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ORAL COMMUNICATION

Restless legs syndrome and primary headaches: a clinical study

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Abstract Based on recent data about the association between restless legs syndrome (RLS) and migraine, we performed an observational study on the occurrence of RLS in patients affected by primary headaches. Two hundred headache patients (149 women and 51 men) and 120 (90 women and 30 men) sex- and age-matched control subjects were included. In the headache group, migraine without aura (MO) was the most represented headache type (n=114), followed by the "mixed" group (n=40) with MO, migraine with aura (MA) and frequent episodic tension-type headache (ETTH) in various combinations, and by ETTH alone (n=22). The remaining patients suffered from MA alone (n=10 MA), episodic cluster headache (ECH n=12) and primary stabbing headache (n=2). RLS frequency was significantly higher in headache patients than in control subjects (22.4% vs. 8.3, p=0.002) independently of sex, although with a female preponderance (84%) in both groups. More than 60% (n=27) of RLS patients were affected by MO and 30% (n=13) by a combination of two headache types ($p \geq 0.001$), with a very low frequency of RLS for the other types of headache. No RLS patient had ECH. No statistical differences were observed among clinical characteristics of different types of headache in groups with and without RLS. In both headache and control groups, higher scores for depression and anxiety were more frequent in subjects with RLS compared with those without RLS. Furthermore, headache patients with RLS reported sleep disturbances more frequently compared to those without RLS (50.0% vs. 32.7%; $p<0.0001$) and showed a normal or underweight body mass index. Our data seem to confirm the existence of an association between RLS and primary headaches, particularly with migraine, as already demonstrated. The absence of RLS in ECH patients is very interesting. Many pathogenetic considerations about links between RLS and primary headaches could be given, the most fitting involving dopamine and melatonin.

Keywords Primary headache · Restless legs syndrome · Prevalence · Clinical population · Migraine

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Introduction

Primary headaches have been associated with various movement disorders. In particular, higher prevalence of migraine in essential tremor [1], Tourette's syndrome [2] and Sydenham's chorea [3] and a lower prevalence in Parkinson's disease have been reported [4]. On the other hand, an association between headache and sleep has long been recognised in the medical literature [5]. Very recently, restless legs syndrome (RLS) has been associated with

migraine [6], opening new perspectives for a pathogenetic link other than a comorbidity between the two conditions. RLS, first termed by Ekbom in 1945 [7], is a common neurological condition characterised by unpleasant sensations deep inside the legs, accompanied by an urge to move the limbs and motor restlessness, occurring at rest, especially at bedtime. Its clinical diagnostic criteria were established by the International Restless Legs Syndrome Study Group (IRLSSG) in 1995 [8]. The criteria were reviewed and published in 2003 [9]. Idiopathic and symptomatic RLS forms have been recognised, the latter occurring during pregnancy or associated with uraemia, iron depletion, polyneuropathy, spinal disorders and rheumatoid arthritis. The prevalence of RLS varies from 2% to 15% in the general population [10, 11], but it is often not recognised or misdiagnosed. The frequency increases with age and its prevalence is higher in women than in men. The aim of this study was to investigate the prevalence of RLS in an adult clinical population affected by primary headaches, matched by age and sex with a control group of non-headache subjects, in order to confirm the known association between RLS and migraine and to identify any relationship with other primary headaches and their hypothetical pathogenetic links.

Methods

We enrolled 200 consecutive headache patients (149 females, 51 males) aged 18–65 years, referring to three Italian headache centres, during a six-month period. One hundred and twenty healthy headache-free subjects (90 females, 30 males), matched by age and sex, were recruited from among hospital employers and visitors and served as controls. Both headache patients and control subjects underwent a direct interview and neurological examination. The diagnosis of the type of headache was made according to ICHD-II criteria [12] by a headache specialist. All headache patients were not headache prophylaxis medications or antidepressants for at least three months prior to our observation. Episodic cluster headache patients (ECH) were investigated outside the cluster period. Headache clinical features were registered including headache lifetime duration, frequency per month and pain intensity. Diagnosis of RLS (idiopathic or symptomatic) was made by another neurologist blinded for headache diagnosis, following the revised criteria of IRLSSG [9]. All subjects also underwent a semi-structured interview in order to investigate the association with insomnia, body weight and psychiatric disturbances. Insomnia was diagnosed according to international criteria [13]. For all subjects body mass index (BMI) was calculated. We divided subjects into 3 categories based on BMI score: underweight (<18.5 kg/m^2), normal (18.6–24.9 kg/m^2) and overweight (25.0–29.9 kg/m^2). The Hamilton Anxiety Rating Scale (HAMA) [14] and the Beck Depression Inventory (BDI) [15] were used to disclose the presence of anxiety and depression disorders. Diagnoses of anxiety and depression were made with a score of ≥18 respectively. Psychopathological evaluations were conducted by a third specialist who was blind to subject condition. Data are presented as percentage or as arithmetic mean with SD. Statistical analysis was performed by analysis of variance for continuous variables and by non-parametric Chi-square testing for categorical variables. Logistic regression was employed for assessing determinant of RLS in migraine patients. Significance level was set at p=0.05.

