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Observational study

Perceived sleep deficit is a strong predictor of RLS in multisite pain – A population based study in middle aged females

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HIGHLIGHTS

- This study showed that sleep deficit and sleep fragmentation are strong predictors of RLS in multisite pain.
- This study identified other sleep characteristics in this RLS phenotype of females with multisite pain.
- This study characterized RLS and multisite pain together with impaired sleep quality as strong predictors for daytime sleepiness.

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ABSTRACT

Background: Chronic pain conditions as well as Restless Legs Syndrome (RLS) are known to be associated with subjectively and objectively disturbed sleep. RLS has been recently described as highly prevalent in multisite pain and the role of sleep as a modifying factor in this RLS phenotype is unknown. This study aimed to investigate if perceived sleep deficit and other sleep related parameters predict RLS in subjects with multisite pain.
Current knowledge/study rationale: We have recently demonstrated a strong association between Restless Legs Syndrome (RLS) and number of pain locations. In the current analysis we hypothesized that impaired sleep predicts RLS in subjects with multisite pain.
Method: Questionnaire-based data from 2727 randomly selected women aged 18–64 years were used to analyze RLS symptoms, self-reported sleep quality, and the degree of daytime sleepiness (Epworth Sleepiness Scale (ESS)) in relation to type, degree and localization of body pain. Potential confounders including anthropometrics, pain localization, co-morbidities, and medication were adjusted for in the Generalized Linear Models (GLM).
Results: Perceived sleep deficit ≥90 min (OR 2.4 (1.5–3.8), $p < 0.001$) and frequent nocturnal awakenings (OR 2.3 (1.4–3.6), $p < 0.001$) were the strongest sleep related predictors for RLS in subjects with multisite pain. Additional factors include prolonged sleep latency (≥30 min, OR 1.8 (1.1–2.8), $p = 0.01$) and daytime symptoms like elevated daytime sleepiness (ESS score ≥9, OR 1.8 (1.2–2.7), $p = 0.005$). Accordingly, RLS diagnosis was associated with impaired sleep quality (TST (Total Sleep Time) −8.2 min, sleep latency +8.0 min, and number of awakenings from sleep +0.4, $p < 0.01$). ESS score increased with RLS diagnosis (+0.74, $p < 0.01$) and number of pain locations (0.5, 1.7, and 1.8 for 1, 3, and 5 pain areas, $p < 0.001$). In addition, confounders like pain severity, the history of psychiatric disease, and current smoking were associated with impaired sleep quality in this group of females.
Conclusions: Perceived sleep deficit and sleep fragmentation are the strongest sleep related predictors of RLS in multisite pain. Potential implication of our results are that clinical management programmes of RLS in subjects with multisite pain need to consider both sleep quality and sleep quantity for individually tailored treatment regimes.
Study impact: RLS, pain, and sleep disorders are highly interrelated. Our study strongly suggests that clinical management of RLS in patients with multisite pain needs to consider sleep quality as an independent risk factor.

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1. Introduction

Subjectively and objectively disturbed sleep are regarded as hallmark symptoms in chronic pain [1,2], a condition characterized by pain persisting beyond the expected time for tissue healing [3,4]. The relationship between pain and sleep disturbances is considered to be bidirectional. For example, sleep deprivation lowers the pain threshold [5] and both slow-wave sleep and REM-sleep modulation are known to affect pain perception during wakefulness [6]. Reciprocally, chronic pain may induce disturbed sleep which in the long-term is known to negatively further affect both pain perception and coping strategies with pain during daytime [7,8].

Restless Legs Syndrome (RLS), often described also as Willis Ekbom Disease (WED), is defined as an unpleasant sensory experience in the extremities [9] characterized by a circadian peak incidence during the last third of the day. RLS causes an urge to move and symptoms are relieved following limb movement. Proposed underlying pathomechanisms in RLS include an altered dopaminergic transmission [10], potential micro-circulatory dysfunction with local hypoxia in the extremities [11,12], and central nervous system iron metabolic dysfunction [13,14]. RLS typically induces increased sleep latency or loss of sleep. As a consequence, patients may report difficulties in falling asleep or frequent awakenings which negatively affect overall sleep quality and daytime function [15,16].

Multisite pain and fibromyalgia are subtypes of chronic pain characterized by the spreading of pain areas over the entire body [17]. In a recent study we could, for the first time, demonstrate that spreading of pain was an independent and dose dependent predictor for RLS [18]. The pathophysiological link between the two conditions is currently not evident but other common factor in both pain and RLS may be poor sleep [10] and its impact on daytime functioning.

