The onset of the migraine attack

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Chapter 4.

Restless legs syndrome in migraine patients: prevalence and severity

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Abstract

Background
We aimed to study not only prevalence but more importantly severity and correlation between sleep quality and restless legs syndrome (RLS) in a large population of well-defined migraine patients as poor sleep presumably triggers migraine attacks.

Methods
In a large cross-sectional and observational study, data on migraine and RLS were collected from 2,385 migraine patients (according to ICHD-IIIb) and 332 non-headache controls. RLS severity (International RLS Study Group severity scale) and sleep quality (Pittsburgh Sleep Quality Index) were assessed. Risk factors for RLS and RLS severity were calculated using multivariable-adjusted regression models.

Results
RLS prevalence in migraine was higher than in controls (16.9% vs. 8.7%; multivariable-adjusted OR 1.83; 95% C.I. 1.18-2.86; p=0.008), and more severe (adjusted severity score: 14.5±0.5 vs. 12.0±1.1; p=0.036). Poor sleepers were overrepresented among migraineurs (50.1% vs. 25.6%; p<0.001). Poorer sleep quality was independently associated with RLS occurrence (OR 1.08; p<0.001) and RLS severity (p<0.001) in migraine patients.

Conclusion
Restless legs syndrome is not only twice as prevalent but also more severe in migraine patients, and associated with decreased sleep quality.

Introduction

Migraine is a disabling episodic headache disorder[1]. It is associated with a variety of both psychiatric and somatic comorbidities such as depression[2] and restless legs syndrome (RLS)[3-8]. RLS, also known as Ekbom's syndrome, is characterized by an urge to move, mostly associated by unpleasant leg sensations, occurring at rest, in a circadian pattern diminishing with motor activity[9,10].

Several studies have provided evidence for a positive bi-directional association between migraine and RLS in clinical cohorts[3-6]. RLS prevalence rates in migraine populations range from 11.4%-17.7%[3,6], and are about twice as high as prevalence in the general Western population of 5-10%[11,12]. Additionally, it is suggested migraine is very prevalent among RLS patients[6]. Recently, data from population-derived migraine cohorts have suggested a ~1.2 fold increased risk for RLS in both sexes[7,8]. In case-control studies, a four-fold increase in RLS prevalence among migraineurs was reported[13].

It is not known, however, if RLS is also more severe in migraine patients and whether it relates to poorer sleep quality in migraine patients, thereby possibly triggering new migraine attacks. So far, only a small study with not well-defined headache patients, and without adjustment for important confounders, studied severity of RLS[14].

The aim of this study was to investigate not only the prevalence but also severity of RLS in a large population of well-defined migraine patients, and investigate the association with sleep quality.

Material and methods

Subjects

Our study was conducted as a part of the LUMINA project[15]. Participants were Dutch adults aged 18 to 74 years of age, both migraine patients and healthy controls. Patients with migraine with and without aura fulfilled the International Classification of Headache Disorders (ICHD-IIIb) criteria. Controls did not suffer from migraine, cluster headache, chronic tension type headache, or medication overuse headache. Both migraine patients and controls were recruited via public announcement, advertising in lay press and via the research website, and were considered eligible after a two-step inclusion process using validated questionnaires (see Supplementary Text 1 for details). The study had been approved by the medical ethics committee of the LUMC. All subjects provided written informed consent prior to the procedure.

Study design

The design of the study was observational and on a cross-sectional base. In total, n=2,875 eligible migraine patients, fulfilling ICHD-IIIb migraine criteria[16] and n=347 healthy controls were sent an invitation to a digital questionnaire including questions on RLS and RLS severity. Questionnaires could be filled out between September 2010 and January 2014.

Subjects were reminded to participate twice per e-mail, and non-responders were defined as those who did not participate after the reminders.