Results

Demographic and clinical data of the headache patients and control subjects are presented in Table 1. One hundred and fourteen headache patients (90F, 24M) were affected by migraine without aura (MO), 22 patients (16F, 6M) by frequent episodic tension-type headache (ETTH), 10 patients (5F, 5M) by migraine with aura (MA), 12 patients (1F, 11M) by ECH and 2 patients (2F) by primary stabbing headache (PSH). The remaining 40 patients (35F, 5M) suffered from two primary headaches (MO, MA and ETTH in various combinations). No significant differences were found in the mean age at onset and lifetime duration for any subtype of headache. The prevalence of RLS was 22.4% (n=44) in headache patients and 8.3% (n=10) in control subjects (p=0.002), with a female preponderance in both groups. No statistical differences were observed about demographic characteristics between headache patients and controls affected by RLS and those without RLS. In the RLS-headache group, migraine was the more frequent type of primary headache (MO n=27; MA n=2; "Mixed group" n=13; p<0.001), with a higher frequency of symptomatic cases of RLS compared to controls (38.19% vs. 20.0% of controls; p=NS). In the remaining forms of primary headache, RLS was present in 1 patient with ETTH and 1 patient with PSH. It is worthwhile to observe that no ECH patients were affected by RLS. Among headache clinical features, our results did not show any relationship between RLS and monthly attack frequency, intensity of pain and lifetime duration of headache. Concerning medical conditions investigated in both groups of subjects, higher scores for depression and anxiety were detected in headache patients and controls with RLS compared with those without RLS, with a significant difference only for the headache patients (45.5% vs. 29.5%; p<0.05< 0.05 for headache patients and 50.0% vs. 27.3%; p=NS< 0.05 for controls). Among headache patients, those affected by MO and RLS reported higher scores for anxiety and/or depression with a statistical significant difference compared to those without RLS (p=0.012). Headache patients

Table 1 Demographic and clinical data of the headache patients and control subjects (presented as arithmetic mean and SD or as percentage)

	Headache patients (n=200)	Control subjects (n=120)	*p*-value
Age (years)	37.2±11.1 (18–65)	37.2±8.5 (20–56)	NS
Female age	37.6±11.5 (18–65) (n=149)	36.7±8.1 (20–53) (n=90)	NS
Male age	36.1±10.0 (21–59) (n=51)	38.8±9.6 (20–56) (n=30)	NS
Headache age at onset	22.9±9.4 (8–60)	NA	NA
Headache duration	14.3±10.1 (1–40)	NA	NA
Attack frequency per month	Low (<1/month): 41.0% Medium: (1–3/month): 20.5% High (>3/month): 38.5%	NA	NA
Intensity of pain	Mild: 9.5% Moderate: 50.5% Severe: 40.0%	NA	NA
RLS prevalence	22.4% (n=44)	8.3% (n=10)	0.002
Sex-Female	84.1% (n=37)	80.0% (n=8)	NS
Sex-Male	15.9% (n=7)	20.0% (n=2)	
RLS age at onset (years)	33.23±8,4	29.40±6.,83	0.187
RLS duration (years)	5.6±4.5 (1–20)	4.6±3.1 (1–10)	0.520

NA, not applicable

and controls with RLS report insomnia more frequently compared to those without RLS ($p<0.0001$). This trend was more pronounced in MO patients with no significant statistical difference compared to controls and other headache subtype patients (p=NS).

