



Original Article

Narcolepsy is complicated by high medical and psychiatric comorbidities: a comparison with the general population

Maurice M. Ohayon*

Stanford Sleep Epidemiology Research Center, Stanford University School of Medicine, Palo Alto, CA, USA

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ABSTRACT

Background: Individuals affected with narcolepsy represent a vulnerable segment of the population. However, we only have a partial understanding of this vulnerability. Our study aims to examine psychiatric disorders and medical conditions associated with narcolepsy.

Methods: A total of 320 narcoleptic participants were interviewed regarding sleeping habits, health, medication consumption, medical conditions (International Statistical Classification of Diseases and Related Health Problems, 10th edition), sleep disorders (International Classification of Sleep Disorders, second edition [ICSD-2]) and mental disorders (Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision [DSM-IV-TR]) using Sleep-EVAL. A general population comparison sample ($N = 1464$) matched for age, sex, and body mass index (BMI) and interviewed with the same instrument was used to estimate odds ratios (OR).

Results: Five diseases were more frequently observed among narcoleptic participants, including hypercholesterolemia (OR, 1.51), diseases of the digestive system (OR, 3.27), heart diseases (OR, 2.07), upper respiratory tract diseases (OR, 2.52), and hypertension (OR, 1.32). Most frequent psychiatric disorders among the narcolepsy group were major depressive disorder (MDD) (OR, 2.67) and social anxiety disorder (OR, 2.43), both affecting nearly 20% of narcoleptic individuals. However, most mood and anxiety disorders were more prevalent among the narcoleptic group. Alcohol abuse or alcohol dependence was comparable between groups.

Conclusions: Narcolepsy is associated with a high comorbidity of both medical conditions and psychiatric disorders that need to be addressed when developing a treatment plan.

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1. Introduction

Narcolepsy is a debilitating neurodegenerative disorder characterized by daytime sleep attacks and rapid eye movement (REM) sleep abnormalities (e.g., sleep-onset REM periods, sleep paralysis, hypnagogic hallucinations). Narcolepsy is a rare disorder affecting less than 0.05% of the general population [1]. However, impacts on daytime functioning are considerable and many affected individuals have severe limitations in their daily life activities [2]. Some studies have reported a poorer health-related quality of life, as measured by the Short Form (36) Healthy Survey in narcoleptic patients when compared to the general population [3,4]. However, quality of life for these individuals tends to improve over time [4], possibly due to adaptation strategies for coping with the impact of the disease [4,5].

Individuals affected by narcolepsy represent a vulnerable segment of the population. However, we only have a partial under-

standing of this vulnerability. Narcoleptic individuals often have morbid obesity, and several also have sleep apnea syndrome (up to 25%) [6]. Both conditions put these individuals at greater risk for developing other serious health concerns such as cardiovascular diseases. Unfortunately, few studies have examined which health conditions and psychiatric disorders are associated with narcolepsy [7,8]. Understanding comorbid conditions associated with narcolepsy is of utmost importance when devising an appropriate treatment plan. Our study aims to present a detailed look at the mental and organic health concerns that affect narcoleptic individuals when compared with a matched general population sample.

2. Methods

2.1. Samples

2.1.1. Narcolepsy sample

A total of 320 narcoleptic participants were included in the study. Most of them were referred by sleep specialists. Twenty-two participants came from the general population and were diagnosed with narcolepsy by a sleep specialist.

* Tel.: +1 650 494 1137; fax: +1 650 493 1225.

E-mail address: mOhayon@stanford.edu

2.1.2. General population sample [9]

Fifteen states were selected to represent the US population based on the number of residents and geographic area. The 15 states that were included were Arizona, California, Colorado, Florida, Idaho, Missouri, New York, North Carolina, North Dakota, Oregon, Pennsylvania, South Dakota, Texas, Washington, and Wyoming. The final sample included 19,136 participants ages 18 years or older, who represented the general population of these states (138 million). Of 19,136 eligible adults, we obtained completed interviews from 15,929, providing an 83.2% cooperation rate using the Council of American Survey Research Organizations standards.

A total of 1464 participants from the general population who matched with the narcolepsy sample for age, gender, and body mass index (BMI) were retained from the total sample of 15,929 participants. Both studies, narcolepsy and general population, were done using the same tool and the same questionnaire. For both samples, interviewers explained the goals of the study to potential participants and requested verbal consent before conducting the interview. The participants had the option of calling the principal investigator if they wanted further information. The study was approved by the Stanford University Institutional Review Board.

2.2. Instrument

All participants were interviewed by telephone using the Sleep-EVAL system [10,11], a computer software specially designed to conduct epidemiologic studies in the general population and to administer questionnaires. Interviews with narcoleptic participants lasted an average of 71 (± 38.44) minutes; the median duration was 60.51 minutes.