Clinical characteristics

Within LUMINA, premonitory symptoms (symptoms <48 hours prior to headache onset), headache characteristics, and accompanying symptoms were assessed. Since no validated questionnaire on premonitory symptoms exists, a simple inventory was used. Premonitory symptoms were scored dichotomised and included n=17 items, of which n=5 can be considered 'dopaminergic' (yawning, craving, tiredness, depressive mood and hyperirritability) [17, 18]. The premonitory symptom score was calculated by summing individual items (*yes* = 1, *no* = 0 points; range 0-17). In all subjects (both migraine patients and controls), demographics, data on intoxications, sleep quality data and depression data were gathered. Medication overuse was defined as either i) ever use of simple analgesics on >15 days/month during >3 months; ii) ever use of ergotamines on >10 days/month during >3 months; iii) ever use of triptans on >10 days/month during >3 months, or any combination of the above.

RLS screening and severity questionnaires

As part of an extended questionnaire on sleep habits and sleeping problems, we included a screening questionnaire for RLS. This questionnaire comprised four "yes/ no" type questions based on the essential criteria proposed by the international RLS Study Group [19] and has been validated previously by a physician's diagnosis [20]. When all four criteria were fulfilled, RLS severity in the past week was measured using the International RLS Study Group severity rating scale [21], that consists of 10 items related to severity and frequency of RLS symptoms. Each question is a five-point Likert-scale, with a range from 0 (no RLS or no impact) to 4 (very severe RLS or very severe impact), so total score ranges from 0 to 40. Subjects with RLS were divided in groups with mild (0-10 points), moderate (11-20 points), severe (21-30 points), or very severe (31-40 points) RLS [22].

Depression

For depression, data from the self-administered Hospital Anxiety and Depression Scale (HADS) [23], Center for Epidemiologic Studies Depression Scale (CES-D) [24], and a combined life-time depression algorithm [25] (HADS-D≥8 or CES-D>16 or physician-made diagnosis of depression or use of antidepressants with indication of depression) were used.

Sleep quality and insomnia

The Pittsburgh Sleep Quality Index is designed to measure the quality and patterns of sleep in the past month and contains 19 self-rated questions from which seven component scores are calculated and summed into a global score. Higher scores denote a poor sleep quality: component score range from 0 to 3, and global scores range from 0 to 21. Poor sleep quality is defined with a PSQI score of ≥6 [26]. The Insomnia Sleep Index (ISI) is a self-administered questionnaire to assess insomnia and insomnia severity in the past week, with 7 self-rated questions using a 5 point Likert like scale (none/ mild/ moderate/ severe/ very severe; ranging from 0-4) [27]. The total score ranges from 0-28, with higher scores denoting more insomnia complaints, and dichotomisation into 'no insomnia'(≤14) and 'insomnia' (≥15) [28].

Statistics

General characteristics were compared between migraine patients and controls using a Student's t-test for continuous variables, and a Chi square test for categorical data. To assess whether migraine and RLS were associated (primary analysis), a binary logistic regression was performed with RLS status as dependent variable. In analysing determinants for RLS severity, we performed a linear regression analysis with continuous RLS severity score as outcome measure. The primary regression analysis was adjusted for age, gender, BMI, smoking (packyears), alcohol use and life time depression. All other analyses were adjusted for age and gender. Data analyses were performed using SPSS 17.0 (SPSS inc., IBM, USA). The statistical threshold was set to $p<0.05$.

Results

Study population

Questionnaires were sent to 2,875 migraine patients (1,755 migraine without aura, 1,120 migraine with aura) and to 347 controls, of which 2,385/2,875 (82.9%) and 332/347 (95.7%) responded respectively. Non-responder analysis showed that responders were older (44.9±12.1 vs. 41.2±12.9; $p<0.001$), had a higher BMI (24.5±4.1 vs. 23.9±3.8; $p=0.044$) and had a lower HADS score compared to non-responders (10.1±6.7 vs. 11.5±7.1; $p<0.001$). Gender, smoking, use of alcohol, use of caffeine and PSQI score did not differ. In the study population, migraineurs were more often female, lower educated, had lower alcohol and higher caffeine intake (Table 1).

