Comorbidities, medications and depressive symptoms in patients with restless legs syndrome and migraine

Comorbidades, medicações e sintomas depressivos em pacientes com síndrome das pernas inquietas e enxaqueca

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ABSTRACT

Objective: The pathophysiology of migraine and restless legs syndrome (RLS) seems to involve inherited mechanism and dysfunction of the dopaminergic system. Previous articles have shown that the frequency of RLS is higher in migraine patients than in controls. We conducted a study to evaluate comorbidities, medication used and depressive symptoms that can explain the relation between migraine and RLS. **Methods:** A case-control study was performed in which patients with migraine (n=72) and a control group without migraine (n=72) were interviewed. Data including RLS diagnosis, depressive symptoms, comorbidities and drugs used were evaluated. **Results:** There was a significant association between migraine and RLS (p=0.01), but comorbidities such as diabetes, hypertension, anemia and drugs used did not explain this association. Depression scores, as measured by the Beck Depression Inventory, were higher in migraine patients with RLS (p =0.04). **Conclusion:** No specific factors explaining the association between migraine and RLS were found. Symptoms of depression were more frequent in patients with migraine and RLS.

Key words: migraine, restless legs syndrome, comorbidity, medication, depression.

RESUMO

Objetivo: A fisiopatologia da enxaqueca e da síndrome das pernas inquietas (SPI) parece envolver mecanismos genéticos e disfunção do sistema dopaminérgico. Artigos anteriores mostraram que a frequência de SPI em pacientes com enxaqueca é maior do que nos controles. Desenvolvemos um estudo para avaliar comorbidades, medicamentos utilizados e sintomas depressivos em pacientes com migrânea e SPI. **Métodos:** Foi desenvolvido um estudo de caso-controle. Foram entrevistados pacientes com enxaqueca (n=72) e sujeitos de um grupo controle (n=72). Foram avaliados dados incluindo diagnóstico de SPI, sintomas depressivos, comorbidades e medicamentos usados. **Resultados:** Houve associação significativa entre enxaqueca e SPI (p=0,01). Comorbidades como diabetes, hipertensão, anemia ou drogas utilizadas não explicam esta associação. Escores de depressão, medidos pelo Inventário de Beck, foram mais altos em pacientes com enxaqueca e SPI (p=0,04). **Conclusão:** Não foram encontrados fatores específicos que explicam a associação entre enxaqueca e SPI. Sintomas de depressão foram mais frequentes em pacientes com enxaqueca e SPI.

Palavras-Chave: enxaqueca, síndrome das pernas inquietas, comorbidade, medicamentos, depressão.

Restless legs syndrome (RLS) was first reported in 1672 by Sir Thomas Willis, a British anatomist and physician who described a patient with subjective discomfort in the legs interfering with his sleep[1]. In 1944, Ekbom, in Sweden, provided an accurate description of the syndrome[2].

RLS is a neurological disorder characterized by disagreeable (uncomfortable) subjective feelings such as burning, itching, cramps and tingling in extremities of the legs. Patients feel compelled to move their legs (and sometimes other body parts), and the symptoms typically worsen at night. Symptoms significantly interfere with the sufferer's quality of life, both during the night (sleep disturbance) and while awake, thus impacting social activities[3-5].

Diagnostic criteria for RLS were established by the International Restless Legs Syndrome Study Group (IRLSSG)[4] in 2003, and according to these criteria the prevalence of RLS ranges from 2.5% to 10% with important geographic differences[6-8]. The pathophysiology of RLS is poorly understood,

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but factors associated with dysfunctions of D2 dopamine receptors seem to be important. Other factors include iron deficiency, dysfunctions of the tyrosine kinase and peripheral neuronal sensitization[5]. The first genetic locus associated with RLS was mapped to chromosome 12q, and five other loci have been described (13q, 14q, 9p, 2q, 20p)[9-11].

Migraine is a chronic episodic disorder characterized by attacks of headache associated with nausea, photophobia and phonophobia. Over 17% of adult women and 6% of adult men suffer from migraine. Nearly 70% of migraineurs have at least one affected first-degree relative[12,13].

The pathophysiology of migraine seems to involve neuronal hyper-reactivity that is often inherited[14]. Dopaminergic involvement in the pathophysiology of migraine is well known and is likely to be due to hypersensitivity of dopaminergic receptors involved in the onset of attacks and in the onset of premonitory symptoms (somnolence, yawning, nausea)[15-16]. On the other hand, migraine attacks may often be aborted by using antidopaminergic medications, such as metoclopramide and chlorpromazine[15-16].

The comorbidity between migraine and RLS was suggested before and shared dopaminergic dysfunctions may explain the association[17-21]. We do not know if comorbidities, medication used or depressive symptoms can explain the relation between migraine and RLS. Furthermore, only partial assessment of hidden comorbidities, such as diabetes, neuropathies or depression (often treated with medications that block dopamine) has been conducted[17-22]. Nonetheless, since migraineurs are often treated with dopaminergic antagonists, which, in turn, increase the risk of RLS, it is important to consider treatment when assessing the comorbidity, and this is yet to be done. Therefore, we conducted a study to assess the prevalence of RLS in patients with migraine and to verify the possible influence of comorbidities, depressive symptoms and medication in this population.