All interviews began with questions about sociodemographic information and sleep-wake schedule, physical health queries, and questions related to sleep and mental disease symptoms. Once the answers were collected, the system looked for a series of plausible diagnostic hypotheses (causal reasoning process). Further questioning and deductions of the consequences of each answer allowed the system to confirm or reject these hypotheses. The system contained all questions required for entire diagnostic descriptions according to the International Classification of Sleep Disorders (ICSD-2) [12] and the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision (DSM-IV-TR) [13] classifications. The differential diagnosis process was based on a series of key rules allowing or prohibiting the co-occurrence of 2 diagnoses in accordance with ICSD and DSM-IV-TR prescriptions. The interview ended once all diagnostic possibilities were exhausted.

The system has been tested in various contexts, such as in clinical psychiatry and sleep disorders clinics [14–17]. In psychiatry overall κ between psychiatrists and the system was 0.71 [14]; κ has ranged from 0.44 (schizophrenia disorders) to 0.78 (major depressive disorder [MDD]). Agreement for insomnia diagnoses was obtained in 96.9% of cases (κ , 0.78). Overall agreement on any breathing-related sleep disorder was 96.9% (κ , 0.94) [15,16]. For excessive sleepiness as a symptom, κ between Sleep-EVAL and 3 sleep specialists ranged from 0.62 to 0.70, with an overall sensitivity of 98.3% and a specificity of 62.5%. For narcolepsy with cataplexy, κ between sleep specialists on the presence of narcolepsy ranged from 0.83 to 0.93, while κ between Sleep-EVAL and each sleep specialist were 0.89, 0.93 and 1.0 [17]. A subsample of 284 participants in this study also answered to the Stanford Sleep Inventory. Correlations between the 2 instruments administered within a 6-month interval were adequate: $r = 0.77$ on cataplexy, $r = 0.80$ on sleep paralysis, $r = 0.62$ on hypnagogic or hypnopompic hallucinations, and $r = 0.62$ on automatic behaviors. A κ of 0.84 was obtained between the 2 instruments on the narcolepsy diagnosis. Sleep-EVAL has a sensitivity of 82.7% and a specificity of 98.4%.

2.3. Variables

Information collected by the system included a complete description of symptoms of narcolepsy: (1) daytime sleepiness was assessed with a series of questions covering the severity of the sleepiness, frequency per week and per day, situations when the sleepiness occurred (i.e., during conversations, at work, quiet situations), age of onset, and consequences on daytime functioning. (2) Cataplexy was assessed by the description of affected muscles, situations triggering an episode, frequency of occurrence, age of onset, and moment of last episode. (3) Hypnagogic and hypnopompic hallucinations were assessed by types of hallucinations, frequency of occurrence, age of onset, and moment of last hallucination. (4) Sleep paralysis was assessed by frequency of occurrence, age of onset, and moment of last episode.

Information also was collected on sleep habits, sleep quality, medication, hospitalizations, and sleep and mental disorder diagnoses according to the DSM-IV-TR and ICSD classifications.

2.4. Narcolepsy treatment

Adequate treatment for narcolepsy was defined according to the standard of care proposed by the American Academy of Sleep Medicine [18] and the European Federation of Neurological Societies [19] for the treatment of narcolepsy, which includes the use of modafinil for the treatment of daytime sleepiness or sodium oxybate for the treatment of cataplexy, daytime sleepiness, and disrupted sleep due to narcolepsy.

The guidelines of care (i.e., treatments that have shown at least a moderate degree of clinical certainty) also were considered and included the use of amphetamine, methamphetamine, dextroamphetamine, and methylphenidate for treatment of daytime sleepiness and tricyclic antidepressants, selective serotonin reuptake inhibitors, venlafaxine, and reboxetine for the treatment of cataplexy.

2.5. Data analyses

Comparisons of age, sleep-wake schedule, and BMI were calculated using analyses of variance with post hoc Dunnett multiple comparisons C test. Variables abnormally distributed also were analyzed using the Mann-Whitney *U* nonparametric test. Logistic regression analyses were used to compute the odds ratios (OR) associated with narcolepsy. Reported differences were significant at the 0.05 level or less. SPSS version 19 was used to perform statistical analyses.

3. Results

3.1. General description of the samples

The narcolepsy sample was composed of 109 men and 211 women. The mean age was 40.27 (± 14.73) years and the BMI was 28.53 (± 6.78). Half of the participants were married (50.3%) and working (55.6%). Most of them were white (82.3%). The matched general population sample included 472 men and 992 women. The mean age was 43.78 (± 14.57) years, and the BMI was 26.79 (± 3.98). Half of them were married (50.9%) and most were working (66.1%). Most of them also were white (78.6%).

3.2. Comorbid organic conditions

Table 1 presents the most frequent organic conditions observed among narcoleptic participants and the matched general population. Five diseases were more frequently observed among

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