RLS prevalence in migraine patients and controls

A total of 403/2,384 migraine patients (16.9%) fulfilled the essential criteria for definite RLS, compared to 31/332(9.3%) in controls($p<0.001$). RLS prevalence did not differ between migraine with aura and migraine without aura patients: 170/919 (18.5%) vs. 233/1,465 (15.9%); $p=0.100$. RLS prevalence was 19.7% in the subgroup of migraine patients aged 50 years and older (166/844). The multivariable-adjusted odds ratio (OR) for RLS in migraine vs. the control group was 1.83 (95% C.I. 1.18-2.86; $p=0.008$). ORs (95% C.I.) for RLS were 1.74 (1.08-2.79; $p=0.02$) in migraine without aura and 1.99 (1.24-3.20; $p=0.005$) in migraine with aura subgroups. Within the migraine group, migraine subtype was not a determinant for RLS (age and gender adjusted; OR 0.83; $p=0.10$), but medication overuse was (OR 1.54; $p<0.001$).

RLS severity

Overall, 146/434 (33.6%) respondents had mild RLS, 227/434 (52.3%) had moderate RLS, 58/434 (13.4%) had severe RLS, and 3/434 (0.7%) had very severe RLS. Severe to very severe RLS was more present among migraine patients than in controls: 60/403 vs. 1/31; $p=0.036$. The adjusted mean RLS severity score in migraine patients with definite RLS was higher compared to controls with definite RLS: 14.5±0.5 vs. 12.0±1.1; $p=0.036$ (adjusted for age and gender). In migraineurs with RLS, a higher number of dopaminergic premonitory symptoms was associated with higher RLS severity ($p=0.008$). Additionally, a history of acute migraine headache medication overuse ($p=0.026$), use of ergots ($p=0.045$), and prophylactics ($p=0.002$) were also linked to more severe RLS (Table 2).

Table 1; Baseline characteristics of study population. Baseline characteristics of migraine patients (n=2,385) and healthy controls (n=332). MO = migraine without aura; AF = attack frequency

Variable	Total n=2,717	Migraine patients n=2,385	Controls n=332	*p*[a]
Demographics				
Age y, mean (SD)	44.9 (12.1)	45.1 (11.6)	43.8 (15.2)	0.145
Gender F, n (%)	2,230 (82.1%)	2,045 (85.7%)	185 (55.7%)	<0.001
BMI kg/m^2, mean (SD)	24.5 (4.1)	24.6 (4.1)	24.2 (4.0)	0.154
Education level, n (%)[b]				0.008
Low	161 (6.3%)	144 (6.5%)	17 (5.1%)	
Middle	862 (34.0%)	771 (35.0%)	91 (27.4%)	
High	1,513 (59.7%)	1,289 (58.5%)	224 (67.5%)	
Migraine				
Subtype MO		1,466 (61.5%)		
AF 1-4/month		2,182 (91.5%)		
RLS				
Definite RLS, n (%)	434 (16.0%)	403 (16.9%)	31 (9.3%)	<0.001
RLS severity, mean (SD)[c]	14.1(0.4)	14.5 (0.5)	12.0 (1.1)	0.036
Anti-RLS medication[d]	13/220	13/204 (6.4%)	0/16 (0%)	0.298
Intoxications				
Nicotine, packyears, mean (SD)	4.6 (8.9)	4.5 (8.7)	5.4 (10.0)	0.088
Alcohol; units/ week, mean (SD)	3.1 (4.4)	2.7 (3.8)	6.3 (6.7)	<0.001
Caffeine; units/ day, mean (SD)	5.8 (3.0)	5.9 (3.0)	5.3 (2.6)	0.001
Other				
PSQI total score, mean (SD)	6.2 (3.6)	6.5 (3.6)	4.1 (2.7)	<0.001
PSQI ≥6, %	1,360 (50.1%)	1,275 (53.5%)	85 (25.6%)	<0.001
HADS, total score, mean (SD)[e]	10.1 (6.7)	10.6 (6.7)	6.4 (5.45)	<0.001
Anti-RLS medication	13/220 (5.9%)	13/204 (6.4%)	0/16 (0%)	0.298

