

## How age influences the expression of narcolepsy

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### Abstract

**Objectives:** The aim of this study was to investigate the influence of age on the manifestation of narcolepsy symptoms and cognitive difficulties in patients with narcolepsy. **Methods:** A total of 321 participants were included in the study: 157 were patients with narcolepsy from two Sleep Disorders Clinics and 164 were control participants. Narcoleptic patients were evaluated and diagnosed at the Sleep Disorders Clinic. All participants were interviewed by telephone using the Sleep-EVAL System. The interview comprised, among else, a detailed evaluation of narcolepsy symptoms and of cognitive difficulties. **Results:** The first manifestation of the disease appeared early in life for most narcoleptic patients: 54.1% had their first symptom before the age of 20 years. Daytime sleepiness was the first symptom to appear in 65.5% of cases. In narcoleptics 60 years or older, cataplexy was more likely to

be the first symptom to appear (47.4%) compared with other narcoleptic patients (21.4%;  $P < .05$ ). Reported cognitive difficulties (attention–concentration, praxis, delay recall, orientation for persons, temporal orientation, and prospective memory) were higher in narcoleptic patients compared with the controls. The severity of daytime sleepiness and the presence of a major depressive disorder partly explained the cognitive difficulties. However, attention–concentration deficits and difficulties in prospective memory remained significant. Age was unrelated to cognitive difficulties in narcoleptic patients. **Conclusions:** The first manifestation of narcolepsy appears early in life. Reported cognitive difficulties are important in narcoleptic patients and are only partly explained by age, severity of daytime sleepiness, and major depressive disorder. © 2005 Elsevier Inc. All rights reserved.

*Keywords:* Narcolepsy; Cataplexy; Cognitive functions; Symptom onset

### Introduction

Narcolepsy is a rare neurological disorder affecting less than 0.05% of the general population [1,2], although Japanese population surveys found higher rates [3,4]. Earlier reports from cohort and clinical studies [5,6] were already signaling the scarcity of this affection. This disease is characterized by daytime sleep attacks and manifestations of

various REM sleep abnormalities (cataplexy, sleep paralysis, and hypnagogic hallucinations).

Unfortunately, few studies have investigated the influence of age on the characteristics of narcolepsy, perhaps because this disorder is usually diagnosed late in the life of the patient. A recent study was underlying a fact: In half of the cases, narcolepsy was recognized after the age of 40 years [7]. At the level of clinical, polysomnographic, and multiple sleep latency test (MSLT) assessments, although most of the studies did not find significant changes with age [7,8], a recent study reported a decrease with age in the number of sleep-onset REM periods and an increase in the mean sleep latency on the MSLT [9].

Studies that investigated memory and attention in participants with narcolepsy had mixed results. Some studies that

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examined the level of sleepiness in relationship with cognitive performance in healthy participants found that sleepiness has an impact on memory [10], while others found that memory function remained intact [11,12]. Some studies reported that up to half of narcoleptic patients complained of memory problems [13,14], while other studies found that narcoleptics did not differ from normal participants on memory tasks [15,16]. Studies assessing the performance of narcoleptics on attention tasks found, on one hand, that there was little or no impairment in the ability to sustain attention [15,17], while, on the other hand, others demonstrated a clear deficit in vigilance and attention [18,19]. Moreover, the cognitive impairment related to age was not clearly identified in those patients. This issue could be of importance in determining the real impact due to the disease on cognitive functions. This disabling disorder has a deep impact on psychosocial functioning of the patients [20,21].

In fact, age and narcolepsy in its expressivity has not yet been thoroughly investigated. Consequently, this study aims to answer the following questions: (1) what are the first manifestations of the disease as reported by the patients? At what age did they appear? (2) What are the current clinical symptoms? Are they the same at different ages? (3) What are the specific sleep characteristics of narcoleptic patients by age categories? (4) What is the impact of narcolepsy on cognitive functions? Are these cognitive impairments related to age?

## Methods

The patients were recruited from two sleep clinics. They were recorded and diagnosed in these two sleep laboratories. Blood samples also were collected for HLA typing.

### Participants

Two groups were constituted for the purpose of this study:

- (1) A group of 157 narcoleptic patients 15 years of age and over. The patients were all diagnosed with narcolepsy and were followed at the Sleep Disorders Center of the San Raffaele Hospital (Milan, Italy) or at the Sleep Disorders Clinic of the Institute of Clinical Neurology at the University of Bologna (Bologna, Italy).
- (2) A control group composed of 164 adults composed of 64 spouses of the narcoleptic patients and 100 spouses of patients with other sleep disorders. No exclusion criteria were applied.

### Procedures

The narcoleptic patients were all assessed and diagnosed in one of the two sleep disorders clinics. One of the interviewers subsequently contacted the patients by telephone.

After explaining the study, verbal consent was obtained before collecting any information and starting the interview. The Sleep-EVAL interviews were done by university students at the San Raffaele Hospital (Milan, Italy). The study was approved by the ethical committee of the San Raffaele Hospital. Interviews lasted, on average, 72( $\pm$ 45) min.

Interviews were conducted using the Sleep-EVAL System [22,23], an expert system designed to administer questionnaires and conduct studies on mental and sleep disorders.

Two classifications are implemented in the knowledge base of Sleep-EVAL: the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV; [24]) and the International Classification of Sleep Disorders (ICSD; [25]). The system formulates initial diagnostic hypotheses on the basis of responses to a standard set of questions posed to all participants. Concurrent mental diagnoses are allowed in accordance with the DSM-IV. The system terminates the interview once all ICSD and DSM-IV diagnostic possibilities are exhausted. The system selects and phrases the questions to be administered and provides examples and instructions on how to ask them. The interviewer simply reads out the questions as they appear on the monitor and enters the responses. Questions can be close (e.g., yes–no, present–absent–unknown, five-point scale) or open ended (e.g., name of illness and duration).

The Sleep-EVAL System was tested within several designs [26–30]. Validation studies performed in sleep disorders clinics (Stanford University, Regensburg University, and Toronto Hospital) testing the diagnoses of the system against those of sleep specialists using polysomnographic data gave excellent results with the diagnosis of Obstructive Sleep Apnea Syndrome ( $\kappa$  of .93 and .92) and very good results with insomnia ( $\kappa$  of .78 and .71; [27,28]). A study using the Sleep-EVAL System was done with 96 narcoleptic individuals. They were all diagnosed and blood tested by sleep specialists. The Sleep-EVAL System had a nearly perfect recognition of narcoleptic individuals:  $\kappa$  of .96, with a sensitivity of 94.7% and a specificity of 100% [29]. Answers on narcolepsy symptoms provided during the Sleep-EVAL interviews were also compared with those provided on the Stanford Sleep Inventory (SSI). Data on both instruments were available for 82 narcoleptics and 202 family members. Sleep-EVAL's cataplexy questions had a sensitivity of 75.5% and a specificity of 95.8% and a correlation of .75 with the SSI [30].

### Assessment

The standard questionnaire of the Sleep-EVAL System covered (1) sociodemographic information; (2) the sleep–wake schedule; (3) symptoms of sleep disorders; (4) sleep hygiene; (5) current and past consumption of alcohol, tobacco, and coffee; (6) current and past consumption of medication for sleep, to reduce anxiety, antidepressants; (7) any other type of medication; (8) medical information: organic diseases, hospitalizations, medical consultations, and

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