“Anxietas Tibiarum”

Depression and anxiety disorders in patients with restless legs syndrome

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Abstract

Background: Symptoms of anxiety and depression in patients with restless legs syndrome (RLS) have been observed. However, it is unclear whether rates of threshold depression and anxiety disorders according to DSM-IV criteria in such patients are also elevated.

Methods: 238 RLS patients were assessed with a standardized diagnostic interview (Munich-Composite International Diagnostic Interview for DSM-IV) validated for subjects aged 18–65 years. Rates of anxiety and depressive disorders were compared between 130 RLS patients within this age range and 2265 community respondents from a nationally representative sample with somatic morbidity of other types.

Results: RLS patients revealed an increased risk of having 12-month anxiety and depressive disorders with particularly strong associations with panic disorder (OR=4.7; 95% CI=2.1–10.1), generalized anxiety disorder (OR=3.5; 95% CI= 1.7–7.1), and major depression (OR=2.6; 95% CI=1.5–4.4). In addition, lifetime rates of panic disorder and most depressive disorders as well as comorbid depression and anxiety disorders were considerably increased among RLS patients compared with controls.

Conclusions: The results suggest that RLS patients are at increased risk of having specific anxiety and depressive disorders. Causal attributions of patients suggest that a considerable proportion of the excess morbidity for depression and panic disorder might be due to RLS symptomatology.

Key words restless legs syndrome, anxiety, depression

Introduction

In the 19th century Wittmaack first described the co-occurrence of restless legs syndrome (RLS) with symptoms of depression and anxiety and suggested the term “anxietas tibiarius” for the condition [29]. He further proposed the classification of this syndrome as a form of “neurasthenia” [13]. Early investigators noted that RLS occurs particularly in “anxious, tense, or depressed patients” [6]. Using questionnaires, recent studies have shown up increased symptoms of anxiety and depression among RLS patients [1, 9, 10, 17]. However, up to now no data have been available to investigate whether RLS patients are at increased risk for specific psychiatric disorders, especially those from the anxiety and depression spectrum. The present study examined rates of depression and anxiety disorders according to DSM-IV diagnostic criteria [20] in patients with RLS, and compares these rates with controls from a community sample with a somatic illness.

Methods

Consecutive inpatients and outpatients of the Movement Disorder Unit at the Max Planck Institute of Psychiatry, Munich diagnosed with idiopathic RLS [23] were included in the study. The patients were contacted by letter describing the aim and design of the study. After written informed consent was obtained patients were scheduled for a telephone interview. The subjects were studied within a previously reported investigation addressing the mode of inheritance of RLS [25]. Assessments were based on a computer-assisted personal interview

using the Munich-Composite International Diagnostic Interview for DSM-IV (DIA-X/M-CIDI), a modified version of the World Health Organisation CIDI, version 1.2., supplemented by questions to cover DSM-IV and ICD-10 criteria [28]. The M-CIDI allows for the assessment of symptoms, syndromes and diagnoses according to DSMIV criteria of specific mental disorders along with information about onset, duration, and clinical and psychosocial severity. Test-retest reliability and validity for the full M-CIDI have been reported elsewhere [16, 27]. The performance of the interview took 30 minutes and was completed in a single contact. For the purpose of this report, CIDIDSM- IV algorithms [15] for the diagnosis of depression (major depressive episode DSM-IV: 296.2 and dysthymia DSM-IV: 300.4) as well as anxiety disorders (panic disorder DSM-IV 300.21 and generalized anxiety disorder (GAD): DSM-IV 300.02) are considered. It was also investigated within the CIDI assessment whether the depressive or anxiety disorder – according to the patient’s attribution – was almost (exclusively) due to a significant somatic condition as summarized in the DSM-IV exclusion criteria [20] (depression due to a general medical condition DSM-IV: 293.83 and anxiety disorder due to a general medical condition DSM-IV: 293.89). In addition, the sole occurrence of panic attacks not meeting the full diagnostic criteria for a panic disorder was considered. All diagnoses were assessed for the past 12-month time frames along with information about the age of first onset. Apart from GAD, the lifetime history of the respective condition was also assessed. Any differences between pharmacologically treated and untreated RLS patients were also investigated.