MO, migraine without aura; AF, attack frequency. *P* values are uncorrected for multiple comparison. [a]In view of the significant gender disproportion between migraine patients and non-headache controls in combination with known higher RLS prevalence amongst females and higher alcohol consumption in males, *p*-values may reflect biased estimates and should therefore be interpreted with caution; [b]data available from n = 2204 migraine patients and n = 332 controls; [c]adjusted for age and gender; [d]additional data from n = 220/419 subjects with definite RLS; [e]data available from n = 2254 migraine patients and n = 316 controls.

Impact of RLS on sleep quality in migraine patients

Significantly more migraine patients with RLS (64.4%) compared to migraine patients without RLS (51.4%; $p<0.001$) had poor sleep quality, and severity of the global PSQI sleep quality score was higher (7.4±3.7 vs. 6.3±3.6; $p<0.001$). The different PSQI components are indicated in Table 3. Migraine patients with RLS also scored higher on the Insomnia Severity

Index than migraine patients without RLS (9.5±6.7 vs. 8.1±6.5; $p<0.001$). Clinical insomnia was more prevalent in the RLS subgroup: 97/403 (24.1%) vs. 361/1.979 (18.2%); $p=0.007$.

Migraine, RLS and depression

Mean HADS score was higher in the migraine group compared to healthy controls (10.6±6.7 vs. 6.0±5.4; $p<0.001$), and life-time depression was also more prevalent: 45.5% vs. 16.8%; $p<0.001$ (age and gender adjusted). In both groups, life-time depression was associated with RLS prevalence (overall odds ratio 1.60; $p<0.001$) and RLS severity (overall B=2.67; $p<0.001$), but this effect was strongest in the migraine group.

Table 2. Determinants for Restless Legs Syndrome severity. Multivariable-adjusted B's for RLS severity (according to IRLSSG-criteria). MO = migraine without aura; MA = migraine with aura; DPS = dopaminergic premonitory symptoms; PSQI = Pittsburgh Sleep Quality Index; n.a. = not applicable. Linear regression analyses were adjusted for age and gender.

Variable	Multivariable-adjusted determinants for RLS severity					
	Total n=434		Migraine patients n=403		Controls n=31	
	B	*p*	B	*p*	B	*p*
Demographics						
Age (y)	-0.002	0.937	0.011	0.704	-0.121	0.107
BMI (kg/m²)	0.149	0.033	0.144	0.047	0.187	0.457
Gender, F	-0.610	0.488	-0.739	0.466	-2.620	0.110
Migraine vs. controls						
Migraine vs. controls	2.475	0.036	n.a.	n.a.	n.a.	n.a.
MO vs. controls	2.175	0.085	n.a.	n.a.	n.a.	n.a.
MA vs. controls	2.914	0.015	n.a.	n.a.	n.a.	n.a.
Mig. characteristics						
MO subtype	n.a.	n.a.	0.058	0.926	n.a.	n.a.
>4 attacks/month	n.a.	n.a.	1.294	0.237	n.a.	n.a.
Medication overuse	n.a.	n.a.	1.440	0.026	n.a.	n.a.
Use of triptans	n.a.	n.a.	0.882	0.243	n.a.	n.a.
Use of ergots	n.a.	n.a.	2.993	0.045	n.a.	n.a.
Use of prophylactics	n.a.	n.a.	2.043	0.002	n.a.	n.a.
DPS (continue)	n.a.	n.a.	0.540	0.008	n.a.	n.a.
Intoxications						
Nicotine, packyears	0.054	0.095	0.063	0.068	0.005	0.943
Alcohol, units/ week	-0.138	0.063	-0.126	0.114	-0.095	0.620
Caffeine, units/ day	-0.025	0.814	-0.038	0.736	-0.002	0.996
Other						
PSQI total score	0.573	<0.001	0.579	<0.001	0.320	<0.001
PSQI ≥6	3.153	<0.001	3.229	<0.001	0.961	0.605
Life-time depression	2.666	<0.001	2.725	<0.001	0.398	0.811

p-values are uncorrected for multiple comparisons

Table 3. Pittsburgh Sleep Quality Index (PSQI) scores. Depicted are PSQI component and global scores (mean (SD)) of migraine patients with and without restless legs syndrome (RLS). Migraine patients with RLS have higher scores on almost all PSQI component scores, indicating worse functioning on these domains.

