Sleep Disorders Diagnostic and Coding Manual. The patients met the minimal criteria for the diagnosis of narcolepsy. There are two sets of minimal criteria recommended for the diagnosis of narcolepsy. The first includes a combination of recurrent daytime naps or sleep attacks that occur almost daily for at least three months and the presence of cataplexy. The second is the combination of sleepiness or sudden muscle weakness plus associated features which may include sleep paralysis, hypnagogic hallucinations, automatic behaviors, disruptive major sleep episodes, and polysomnographic findings demonstrating one or more of: sleep latency <10 minutes; REM sleep latency <20 minutes; a multiple sleep latency test demonstrating a mean sleep latency of <5 minutes; two or more sleep onset REM periods; and the absence of any documented medical or psychiatric disorder that could account for the symptoms. All of our patients met one of the sets of diagnostic criteria.

Exclusions

We excluded all patients who had another primary sleep disorder such as sleep apnea, restless legs syndrome, or a medical condition (e.g., hypothyroidism), or a medication (e.g., benzodiazepines) that might explain the daytime sleepiness. We also excluded patients being treated for a chronic medical condition that would substantially confound our findings. This included dialysis for renal failure.

Selection of Controls

Using the population registry, and the database containing the health care utilization data, 15 control subjects from the general population were obtained for each case with narcolepsy. The patients and controls were matched by birth year, gender, and postal code. Matching for age controls for that fact that older people go to the doctor more often; matching for gender controls for the fact that females go to the doctor more often; matching by postal code helps control for area of residence, distance, and access to health services, and socio-economic factors.

Statistical Methods

Odds ratios for cases being diagnosed in each of several diagnostic categories compared to controls were calculated using the Mantel-Haenzel method. Counts of ambulatory visits for cases and controls were compared using Poisson regression, correcting for overdispersion. Dummy variables corresponding to the age-sex groupings were entered into the model to control for the group effects. All analysis was conducted on a Sun Microsystems workstation running SAS version 8.1 (SAS Institute, Cary, North Carolina). Probability values less than 0.05 were considered significant.

RESULTS

Diagnoses

Seventy-seven cases and 1155 matched controls were available for analysis (see Table 1). We determined the odds ratio of a case being diagnosed with a disorder in the year prior to the diagnosis of narcolepsy being confirmed. First, we examined the broad diagnostic categories based on system and then examined the specific diagnoses within that system. We found that cases were more likely (see Table 2) than controls to have received a diagnosis in the category of mental disorders (36% of cases vs. 11.7% of controls), nervous system disorders (57.1% vs. 2%) and congenital anomalies (3% vs. 0.3%). Congenital anomalies had

<table>
<thead>
<tr>
<th>Table 1—Patient demographics</th>
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<tbody>
<tr>
<td>Age (SD) Cases (n=77) Controls (n=1155)</td>
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<tr>
<td>Male/ female 37.95 (19.02) 37.94 (18.91)</td>
</tr>
<tr>
<td>Male/ female 33/44 495/660</td>
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been diagnosed in 2 of the 77 cases and in only 4 of the 1155 controls. Practitioners were also much more likely to use the non-specific or symptom-based diagnoses in the cases. Several nearly significant trends were also observed: increased injury or poisoning (p=0.051), and increased musculoskeletal or connective tissue disorders (p=0.059).

Although cases were much more likely to have been diagnosed with a mental disorder, in general, on examining specific disorders the differences were only significant for the non-psychotic disorders. We found that cases were statistically much more likely (see Table 3) than controls to have received a diagnosis for neurotic disorders (17% of cases vs. 7% for controls), personality disorders (3% vs. 0.3%), adjustment reaction (4% vs. 0.7%), and depression (16% vs. 3%).

Although cases were much more likely to have been diagnosed with a neurological disorder, on examining specific disorders the differences were only significant for the disorders of the central nervous system, not the peripheral nervous system. We found that cases were more likely (see Table 4) than controls to have received a diagnosis for narcolepsy and cataplexy (38% of cases vs. 0% for controls), epilepsy (4% vs. 0.2%), migraine (3% vs. 1.6%). Not one of the control subjects had been diagnosed with narcolepsy. Doctors frequently used non-specific diagnoses in this group of cases (Table 5).

**Physicians**

We determined what type of medical practitioner the cases had seen in the year before sleep laboratory confirmation of their sleep disorder. The 77 cases had 715 ambulatory visits in the year prior. In 137 of the visits there was a diagnosis of narcolepsy. Cases had twice as many doctor visits (9.3±0.97 (sem) vs.
There was great variability between the specialties in how often narcolepsy was diagnosed (Table 6). We examined all visits that a patient made to an individual doctor (Patient/MD clusters in Table 6) and whether a diagnosis of narcolepsy was made in any one of the visits. Neurologists had the highest “success rate” for correct diagnosis: neurologists diagnosed narcolepsy in 55% of the cases they had seen. The other medical practitioners diagnosed narcolepsy in a much smaller percentage of the cases they had seen: 23.5% for internists (excluding neurologists), 21.9% for general practitioners, 11.1% for psychiatrists, and 0% for pediatricians.

