Sleep Medicine 12 (2011) 572–577

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Original Article

High pain frequency in narcolepsy with cataplexy

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ARTICLE INFO

Article history:
Received 27 July 2010
Received in revised form 21 December 2010
Accepted 9 January 2011
Available online 12 May 2011

Keywords:
Pain
Narcolepsy
Cataplexy
Hypocretin
Depression
Sleep quantity
Sleepiness

ABSTRACT

Background: Narcolepsy with cataplexy (NC) is caused by the loss of hypocretin neurons. Recent studies highlighted the roles for hypocretins in the modulation of nociceptive transmission. The aims of the present multicenter case-control study were to look at the frequency of pain in NC and to study the determinants and impact of pain on narcolepsy symptoms and quality of life (QoL).
Methods: Sixty-seven adult patients with NC, together with their physician, partner/friend, and sex- and age-matched normal controls underwent a face-to-face interview and completed questionnaires on the presence and frequency of pain, narcolepsy symptoms and QoL (Short-Form 36-item score, Functional Outcomes of Sleep Questionnaire, Medical Outcomes Study, Fatigue Severity Scale, and Beck Depression Inventory).
Results: One-third (32.8%) of NC patients experienced pain at least monthly, with a significantly higher frequency and impact than controls (17.9%) and independent of the patients' narcolepsy medication. The reporting of pain was well matched between patients and partners/friends but significant differences were observed between patients and physicians, with physicians significantly underestimating its frequency and impact. The location of chronic pain varies within subjects with differences between NC and controls. We pinpointed that sleep quantity and depression were determinants for pain, and chronic pain had significant impact on sleep quantity, depression and QoL in NC.
Conclusion: We report, for the first time, evidence that chronic pain is significantly more common and disabling in NC compared to the general population. The findings call for improved attention to assessment and treatment of pain in the follow-up of NC.

1. Introduction

Narcolepsy with cataplexy (NC) is a rare debilitating sleep disorder mainly characterized by excessive daytime sleepiness (EDS) and cataplexy [1]. However, non sleep symptoms have been described recently or reconfirmed, such as obesity, olfaction problems, mood disorders, and headache [2–6].

The pathophysiology of NC is still unclear; however, deficiency of hypocretin-1 in the cerebrospinal fluid (CSF) has been found in most patients with a marked decrease of hypocretin neurons [7–9]. Hypocretin neurons are located in the lateral hypothalamus with many projections to the CNS [10]. Several lines of evidence suggest a role for hypocretin in nociceptive processing. First, localization of hypocretin fibers to the hypothalamus, thalamus, spinal trigeminal nucleus, and periaqueductal gray is consistent with a role in sensory processing [10,11]. Second, other hypocretin projections to the dorsal horns of the spinal cord and dorsal root ganglia argue its involvement in the descending control of pain [12]. Third, behavioral studies report that hypocretin is analgesic in animal models of nociception [13–17]. Finally, hypocretin-1 receptor antagonists were pro-hyperalgesic in inflammatory conditions [13–17]. Therefore, one may ask whether a dysregulation in the control of nociception may exist in the context of hypocretin deficiency.

From a clinical point of view, except for the studies reporting higher headache frequencies [5,6], the prevalence and impact of pain have never been reported in NC. The aims of the present study were (1) to look at the frequency of pain in NC compared to matched normal controls; (2) to compare perception of pain between patients, friends/partners and physicians; and (3) to study its determinants and impacts on narcolepsy symptoms and quality of life (QoL).

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doi:10.1016/j.sleep.2011.01.010

2. Methods

2.1. Subjects

This case-control cross-sectional study included 67 adult patients with NC identified during routine consultations in specialist sleep centers. Eighteen sleep specialists and experts in narcolepsy from four European countries (France [$n = 5$], Spain [$n = 5$], UK [$n = 4$], and Germany [$n = 4$]) participated in this study. The experts were recruited and managed by local fieldwork agents allowing the research to be efficiently completed while maintaining the anonymity of both the physicians and patients. The 67 patients with NC, together with their partner/friend and their physician were recruited from these centers: 25 patients from France, 23 from Spain, 11 from the UK, and 8 from Germany.

Inclusion criteria for NC were the presence of both EDS and clear-cut cataplexy, at least two sleep-onset rapid-eye-movement periods (SOREMP), mean sleep latency below 8 min on the multiple sleep latency tests (MSLT), and HLA DR2-positive [18]. Narcolepsy patients were receiving treatment for their condition, including 32.8% with psychostimulants only (modafinil, methylphenidate, or dextroamphetamine), 31.3% with both psychostimulants plus anticataplectics (venlafaxine, clomipramine, fluoxetine, or paroxetine), 13.4% with anticataplectic medications only, and 14.9% with sodium oxybate (7.5% with sodium oxybate only, 4.4% with sodium oxybate plus psychostimulant, and 3.0% with sodium oxybate plus psychosimulant and anticataplectic drugs). None of the patients received any analgesic medication at time of study.