The BMI calculated for each subject was in the normal range in 68.2% of headache patients and half of controls. In contrast to that previously reported for RLS patients [10], few headache patients with RLS were overweight compared to headache patients without RLS (p=NS). Among all clinical headache features investigated, migraine and MO and BMI in the normal range increase the risk for RLS from five-four to six-fold (migraine: 4.974; normal BMI: 5.840).

Discussion

Since standard diagnostic criteria of RLS were proposed by IRLSSG [8, 9], several epidemiological investigations have reported similar rates of prevalence in the general population for a broad spectrum of adult ages. The widest epidemiological study performed in the USA and in five European countries showed an overall RLS prevalence of 7.2% [16], a rate similar to that found in our control subjects population (8.3%). RLS was found to be associated with several somatic and neuropsychiatric conditions irrespective of a possible causal link. Sleep-related complaints were more frequent among RLS sufferers [17] and also depressed mood [18], reduced libido, hypertension and heart problems [19]. Headache at awakening and daytime headache were reported 3–5 times more frequently among RLS sufferers, although in a male clinical population [19]. Recently, a German case-control study revealed the existence of an association between migraine and RLS [6].

Our study confirmed a higher prevalence of RLS in patients affected by primary headaches (22.4%) compared to headache-free subjects (8.3%). The results revealed that RLS is independent of age and sex both in headache patients and in controls, although it is more frequent in females in both groups.

The evaluation of different headache subtypes showed that MO can increase the risk of RLS, unlike other headache types like ETTH and ECH. In ECH patients, although the size of the sample appears small, it is adequate if we consider the low prevalence in the general population of this kind of headache (0.03%) [20]. So, we could postulate that ECH represents a protective factor from RLS.

Regarding medical conditions investigated, the higher frequency of depression and anxiety found in headache patients with RLS, in particular in those affected by MO, confirmed data already existing in the literature for both disorders. On the contrary, being overweight did not represent a variable that influences the risk of RLS, as previously reported [10], in headache patients. Contrary to expectations, insomnia influences the presence of RLS only in controls but not in headache patients.

The association between RLS and primary headaches, especially for migraine, probably presumes pathogenetic links. Many topics could be implicated: (1) both are central nervous system disorders; (2) RLS pathology likely involves cortical and subcortical areas of the brain, with decreased inhibition of the sensorimotor cortical and an increased cortical silent period [21]; primary headaches, migraine and in particular MA, are related to a status of cortical hyperexcitability or reduced cortical inhibition [22]; (3) the RLS response to dopaminergic therapy suggests a possible role of dopamine in its pathogenesis [23], although functional neuroimaging studies have produced conflicting results [24]; dopaminergic abnormalities have been demonstrated in migraine [25]; (4) a melatonin imbalance could be involved in RLS and cluster headache, both circadian disorders where changes in melatonin secretion have been shown, but with an inverse relation-

ship: nocturnal increase in melatonin secretion correlates with onset and worsening of RLS symptoms mediated by a melatonin inhibition of the central dopamine secretion [26], while a decrease in nocturnal melatonin secretion with lower levels during cluster periods than remissions was demonstrated in CH patients [27, 28].

A link between dopamine and melatonin in RLS has been suggested by RLS animal models where a dysfunction or atrophy of the dopaminergic A11 cell group, the only cells that provide dopaminergic axons to the spinal cord, was reported as the possible pathophysiological correlate of the syndrome. This could explain both the excellent response to dopaminergic drugs and the circadian rhythm of the syndrome, as these cells are in close proximity to the whose hypothalamic circadian pacemaker [29], activation of which is also demonstrated in CH. In this direction we could explain the peculiar absence of RLS in our ECH patients.

Finally, another pathogenetic contact point between RLS and primary headaches is the abnormality of brain iron metabolism. Iron is an important cofactor in dopamine synthesis and this represents a bridge between the two major pathogenetic mechanisms involved in RLS [23]. In migraine, especially in chronic migraine with long duration of illness, brain iron storage has been found in periaqueductal grey matter, indicating an abnormal iron metabolism also in migrainous brain [30]. In conclusion, our data show that migraine could represent a risk factor for RLS, while CH might be an hypothetical protective factor. These findings could shed light on the pathogenesis and treatment of migraine when associated with RLS.

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