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Original Article

A case-control study on excessive daytime sleepiness in chronic migraine

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ABSTRACT

Background: Excessive daytime sleepiness is a major clinical and health concern that can have varied and sometimes harmful consequences. Findings from uncontrolled studies suggest a high prevalence in patients with chronic migraine.
Methods: In a case-control study, we compared frequency data for excessive daytime sleepiness in 100 patients with chronic migraine and 100 healthy controls paired for sex and age, and assessed risk factors including lifestyle, sleep quality, anxiety, depression, concomitant disease and medications.
Results: The frequency of excessive daytime sleepiness was higher in migraineurs (especially in those with medication overuse) than in controls (20% versus 6%; odds ratio 3.92, 95% CI 1.5–10.22), but was lower than previously reported and correlated with poor quality sleep and anxiolytic and antidepressant use.
Conclusions: Again confirming that disability in chronic migraine is multifactorial in origin, excessive daytime sleepiness, especially in migraineurs who overuse medications, adds to the multiple factors known to impair social and working function. Patients with chronic migraine might benefit from diagnostic interviews focussing also on sleep problems and from targeted psychoactive drug prescribing.

1. Introduction

Excessive daytime sleepiness (EDS) is a major clinical and public health concern affecting between 10% and 25% of the general population, mainly adolescents, older persons and shift workers [1]. EDS causes affective [2], psychomotor [3] and cognitive [4] impairment, reduces quality of life and can also have severe consequences such as, increased cardiovascular mortality [5], car crashes [6] and work related accidents [7]. EDS also adds further disability to diverse neurological disorders [8,9].

The frequency of EDS is significantly higher in patients with episodic migraine than in healthy controls (14% versus 55%) [10]. The frequency of EDS reportedly increases in parallel with the frequency of migraine (frequency of 32.6% in patients with > eight episodes per month), though no significant difference emerged versus healthy controls (22.8%) [11]. In chronic migraine (CM), an even more disabling and burdensome condition than episodic migraine characterized by higher rates for comorbid medical and psychiatric conditions [12], the only published epidemiological study [13], an uncontrolled study investigating few risk factors, reports a disturbingly high prevalence of EDS in CM (39.8%). Others have described an equally high EDS prevalence (36.2%) also in chronic headache sufferers [14]. More precise information is therefore, needed on the frequency of EDS in patients with CM. Reliable data on frequency and risk factors could help to explain the causes of EDS, and thus, improve measures for managing EDS in patients with CM.

We designed this case-control study to assess the frequency of and risk factors for EDS in consecutively enrolled patients with CM attending a tertiary-referral center, all of whom fulfilled the latest revised diagnostic criteria for CM [15] and healthy control subjects. To assess risk factors, we characterized their clinical features in detail and as a frequency measure screened for EDS using the Epworth Sleepiness Scale (ESS) [16], a validated and widely used scale considered among the best tools for assessing subjective sleepiness. We also sought possible associations between medication overuse (MO) and EDS.

2. Methods

We conducted a case-control study comparing patients with CM [15], with or without MO, consecutively recruited from our Headache and Pain Unit from 1st June 2010 to 31st May 2011 and healthy controls paired for sex and age (± two years), recruited over the same period from non-consanguineous relatives of outpatients attending our neurological unit.

After a complete physical and neurological examination, all participants were screened for factors known to interfere with the sleep–wake cycle such as, body mass index (BMI), use of coffee,

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alcohol, drugs of abuse, smoking, type of work, restless legs syndrome, medications, anxiety, depression, and concomitant cardiovascular, pulmonary, metabolic or urological diseases. Information on snoring or obstructive sleep apnea syndrome (OSAS) was gathered by interviewing relatives or partners.

Clinical features of migraine (disease duration, family history of migraine, presence of aura, frequency and duration of attacks, location, quality and intensity of pain, duration of chronic migraine, preventive and acute treatment, presence and duration of MO, other concomitant headaches) were detailed and gathered with face-to-face interviews using structured questionnaires [10]. Migraine disability was assessed with the Migraine Disability Assessment Scale (MIDAS).

To screen for EDS, we used the ESS, an eight item self-administered questionnaire which is used as an instrument to evaluate the tendency to doze off during the daytime in eight different conditions (e.g., while sitting and reading, riding as a passenger in a car, sitting and talking to someone) and correlates with sleep latency as measured during the multiple sleep latency test and overnight polysomnography [16]. Responses were summed to yield a total score from zero to 24, with higher scores indicating greater sleepiness during common daily activities. EDS was defined as an ESS score $\geqslant 10$.

The quality of sleep was measured using the Pittsburgh Sleep Quality Index (PSQI), a self-rated questionnaire scored on a zero to three scale assessing various factors related to sleep quality, including estimates of sleep duration and latency, frequency and severity of specific sleep-problems, then grouped into seven scores [17]. An overall score of >five distinguishes poor (PSQI > five) from good (PSQI < five) sleepers.

Symptoms of anxiety were rated with the State-Trait Anxiety Inventory (STAI-1 and STAI-2) questionnaires and depression was rated with the Beck Depression Inventory (BDI).