METHODS

Study design

The study was conducted at the University Hospital of the Medical School of Ribeirão Preto, University of São Paulo. Firstly, a survey was carried out to identify employees with migraine and restless legs syndrome. Headache was assessed by self-administered questionnaires distributed to all 2,500 employees of the hospital. Out of these, 400 employees reported having no headache in the questionnaires, and 120 reported headache features that suggested migraine. Secondly, these 120 employees were individually interviewed by one of the authors (KSF), and only those fulfilling inclusion criteria were included. Controls without migraine were matched by gender, age and employment type.

Inclusion and exclusion criteria

Participants of both genders ranging from 18 to 65 years of age were included. Other inclusion criteria were migraine with or without aura according to the criteria of the International Headache Society[23]. We excluded patients who had more than 10 headache attacks per month in order to completely exclude those with chronic migraine from our sample. We believe that patients with chronic migraine present more abuse of medications, which could influence the dopaminergic pathways involved in the relationship between migraine and RLS.

Questionnaire

After signing the informed consent form, participants were interviewed with the aid of a questionnaire. The following information was obtained:
1. Sociodemographic data, as well as the presence of self-reported comorbidities (hypertension, diabetes, anemia);
2. Medications in current use;
3. RLS diagnosis, according to the four essential criteria recommended by the International Restless Legs Syndrome Study Group[4];
4. Severity of RLS, according to the International Restless Legs Syndrome Study Group rating scale for restless legs syndrome[24].
5. Clinical characteristics and severity of migraine (visual analogue scale – VAS);
6. Self-assessment of qualitative depressive symptoms as well as severity of depressive symptoms according to the Beck Depression Inventory (BDI).

Statistical analysis

Data were entered and analyzed with the SAS version 8 by the Statistics Department of the Medical School. After exploratory analyses, qualitative variables were compared by Fisher's exact test. Significance (p) was established at the 0.05 level; Odds ratios (OR) and confidence intervals (CI) were constructed by logistic regression models. The non-parametric Wilcoxon test was used to compare quantitative data (age, duration and frequency of symptoms, as well as VAS, severity and Beck scores).

Ethical considerations

The study was approved by the Investigation Review Board (protocol 9712-2008) of our institution.

RESULTS

The sample consisted of 72 cases (62 women and 10 men) and 72 controls (57 women and 15 men). Mean age was 42.5 years for migraineurs and 40 years for controls (Table 1).

RLS was more common among those with migraine than controls (25% *versus* 8%, p=0.01; OR=3.67, 95%CI=1.36-9.88).

Migraineurs and controls did not differ as to other parameters (sex, age, ethnic group) (Table 1).

Migraineurs with RLS did not use more medication than controls with RLS (Table 1).

No differences in relative risk of RLS were observed as a function of presence of aura, premonitory symptoms, pain severity and frequency (Table 2).

In individuals with migraine, no differences in relative risk of RLS were observed caused by the presence of comorbidities such as hypertension, diabetes, anemia or smoking habit (Table 2). We did not detect differences between migraine patients and controls in terms of family history of RLS. (Table 1)

Depressive symptoms (qualitative ones) were more common in individuals with migraine and RLS than in those without RLS (p=0.03; OR=3.98, 95%CI 1.07–18.8). Total BDI scores were higher among those with migraine and RLS than for those with migraine without RLS (p=0.04) (Table 2).

DISCUSSION

We found a significant association between migraine and RLS in a Brazilian population, as reported in previous studies[17-21]. However, most studies were case series or studies of the case-control type, a fact that weakened these results. A recent population-based and methodologically more robust study indicated that migraine is associated with RLS in a population-based cohort of women. Furthermore, as also observed in the present study, this association is not affected by migraine aura status[21].

An association between migraine and RLS is plausible because it is based on clinical findings and pathophysiological considerations. From a clinical point of view, both conditions are characterized for being chronic diseases with periodic exacerbations, involving more women and having an important impact on quality of life and quality of sleep[3,25-27].

Furthermore, premonitory manifestations of migraine associated with dopamine, such as yawning, nausea, somnolence and food craving, are more frequent among migraneurs with RLS than among subjects suffering from migraine alone[22]. From a pathophysiological point of view, evidence suggests that these conditions may involve dysfunction of the A11 hypothalamic dopaminergic nucleus. By binding to D2 receptors, the A11 nucleus inhibits the activation of the trigeminocervical complex, which is a key region for pain transmission in migraine, from the head and orofacial structures

Table 1. Demographic and clinical data of the migraine patients and control subjects.