	Migraine with RLS (n=403)	Migraine non-RLS (n=1,981)	*p*
PSQI mean component score			
Subjective sleep quality	1.3 (0.7)	1.1 (0.7)	<0.001
Sleep latency	1.4 (1.0)	1.2 (1.0)	<0.001
Sleep duration*	0.7 (0.9)	0.6 (0.8)	0.002
Habitual sleep efficiency*	0.9 (1.0)	0.7 (0.9)	0.001
Sleep disturbance	1.6 (0.6)	1.4 (0.5)	<0.001
Sleep medications*	0.4 (0.9)	0.4 (0.8)	0.952
Daytime dysfunction	1.2 (0.8)	0.0 (0.7)	<0.001
PSQI mean global score	7.4 (3.7)	6.3 (3.6)	<0.001
Poor sleeper (PSQI≥6) (n,%)	259 (64.3%)	1,016 (51.3%)	<0.001

* Mann Whitney U-test

Discussion

In the present study, we found that prevalence of restless legs syndrome (RLS) is two times higher in a well-defined group of migraine patients than in non-headache controls. Most importantly, our study shows that RLS is more severe in migraine patients and is associated with poorer sleep quality, a known trigger factor in migraine.

The prevalence of RLS in our migraine and control groups were comparable to previously reported data in both clinic-and population-based cohorts of migraine patients and controls, ranging from 9.5-22.4%[3, 5-8, 29] and from 7.1-13.0%[7, 8, 12, 30-33]. Higher RLS severity in headache patients was recently suggested based on data from a small and less well characterised sample of headache patients[14]. Additionally, we found that RLS in migraine patients is more severe with increasing migraine severity, as reflected by use of prophylactics, or a history of medication overuse. The clinical relevance of this small difference is to be further determined since both reflect mild RLS severity. Unbalanced group sizes in our study could have affected the outcome. However, previous data reporting a higher RLS prevalence in chronic migraine vs. episodic migraine underlines our finding[34].

The strength of our study includes the large sample size, with data from over 2,300 well-defined migraine patients, representative for the population studied. Second, detailed validated questionnaires[15, 19] assured precise categorization, although RLS remains a clinical diagnosis. Third, the personalized web-based questionnaire facilitates filling out and sending in for participants, leading to a high participation rate[15]. Fourth, non-headache controls were recruited in exactly the same way as the migraine patients, minimizing inclusion bias. However, some limitations should also be addressed. First, the control group in our study was considerably smaller than the case group but, we believe, this has hardly

affected the statistical power of the study. The number of cases (n = 2,350) was high and the number of controls (n = 300) was still considerable, resulting in post-hoc power of 0.97 to detect a 8% difference in proportion of RLS prevalence between both study groups at alpha 0.05 (and a post-hoc power of 0.82 to detect a 6% difference). Increasing the number of controls would have involved disproportionately large and in fact unnecessary efforts leading to only moderate increase in study power. Secondly, some medication may affect symptoms of RLS[35]. In our study 18% of subjects with definite RLS used anti-RLS medication, of whom only five used dopaminergic medication. This small subgroup reported highest RLS severity (data not shown). Second, presence of nephrotic syndrome, iron deficiency or diabetes can contribute to RLS symptomatology[36, 37], and RLS mimicks could make classification more difficult[38]. These conditions can not fully be excluded based on the four RLS diagnostic criteria, as was shown before[39]. Furthermore, other co-morbidities could have affected both migraine and RLS. Preferably, analyses should be corrected for these possible confounders. However, these possible biases have affected both the non-headache and the headache group. Thirdly, there were some differences between the migraine and controls groups. Migraine patients were more often female, used less alcohol and more caffeine than controls. They showed lower sleep quality, as reflected by the PSQI score, and a larger proportion suffered from life-time depression. Since identical questionnaires for depression and sleep quality were used in both the migraine and the control group, they would have affected both groups in a similar way, and would therefore not have accounted for inter-group differences. By adjusting all the primary analyses for these factors we tried to minimize potential bias. Fourth, the majority (87%) of the migraine patients in our sample has been diagnosed with migraine by a physician. Therefore, we can not exclude that this group is enriched with more severe migraineurs compared to a genuine population-based sample since not all migraine patients consult a physician. This would then suggest that RLS is associated with more severe migraine.