The protocol was approved by the Institutional Review Board at San Raffaele Scientific Institute and have therefore, been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. All subjects gave their informed consent prior to their inclusion in the study.

The χ^2 test was used to analyze the differences in the frequency of categorical variables. Differences in the means of continuous measurements were determined with student's *t*-test. A logistic-regression model was run to evaluate the relation between ESS and CM adjusted for variables previously identified by univariate analysis as significant or of borderline significance (PSQI, anxiolytics/antidepressants, alcohol), plus age and gender. Odds ratios (ORs) with relative 95% confidence intervals (CIs) were estimated. Values are expressed as mean ± SD. *p*-values of <0.05 were considered statistically significant. Pearson's correlation analysis was used to test the differences between the scores for the scale used. All statistical data were analyzed with the statistical package SPSS (version 13.0; SPSS Inc., Chicago, IL, USA).

3. Results

We studied 100 patients with CM (eight men and 92 women) and 100 age- and sex-paired healthy controls, Table 1. When we analyzed risk factors for EDS, there was no significant between-group differences that were found for smoking, coffee, BMI and working on nightshifts. Alcohol consumption was slightly higher in controls than in patients ($p = 0.054$; OR = 0.50, 95% CI = 0.45–1.02). No subject reported coffee or alcohol overuse or use of drugs of abuse. No between-group differences emerged in sleep disturbances such as, snoring and restless legs syndrome. None of the participants reported symptoms suggesting OSAS. Anxiety and depression, as assessed by STAI2 and BDI scores and the use of anxiolytic and antidepressant drugs were more common in patients than controls. Conversely, no difference was found in other concomitant diseases or treatments, Table 1.

Although we found no significant differences in mean ESS total scores between patients and controls, EDS (ESS $\geqslant 10$) was more frequent in migraineurs than in controls (20% versus 6%; OR = 3.92, 95% CI = 1.50–10.22), Table 1. Total PSQI scores were higher in patients than in controls (9.5 ± 4 versus 4.5 ± 3.4, $p < 0.001$) and PSQI scores >five were more frequent (91% versus 44%; OR = 12.87, 95% CI = 5.83–28.37), Table 1. PSQI subscale analysis showed that patients had higher scores than controls for the all items on this scale (subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication and daytime dysfunction), $p < 0.01$.

Logistic regression analysis showed that ESS scores adjusted for gender, age, alcohol, PSQI, and antidepressant/anxiolytic drugs were not significantly higher in patients than in controls (OR = 1.664, 95% CI = 0.636–4.354; $p = 0.299$) while poor sleepers (PSQI > five) and use of antidepressant/anxiolytic drugs were more frequent in patients than in controls (PSQI OR = 7.273, 95% CI = 2.80–18.88; $p = 0.001$; antidepressant/anxiolytic drugs OR = 15.11, 95% CI = 6.10–37.41; $p = 0.001$), Table 2.

We found no relationship among patients between ESS score and PSQI, STAI1, STAI2, BDI, MIDAS scores and age. In controls, ESS scores correlated with PSQI ($p = 0.001$), STAI1 ($p = 0.009$) and BDI ($p = 0.001$) scores.

Headaches were more severe and more often unilateral, and MIDAS scores were higher in migraineurs with MO than in those without ($p = 0.007$, $p = 0.015$, and $p = 0.002$). Similarly, antidepressant/anxiolytic drug use was higher, but oral contraceptive use lower in migraineurs with MO than those without (OR = 6.83, 95% CI = 1.89–32.24; OR = 0.25, 95% CI = 0.06–0.99). The frequency of EDS was higher in patients with MO than in those without (22.4% versus 6.7%; OR = 4.03, 95% CI = 4.03–179.2).

4. Discussion

In this case-control study on consecutively enrolled patients with CM attending a tertiary-referral center, we found a 20% frequency of EDS in patients with CM compared with only six percent in healthy controls. This finding implies that EDS is less frequent in patients with CM than a previous study suggested [13]. Another new finding emerged from the multivariate risk-factor analysis showing that the difference depended on worse sleep quality and greater use of antidepressant or anxiolytic medications. A new, clinically useful finding was the higher frequency of EDS in patients with MO than in those without MO.

The frequency of EDS in our patients with CM is higher than that reported by our group in episodic migraineurs (20% versus 14%) [10], but is lower than that previously described by Peres et al. (39.8%) in patients with CM [13] and by others in heterogeneous chronic headache populations encompassing small samples of patients with CM [11,14,18]. The discrepancy probably arose because we studied a larger population, used a healthy control group, examined and interviewed each participant directly, assessed EDS using the Epworth Sleepiness Scale, a validated and widely used scale considered among the best tools for assessing subjective sleepiness [16], and also investigated concomitant diseases and medications that are known to markedly influence EDS [8,19].

The RLS frequency we found in patients with CM (4%) is much lower than that reported by Schürks et al. (14.5%) [20] probably owing to differences in the migraine populations studied (chronic versus episodic), patients' mean age and gender (46.8 versus 63.9 years; males + females versus females only), and to the fact that patients with CM often use drugs such as, anticonvulsants,