	Migraine n=72	Controls n=72	p-value	OR (95%CI)
RLS prevalence (%)	25	8	0.01	3.67 (1.36–9.88)
Sex				
Female (%)	86	79	0.59	2.04 (0.34–12.36)
Male (%)	14	21	0.99	0.72 (0.14–3.74)
Age (mean)	42.5	40	0.40	-
Ethnic group (white %)	89	89	0.99	1.00 (0.18–5.46)
RLS severity scale (mean)	18	15	0.20	-
Family history of RLS (%)	17	4	0.99	1.43 (0.13–16.02)
Anemia (%)	16.6	20.8	0.59	2.01 (0.16–15.92)
Smokers (%)	16.6	9.7	0.47	1.97 (0.04–22.81)
Hypertension (%)	16.6	12.5	0.56	1.44 (0.03–15.62)
Diabetes (%)	5.5	4.1	0.23	6.09 (0.09–137.6)
Medication*(%)	16.6	4.1	0.66	-

RLS: restless leg syndrome; OR: odds ratio; CI: confidence interval. *Medication in current use.

Table 2. Clinical data of the migraine patients with or without RLS.

Migraineurs	(-) RLS n=54	(+) RLS n=18	p-value	OR (95%CI)
Aura (%)	29.6	44.4	0.26	1.88 (0.54–6.48)
Migraine attack (means)*	5	4	0.45	-
Intensity (means)**	8	8	0.11	-
Premonitory symptoms (%)	61.1	72.2	0.57	1.64 (0.68–6.77)
Anemia (%)	14.8	22.2	0.48	1.63 (0.31–7.28)
Smokers (%)	11.1	33.3	0.06	3.90 (0.88–17.99)
Hypertension (%)	18.5	11.1	0.72	0.55 (0.05–3.04)
Diabetes (%)	5.5	5.5	0.99	1.00 (0.02–13.44)
Depressive symptoms (%)	46.2	77.7	0.03	3.98 (1.07–18.79)
BDI score (median)	5	7.5	0.04	-

RLS: restless leg syndrome; BDI: Beck Depression Inventory; OR: odds ratio; CI: confidence interval. *Days per month; **(VAS) visual analogue scale.

to the hypothalamus and brain[15,16]. In addition, the A11 nucleus also sends direct inhibitory projections to sympathetic preganglionic neurons and to the dorsal horn, as well as the anterior horn in the spinal cord, which innervates skeletal muscles and are believed to be involved in sensory suppression[5]; hence, dopaminergic dysfunction in this area might contribute with the sensory symptoms of RLS. Therefore, a shared dopaminergic dysfunction in the A11 nucleus may be the neuroanatomical substrate linking migraine and RLS. Also, it is known that there is an important association of RLS with changes in iron metabolism[11], and, similarly, iron deposits have been observed in the periaqueductal gray matter of migraneurs[28].

Another aspect that may be responsible for the association of migraine and RLS is sleep. Since sleep deprivation is an important factor triggering migraine[25,26] and RLS causes a reduction of the quality and quantity of sleep[27], theoretically, it would not be a surprise to consider that RLS may cause a worsening of the symptoms related to migraine, and that this mechanism may justify, at least in part, this association.

Patients with migraine alone or RLS only have a greater chance of developing depression[29-31]. In the present study we assessed depressive symptoms. BDI scores were higher in migraineurs with RLS than among those without RLS (p=0.04). Similarly, 77.7% of those with migraine and RLS self-reported having depressive symptoms compared to 53.7% of those with migraine, but not RLS (p=0.03). Therefore, depressive symptoms seem to be more frequent in patients with both migraine and RLS. However, the true role of depressive symptoms in the association between them needs to be further determined.

We found no association between demographic variables (gender, age, marital status and years of education) and headache or RLS status, as reported by others[17-25].

Regarding the characteristics of migraine, in our study no association was seen between the presence of aura, premonitory symptoms, frequency and severity of pain and RLS, as suggested by previous studies[17,20,21]. Similarly, no differences were observed between clinical features of RLS and migraine status. Variables such as RLS severity were not influenced by migraine status in this study.

We excluded patients with chronic migraine from our sample because they use more medication, which could influence dopaminergic pathways involved in the relationship between migraine and RLS, with consequent potential bias of the results.

Finally, in this study other medical comorbidities, life style and medication used did not increase the risk of the association RLS/migraine. Some of these comorbidities have been demonstrated in previous studies[17-21]. Nonetheless, for some (e.g., anemia), we relied on self-report and did not perform a hematological test, which was a limitation of our study. We suggest that the low prevalence of these comorbidities limited our power to detect association, another limitation of our study.

In conclusion, the prevalence of RLS is higher in migraineurs than in controls, but specific factors to explain the association were not found. On the other hand, clinical features of migraine in patients with RLS do not differ from those of subjects without RLS, and the severity of RLS does not vary as a function of migraine status. Migraineurs with RLS have higher BDI scores when compared to all other groups.

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