**DISCUSSION**

We have found that patients in the year before they were formally assessed for narcolepsy for the first time had a much higher probability of being diagnosed and treated for mental as well as neurological disorders. We also found that patients were much more likely to receive non-specific symptomatic descriptions rather than diagnoses. There was a trend for an increase in musculoskeletal diagnoses in the cases and a statistically significant increase in the number of congenital disorders although the number of these was very small. Of interest, patients frequently did not receive a specific diagnosis with doctors’ visits but instead were categorized as having a symptom rather than a diagnosis. There was also a trend for patients for cases to have more injuries than the controls. In none of the other categories of disease (infectious, neoplastic, endocrine, blood, circulatory, digestive, genitourinary, skin), were the differences statistically significant.

In only a minority of patients was the diagnosis of narcolepsy made in the year prior to referral to a sleep disorders center. The fact that they were referred may indicate a referral bias; it is very likely that this minority of patients who had been diagnosed with narcolepsy still represents an overestimate of how often narcolepsy is diagnosed correctly in the community because all the patients who were referred to the sleep disorders center were thought by their doctors to have a sleep disorder. The lack of correct diagnosis cannot be attributed to reduced contact or access to health care services. In fact the cases had twice as many contacts with doctors as the controls and saw more doctors. These findings are consistent with the previous observation that patients may be undiagnosed for many years after the onset of symptoms.  

Broughton et al. found that the time between onset of symptoms and narcolepsy diagnosis was an astonishing 16 years in a group of 75 patients.

We found that medical practitioners differed in the frequency of diagnosing the cases as having narcolepsy in the year prior to sleep laboratory confirmation. It is not surprising that neurologists frequently did diagnose the patients correctly more than the other practitioners since narcolepsy is a neurologic disorder. The
fact that psychiatrists infrequently diagnosed narcolepsy but instead diagnosed psychiatric disorders may simply indicate a bias towards a practitioner making a diagnosis in his or her specialty.

When we examined specific diagnoses we found that patients had been diagnosed as having non-psychotic mental disorders more frequently than the cases but this was not true for the psychotic disorders in which there was no difference between cases and controls. Cases were much more likely to be diagnosed with neurotic disorders, personality disorders, adjustment reaction, and depression. It is reasonable to wonder whether depression is more frequently diagnosed in other disorders associated with daytime sleepiness. Our group has recently reported that depression is more frequently diagnosed in obstructive sleep apnea syndrome (OSAS) patients than controls in the five years before OSAS diagnosis (OR 1.4; 95% confidence interval 1.0-1.9). In narcolepsy we found the odds ratio for having been diagnosed with depression in the year before sleep center diagnosis was much higher (OR 5.47; 95% CI 2.70 –11.1). One must also bear in mind, however, that the mean age of the narcolepsy patients was much lower than the OSAS patients. It is important to appreciate that if a physician diagnoses a patient with a certain condition it does not mean that the patient has that condition. Many studies have probed a possible association between narcolepsy and psychiatric disorders. It has been suggested that REM sleep disinhibition may play a role in both depression and narcolepsy. However the conclusion of the reports are quite variable: for example, one study found that 60% of narcoleptics did not have present or previous psychiatric disorders, while another report of 12 subjects found that depression was absent in 75% of narcoleptics, and if present was usually mild. Our findings are compatible with the hypothesis that these patients might often be misdiagnosed for these mental disorders. We believe that it is quite possible that patients are frequently misdiagnosed because of some of the features of narcolepsy (sleepiness, sleep attacks, sleep paralysis, and cataplexy) may be a misinterpreted by a clinician not familiar with the clinical features of narcolepsy. This may be related to lack of training about sleep disorders at all levels of medical education. The current edition of perhaps the most widely used textbook of medical history taking does not even mention narcolepsy in the index; neither does the most widely used manual of medical therapeutics, or a recently published medical textbook. A single sentence mentions narcolepsy in a widely used textbook of ambulatory medicine. That misdiagnosis may occur has been previously reported. That misdiagnosis might be quite common in these patients is further supported by the finding that these patients have a much higher probability of being diagnosed as having “epilepsy” than the cases in the controls. The cataplexy (sudden loss of muscle tone) and sleep attacks could be misinterpreted as being features of an epilepsy syndrome. Zenan et al recently emphasized that narcolepsy patients may be misdiagnosed as having epilepsy; in two cases cataplexy was misinterpreted as epilepsy, in another hypnagogic hallucinations were thought to be due to temporal lobe seizures.

It is likely that the long interval between onset of symptoms and correct diagnosis increases health service costs and results in a very poor quality of life for the patients. This former issue, the financial impact on health service utilization, will be examined in greater detail in future research.

Conclusion

In the year prior to documentation of narcolepsy in a sleep disorders centre, patients with narcolepsy were diagnosed with a wide variety of mental and neurologic disorders. Our findings are supportive of either the co-existence of these disorders in narcolepsy patients or a high frequency of misdiagnosis by their clinicians. The latter may help explain the very long interval between onset of symptoms and correct diagnosis.

REFERENCES