The aim of the current study was therefore to analyze the cross sectional association between RLS, sleep quality and daytime vigilance in women with and without pain. We further aimed to identify certain sleep variables indicative for comorbid RLS in multisite pain.

2. Method

2.1. Study population

The study design and study population have been described in detail elsewhere [18]. In short, a questionnaire was mailed to 10 000 females aged between 18 and 64 in the Swedish county of Dalarna. The study population was randomly selected from the population census (>80 000 females in the current age strata) by a blinded automated process. The subject's addresses were retrieved from the National Personal Registry and were randomly chosen by a computer based automated process performed by the Swedish Post Service. Selection has been made on women, living in Dalarna county, and a target group of 10 000 subjects equally distributed in the age range between 18 and 64 years. The study was approved by the regional ethics committee at the Uppsala University (Dnr. 2010/124).

2.2. Classification of pain

In the current analysis, pain characteristics were assessed by means of a validated pain screening questionnaire used in pain centres [19]. The questionnaire asked for pain intensities, pain qualities, the time line of pain location, and included significant parts of the Brief Pain Inventory (Swedish version). Relevant for the analysis, pain intensity was graded using validated VAS scales for the categories no/mild (VAS 0–4), moderate (VAS 5–6) and severe pain (VAS 7–10) [20]. Pain duration was dichotomized in short-term (<3 months) and long-term (≥3 months) pain [21]. Localization of pain was stratified for five pain zones (neck, shoulders/arms, upper back region, lower back region and legs). Number of pain locations was defined according to the number of areas affected (between 0 and 5 areas) and grouped into three categories (0 zone = no number of pain locations, 1–2 zones = limited number of pain locations, 3–5 zones = extended number of pain locations).

2.3. Classification of RLS symptoms

Standardized and validated criteria were used for the four characteristic symptoms of RLS: (I) dysaesthesia and/or urge to move the limbs, (II) difficulties in resting, (III) worsening of symptoms at rest and improvement by movement, (IV) worsening at night [22]. The questionnaire was based on the classification of RLS according to the contemporary recommendations, and an RLS diagnosis was assigned if all 4 criteria were met [13]. Finally, RLS symptom frequency (rare, sometimes, often, always) was also assessed.

2.4. Quantification of sleep and sleep disordered breathing

The history of sleep and daytime function was assessed by means of the Basic Nordic Sleep Questionnaire [23] which included questions on mean subjective sleep latency, actual and preferred sleep duration, and the number of nocturnal awakenings. The variable "perceived sleep deficit" was calculated as the difference between subjective mean and preferred sleep time. Loud snoring was used as a categorical variable (always, 4–5 times a week, 2–3 times a week, 1–2 times a week and 1 time or less) in order to provide a proxy for obstructive sleep disordered breathing.

2.5. Assessment of daytime sleepiness

Daytime sleepiness was assessed by means of the established and validated Epworth Sleepiness Scale (ESS). A score of 11 or higher was considered as subjective excessive daytime sleepiness according to current practice [24].

2.6. Clinical data and confounding factors

Anthropometric data (age as a voluntary information available in 1339 out of 2727 individuals, length, body weight) and important comorbidities (cardiovascular (CVD), metabolic, neurological) were assessed. "Psychiatric disorder" was defined as self-reported depression, anxiety, and/or severe sleep disturbance. Concomitant medication was assessed and classified according to the Anatomical Therapeutic Chemical (ATC) system. Alcohol intake was quantified according to the frequency of intake (never, 1–3 times a month, 1–2 times a week, 3–4 times a week and more often). Smoking status (current or non-smoking) was also assessed.

2.7. Statistical analysis

Statistical analysis was performed using IBM-SPSS version 20.0 software (Illinois, USA). A p-value of <0.05 was considered as statistically significant. Descriptive statistics was used to evaluate sleep variables categorized for pain duration, intensity and spreading. RLS was also categorized (diagnosis yes/no, frequency of symptoms). Frequency distributions for sleep related symptoms were compared using the Chi-Square test whereas continuous variables were compared using ANOVA test (normally distributed variables) or the Kruskal Wallis test (not normally distributed data).

Independent associations were analyzed using Generalized Linear Model (GLM) analysis. Continuous sleep variables as well as the