RLS is associated with lower sleep quality and fragmented sleep, which are known triggers for migraine attacks. Therapeutic options for RLS include among others dopaminergic treatment[19]. Few studies have assessed the effect of anti-RLS therapy on alterations in co-morbid migraine. In a small (n=10) study of patients with concomitant migraine and RLS, dopaminergic treatment with immediate-release pramipexole improved both RLS symptoms in all patients, and headache frequency and severity in half over a period of five months[40]. Headache relieve was also reported in another case-study (n=40) in one-third of migraineurs when treating RLS, most often when using dopamine-3 receptor agonists such as gabapentin of pregabalin[14]. This could either be due to improving central dopaminergic dysfunction or by improving compromised sleep quality due to RLS. Effects of migraine treatment on concomitant RLS have never been studied.

In conclusion, the risk for RLS is doubled in migraine patients, but more importantly RLS is more severe and associated with poorer sleep quality which might trigger new attacks. Further studies are needed to investigate if treatment for RLS positively affects migraine attacks.

Clinical implications

- Migraine patients are less prone to be of a normal chronotype and they are more languid and more rigid when changes in circadian rhythm occur.
- 60% of migraine patients report diurnal periodicity of headache attacks, of which one-third reports attack beginning between midnight and 06:00, and one-third between 06:00 and noon.
- Taken together, these data suggest that chronobiological mechanisms play a role in migraine pathophysiology.

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Supplementary Material

Supplementary Text

Both migraine patients and controls were recruited via nationwide public announcement, advertising in lay press and via the research website, and were considered eligible after a two-step inclusion process using validated questionnaires via the especially designed LUMINA website. Additionally, patients from our outpatient headache clinic were invited to participate by a letter.

On the website, patients were asked to fill out a screening questionnaire that has been validated previously. Firstly, if patients fulfilled the screening criteria, they were sent a web-based extended migraine questionnaire, based on the ICHD-II criteria [15, 16]. This questionnaire was validated before by performing a semi-structured telephone interview in 1,038 patients who had filled out the extended migraine questionnaire [15]. The specificity of the questionnaire was 0.95. We consider the cohort a well-defined web-based cohort, with 4% of subjects included from our dedicated headache outpatient clinic, 87% of the participants having been diagnosed as migraineurs previously by a medical doctor. In addition to questions that were necessary to diagnose migraine accurately, the extended questionnaire also included items on demographic factors, acute and prophylactic headache medication use, migraine attack frequency and allodynia. Participants without the needed internet skills were able to fill out the questionnaires on paper.

Non-headache individuals willing to participate had to pass a screening questionnaire online via the research website. If this screening questionnaire did not show any indication for having migraine, cluster headache, chronic tension type headache or medication overuse headache, individuals were sent a subsequent in depth questionnaire. This second questionnaire again assessed possible headache complaints, together with demographic variables. Only individuals that fulfilled both the criteria of 'non-headache' in the screening and in depth questionnaire were considered eligible controls and were approached for this questionnaire study.

Since recruitment of control subjects started at a later point in time and inclusion rate was slower, the number of migraine patients included exceeds the number of controls included in our study.