

# Evidence of increased restless legs syndrome occurrence in chronic and highly disabling migraine

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## Summary

The existence of an association between migraine and restless legs syndrome (RLS) has recently been reported, although the possible implications of this for migraine clinical presentation remain poorly understood. The objectives of this study were to determine RLS frequency in a population of migraineurs compared with healthy subjects and to assess RLS occurrence in episodic versus chronic migraine patients; the relationship between migraine-related disability and RLS comorbidity was also evaluated.

Two hundred and seventy-seven consecutive migraineurs (ICHD-II, 2004) were enrolled and compared with 200 controls; migraine was episodic in 175 and chronic in 102 patients. RLS (IRLSSG criteria, 2003) was present in 22.7% of the total sample of migraineurs and in 7.5% of the controls ( $p < 0.0001$ ). RLS occurred significantly more frequently in chronic compared with episodic migraineurs (34.3% vs 16%, respectively,  $p = 0.0006$ ); a significant association between RLS diagnosis and moderate-severe migraine-related disability was also documented ( $p = 0.0003$ ).

In conclusion, the results of the present study not only confirm the higher occurrence of RLS in migraine patients compared with the general population, but also suggest that RLS (the condition itself, or the disruption of sleep patterns often found in patients affected by RLS) might affect migraine clinical presentation, being associated with chronic and highly disabling migraine. These findings could have important therapeutic and prognostic implications in clinical practice.

*KEY WORDS:* chronic migraine, migraine, migraine disability, restless legs syndrome, sleep

## Introduction

Migraine is a primary headache disorder characterised by recurrent attacks (lasting 4-72 hours) of pain typically described as unilateral, pulsating, moderate or severe, aggravated by routine physical activity and associ-

ated with nausea and/or photophobia and phonophobia (1). Migraine has a variable clinical course, with some patients remitting, becoming headache-free, others having a stable clinical course, and a subset of individuals progressing from infrequent attacks to frequent episodic attacks and then to chronic migraine; it has been estimated that about 3% of individuals with episodic migraine will progress to chronic migraine over the course of a year (2,3). Migraine is defined chronic when headaches occur on  $\geq 15$  days per month for at least three months, of which  $\geq 8$  days meet criteria outlined for episodic migraine and/or respond to migraine-specific treatment (ergotamine or triptans) (1,4). Chronic migraine is a highly disabling condition, which has a significant impact on quality of life and carries high socioeconomic costs; the burden of chronic migraine is significantly greater than that of episodic migraine and, in addition, treatment of chronic migraine is frequently unsuccessful (5). In recent years many attempts have been made to identify factors associated with the progression of episodic to chronic migraine; risk factors, both non-modifiable (female sex, lower socioeconomic status, previous neck or head injury) and modifiable (obesity, snoring, other pain syndromes, stressful life events, caffeine intake and acute headache medication overuse) have, indeed, been identified (6,7).

Although the existence of a complex and pluridirectional relationship between sleep and migraine is well known, the exact role of sleep disorders in migraine chronification remains poorly investigated. Snoring has been suggested to be a modifiable risk factor for migraine transformation, even though the data were collected from heterogeneous samples of headache patients. Scher et al. (8) investigated the prevalence of snoring in a group of chronic daily headache subjects, comparing the data with those from a control group of episodic patients. Habitual snoring was more common in the chronic daily headache subjects than in the controls (24% vs 14%). More recently Sancisi et al. (9) in a case-control study also found that patients with chronic headache, but not specifically chronic migraine, showed a high prevalence of insomnia, daytime sleepiness and snoring compared with patients with episodic headache (67.7% vs 39.2%, 36.2% vs 23.5%, and 48.6% vs 37.2%, respectively) and documented that insomnia is an independent risk factor for headache chronification.

Recent reports have suggested the existence of an association between migraine and restless legs syndrome (RLS); in Europe, the RLS prevalence reported in two observational case-control studies was 17.3% and 25.6%, in German and Italian samples of migraineurs, respectively, compared with 5.6% and 8.3% in the respective control groups (10,11). Conversely, in two studies conducted in Asian populations, RLS prevalence in

migraine patients was reported to be 11.4% and 13.7% respectively (12,13); an ethnic factor probably contributed to the lower frequency of RLS reported in the Asian studies (the estimated frequency of RLS in the general Asian population is about 1.5-1.8%) (13,14). Even though these clinical data seem to show an association between migraine and RLS, the possible implications for migraine clinical presentation and the risk of chronification remain, to date, poorly investigated.

This study was conducted in order to verify the existence of an association between migraine and RLS in a sample of migraineurs, compared with a control group of healthy subjects, matched for age and gender; furthermore, RLS occurrence was assessed in episodic versus chronic migraine patients with the specific aim of identifying significant differences between the two groups. Finally the existence of a relationship between migraine-related disability and RLS comorbidity was evaluated.