A total of 67 adult control subjects who were matched for age, sex, body mass index (BMI), and level of education were recruited from the general population in France ($n = 48$ matched to French and Spain patients) and in the UK ($n = 19$ matched to UK and German patients). Exclusion criteria for the controls were the presence of a sleep disorder including narcolepsy, and/or the presence of any medical condition which affects the quality of life each day. None of the control subjects received any analgesic, antidepressant and/or anxiolytic medications at time of study.

The study was approved by an institutional review board with appropriate informed consent obtained from the subjects.

2.2. Methods

After the patient had agreed to participate in the study and had identified a partner or friend to participate in the research [19], physicians provided the patient with the contact details of a country-specific fieldwork agency and requested that the patients contact the agency. Enrolment into the study took place after the completion of a structured telephone screening questionnaire that included the Ullanlinna Narcolepsy Scale (UNS) with a score required to be above 10. Patients enrolled underwent a face-to-face interview with highly trained fieldwork agents who individually and privately administered the patient and partner/friend questionnaires. Among the standardized clinical interview, the presence and frequency of several symptoms were specifically analyzed: EDS, trouble staying asleep at night, trouble getting to sleep at night (>30 min), sleep quantity, cataplexy, sleep paralysis, hypnagogic hallucination, mood disorder, and pain.

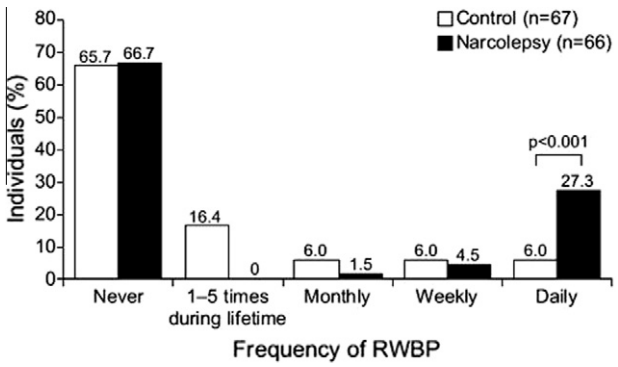

Fig. 1. Frequency of chronic pain in narcolepsy patients and controls.

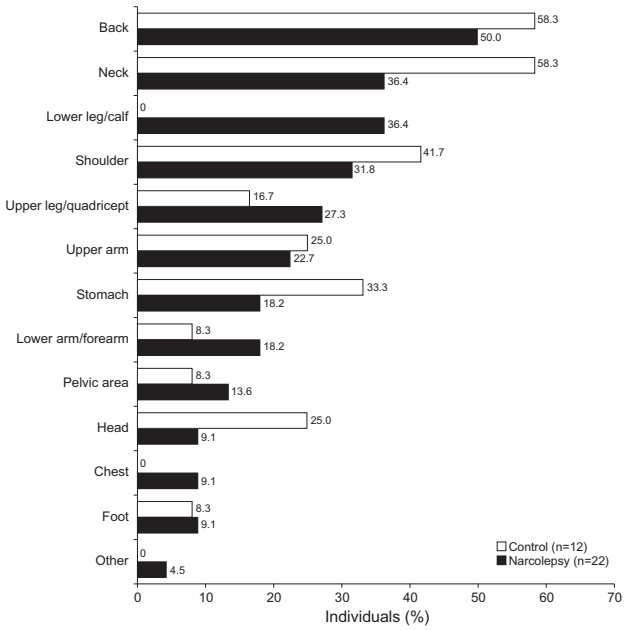

Fig. 2. Location of chronic pain at least monthly for patients with narcolepsy ($n = 22$) and controls ($n = 12$).

Pain was assessed by a self-report questionnaire. First patients were asked whether they experienced the symptom of chronic pain? If the answer was "Yes," the subject was asked an additional question: "How often do you experience pain?" with five possible answers (never, 1–5 episodes in lifetime, monthly, weekly, and daily). For those experiencing frequent pain condition, the location of pain was systematically identified from a list of 13 preselected body regions (see Fig 2). A 10-point weighting scale was also completed for the impact of pain on the patients' QoL (1 = no impact, 10 = severe impact).

The patient's questionnaire included the Short-Form 36-item (SF-36) score [20], the Functional Outcomes of Sleep Questionnaire (FOSQ) [21], the Medical Outcomes Study (MOS) [22], the Fatigue Severity Scale (FSS) [23], and the Beck Depression Inventory (BDI) [24]. Control subjects who were enrolled in the study underwent a face-to-face and/or telephone interview and completed the same questionnaires as the patients with NC, including the list of symptoms and the questions on pain.

2.3. Statistical analysis

The SPSS statistics package was used to analyze the data from respondents. Characteristics of patients and controls were described using mean values and ranges for quantitative variables where appropriate, and proportions for categorical variables. To test for sample distributions, a sample skewness measure was used. Most of the distributions were either positively or negatively skewed; therefore non-parametric tests were used to determine statistical significance. Chi-square and Mann–Whitney tests were thus respectively utilized for between-group comparisons of categorical and continuous variables.