## Materials and methods

Two hundred and seventy-seven consecutive migraine patients, diagnosed according to the International Headache Society (IHS) criteria for migraine with or without aura (ICHD-II, 2004) (1), were enrolled at the Headache Centre of Pisa University (a tertiary care centre) between January 2011 and September 2011; these migraine patients were compared with 200 healthy control subjects, matched for age and gender.

Exclusion criteria were the following: i) use of preventive migraine treatment over the previous three months; ii) use of antidepressants (both tricyclic and SSRIs), dopamine antagonists or gabaergic drugs over the previous three months; iii) a coexisting diagnosis of other primary headaches or of medication-overuse headache, according to the ICHD-II criteria (1); iv) relevant medical comorbidities, with particular attention to iron deficiency and renal failure (serum ferritin and blood creatinine levels were evaluated in all patients); v) a past or current history of psychiatric illness, especially mood and anxiety disorders.

Restless legs syndrome, which is a sensorimotor neurological disorder, was diagnosed on the basis of the four essential criteria of the International Restless Legs Syndrome Study Group (IRLSSG, 2003) (15): i) an urge to move the legs, usually accompanied or caused by uncomfortable or unpleasant sensations in the legs; ii) the urge to move or unpleasant sensations begin or worsen during periods of inactivity such as lying or sitting; iii) the urge to move or the unpleasant sensations are partially or totally relieved by movements, such as walking or stretching, at least as long as the activity continues; iv) the urge to move or unpleasant sensations are worse in the evening or night than during the day, or only occur in the evening or night.

Migraineurs were divided into episodic and chronic; chronic migraine was diagnosed in the presence of headaches for 15 or more days per month for at least three months, of which  $\geq 8$  days met criteria outlined for episodic migraine or were treated with an acute migraine-specific medication (ergotamine or triptans) (1,4). Migraine-associated disability was assessed using the Migraine Disability Assessment Scale (MIDAS), a five-item questionnaire measuring headache-related disability

over a three-month period; on the basis of the MIDAS score, disability was classified into four grades (score 0-5, grade I, little or no disability; score 6-10, grade II, mild disability; score 11-20, grade III, moderate disability; and score  $\geq 21$ , grade IV, severe disability) (16).

Finally, subjective sleep quality was evaluated using the Pittsburgh Sleep Quality Index (PSQI), a self-rated questionnaire, which determines sleep quality and disturbances over one month; a total score  $>5$  is indicative of poor sleep quality (score range 0-21) (17).

Data are presented as percentages or as arithmetic means with standard deviations. The statistical analysis was performed using the chi-square test or Fisher's exact test; the significance level was set at  $p=0.05$ .

## Results

Two hundred and seventy-seven migraineurs (mean age  $41.2 \pm 13.5$  years, range 19-70 years, 190 females and 87 males) were included in the study and compared with 200 healthy subjects (mean age  $41.7 \pm 14.2$  years, range 19-70 years, 137 females, 63 males). The criteria for episodic migraine were met by 175 patients and those for chronic migraine by 102 patients; 243 patients were affected by migraine without aura, 25 by migraine with and without aura, and nine by pure migraine with aura.

The frequency of RLS was significantly greater in the migraineurs compared with the control subjects (22.7% migraineurs vs 7.5% healthy subjects,  $p < 0.0001$ ); in particular, RLS was diagnosed in 63 migraineurs, 55 affected by migraine without aura and eight affected by migraine with and without aura, whereas none of the patients with pure migraine with aura received a diagnosis of RLS.

In the sample of migraineurs, RLS was diagnosed in 47 females and 16 males (24.7% of the females and 18.4% of the males, respectively); in the control group, RLS was diagnosed in 15 subjects, 11 females and 4 males (8% of the females vs 6.3% of the males).

No significant differences were found in the frequency of family occurrence of RLS between the migraineurs and the control subjects; indeed, a positive family history of RLS was found in 18 of the 63 migraineurs affected by RLS (28.5%) and in 4 of the 15 control subjects affected by RLS (26.6%).

Restless legs syndrome was diagnosed in 28 of the 175 episodic migraine patients (16%) and in 35 of the 102 chronic migraineurs (34.3%). The statistical analysis documented the existence of a significant association between RLS diagnosis and chronic migraine ( $p=0.0006$ ), as opposed to episodic migraine.

Analysis of the MIDAS scores showed that migraine-related disability was absent or minimal in 63 patients (grade I), mild in 73 (grade II), moderate in 69 (grade III), and severe in 72 patients (grade IV). In the migraineurs with RLS comorbidity, disability was absent or minimal in seven patients (i.e. 11.1% of the RLS-affected migraineurs had grade I disability), mild in 11 (i.e. 15.1% had grade II), moderate in 17 (i.e. 24.6% had grade III) and severe in 28 patients (i.e. 38.9% had grade IV); the statistical analysis, in which disability grades I-II (absent, minimal or mild disability) were compared with grades III-IV (moderate-severe disability), documented the exist-

tence of a significant association between moderate-severe migraine-related disability and RLS diagnosis ( $p=0.0003$ ).

Subjective sleep quality, as evaluated by means of the PSQI questionnaire, was impaired ("poor sleepers",  $PSQI > 5$ ) in 32 of the 63 migraineurs with RLS comorbidity (50.7%) versus 58 of the 214 migraineurs without a diagnosis of RLS (27.1%), whereas 33.3% of the controls with RLS diagnosis were "poor sleepers" versus 9.7% of the healthy control subjects.

## Discussion

The results of the present study show a higher frequency of RLS in a homogeneous sample of migraineurs compared with a group of healthy subjects (22.7% vs 7.5%) and are in agreement with the findings of previous studies, which reported a 17.3% and 25.6% prevalence of RLS in German and Italian samples of migraineurs, respectively (10,11).

Neither differences in personal data (gender and/or age) nor comorbid conditions can account for the higher occurrence of RLS documented in the migraineurs compared with the control group. The population of migraine patients and the control group included in this study were, indeed, homogeneous and patients with comorbid medical or psychiatric conditions were excluded, as were patients being treated with migraine preventive therapies, antidepressants, dopamine antagonists or gabaergic drugs; finally patients showing excessive use of symptomatic drugs were also excluded.

The frequency of RLS in the control group of healthy subjects (7.5%) was in line with that previously found in the Italian population (8.3%) (11) and also with the 10% RLS prevalence estimated by large population studies carried out in the general European population (18).

Although the biological basis of the association between migraine and RLS remains unknown, recent experimental studies have suggested that dysfunctions in the hypothalamic A11 nucleus may play a role in the pathogenesis of both conditions. In animal studies, it has been shown that lesions of the A11 nucleus can produce an experimental model of RLS (19) and more recent studies documented a modulating function of the A11 nucleus, through dopaminergic and CGRPergic projections, on the trigeminocervical system (20,21); further studies are certainly necessary in order to clarify the biological basis of the association between migraine and RLS. Chronic migraine is a highly disabling condition which has a great impact on the quality of life of affected subjects and carries high socioeconomic costs (5), therefore the identification of comorbid conditions associated with chronic migraine could prove very important, having diagnostic and therapeutic implications.

Our data document, for the first time, the existence of a significant association between chronic migraine and RLS diagnosis; in addition, as regards migraine-related disability, the present findings, showing the existence of a significant association between RLS comorbidity and moderate-severe migraine-related disability, support previous literature reports in which migraine patients with RLS had higher MIDAS scores than those without RLS (12,13).

It is well known from literature data that RLS, either the condition itself or the periodic limb movements during sleep (PLMS) that occur in about 80% of patients affected by RLS and are frequently associated with arousal from sleep, can disrupt sleep patterns (15); sleep disturbances are, indeed, a frequent symptom of RLS and are mainly characterised by increased sleep latency, fragmented sleep and markedly reduced total sleep time.

The results of the present study showed that subjective sleep quality impairment is a frequent complaint in migraine patients, in agreement with previous literature data showing that quality of sleep is decreased in migraineurs as a consequence of migraine itself (22,23), and also that RLS further affects the already impaired sleep pattern of migraineurs i.e. subjective sleep quality impairment is greater in migraine patients with RLS comorbidity (indeed, 50.7% of migraineurs with RLS were "poor sleepers" versus 27.1% of those without RLS comorbidity).

The findings of the present study not only confirm the higher frequency of RLS in migraineurs compared with the general population but also suggest that RLS (the condition itself, or the disruption of sleep patterns often found in patients affected by RLS) might affect migraine clinical presentation, being associated with higher frequency of migraine attacks (chronic migraine) and moderate-severe migraine-related disability.

These data reinforce the need to verify the presence of RLS in all migraineurs, but especially in chronic patients and in subjects with a high degree of migraine-related disability.

In clinical practice the identification of RLS comorbidity in migraine patients could have important therapeutic implications; antidepressants, both tricyclic and SSRIs, currently used in migraine preventive treatment, should be, as far as possible, avoided, on account of their possible role in favouring RLS, whereas gabaergic drugs such as gabapentin and pregabalin could be first-choice treatments, being potentially effective for both conditions. Furthermore, caution is probably warranted in the use of dopamine agonists, commonly employed in RLS treatment, since a condition of hypersensitivity to dopaminergic drugs has been documented in migraine patients (24).

The identification and adequate treatment of RLS comorbidity in migraine patients could immediately help to improve these patients' quality of life and, from a lifetime perspective, possibly contribute to reducing the risk of transformation of migraine from episodic to chronic.

In conclusion, the results of the present study confirm a higher occurrence of RLS in migraineurs compared with healthy subjects; they also document, for the first time, the existence of a significant association between RLS diagnosis and chronic migraine, prompting the hypothesis that RLS comorbidity may play a role in the process of migraine chronification. However, the design of this study does not allow us to establish a role of RLS in the transformation of migraine from episodic to chronic and further longitudinal studies are certainly necessary in order to better understand how RLS and, more broadly, sleep disorders, contribute to the process of migraine chronification.

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