All interviews were performed by two highly trained DIA-X/MCIDI interviewers with clinical backgrounds who had received special training (MP and BS). Interviewers were closely monitored throughout the entire study period.

The control group consisted of subjects selected out of 4181 subjects in the German National Health Interview and Examinations Survey – Mental Health Supplement (GNH – MHS) [8], a community survey of the German general population examined using the same method as the RLS group for mental and somatic morbidity. To control for non-specific effects of somatic illness on the rates of mental disorder, only subjects with one or more somatic diagnoses were included. However, control subjects with any neurological or nephrological disorder were excluded in the comparative analysis because of the known occurrence of secondary RLS [2, 24] (n=2265).

Analyses were performed using Stat 7 [22] and applying the information sandwich estimator for accurate assessment of precision of estimated measures in the case of weighted data [18]. For binary outcomes, associations were quantified with the odds ratios (OR) from logistic regression [11] while adjusting for age and gender. In addition, the interaction restless legs*sex and restless less*age for all mental disorders as outcome were tested. In the case of a significant interaction we included the respective interaction term(s) and calculated then the odds ratio adjusted to the mean age and female rate in the general population, that is:

$OR_{adj} = \exp [b(\text{main effect restless legs}) + b(\text{restless legs} * \text{female gender}) * 0.4767105 + b(\text{age}) * 42.32755]$ with $b(.) = \ln(OR(.))$.

Every control subject had been given a weighting factor by a quantum- weighting program to account for differential sampling probabilities and to match the distribution of the sampling frame.

Results

Because the assessment instrument, the M-CIDI for DSM-IV (DIA-X/M-CIDI) [28] is specifically validated for subjects aged 18–65 years, only patients within this age range (n=130) were included in the final analysis. For the reader’s information, prevalence rates of

depression and anxiety disorders of RLS patients aged 65 or above (n=108) are also presented in the tables. No control group, however, is available for this age range.

The mean age of the patients (n=130, 71 female and 59 males) was 55.3 years (SD=8.2). Of 4181 GNH – MHS controls, 2265 subjects had a somatic but no neurological or nephrological disorder. The mean age of these subjects (1166 female and 1099 male) was 42.3 years (SD=13.1).

Compared with the controls, RLS patients reported higher 12-month rates of any depressive disorder (OR=2.6, 95% confidence interval (CI)=1.5–4.4), panic attacks (OR=2.9, 95% CI=1.4–5.4; OR adjusted for mean control group=5.4; 95% CI=2.5–11.7), panic disorder (OR=5.2, 95% CI=2.4–11.3; OR adjusted for mean control group=10.1; 95% CI=4.5–22.4), or generalized anxiety disorder (OR=3.7, 95% CI=1.8–7.4). When examining comorbidity rates, RLS subjects were also more likely to present with comorbid anxiety-depression (OR=2.1, 95% CI=1.0–4.0); the association between depressive and panic disorder (OR=3.6, 95% CI=1.0–11.8) is particularly noteworthy. Table 1 gives 12-month prevalence rates of any depressive and anxiety disorders as well as selected diagnostic subgroups. Rates for panic attack in both groups and the odds ratio RLS vs. controls are also shown.

Closer inspection further revealed that in comparison with controls with at least one other physical disorder, RLS patients more frequently attributed major depressive episodes to a general medical condition (8.5% vs. 1%, OR=13.2, 95% CI=5.4–32.2) as proposed in DSM-IV. Compared with controls, RLS patients with depression attributed, in particular, their sleep disturbances (47.8 % vs. 5.4%, OR=12.7, 95% CI=4.0–40.7), depressed mood (43.5% vs. 3.1%, OR=24.9, 95% CI=7.5–82.3), reduced interest (34.8% vs. 2.8%, OR=19.7, 95% CI=5.2–74.2) and suicidal thoughts (34.8 % vs. 2.6%, OR=24.1, 95% CI=6.4–90.5) as being entirely and always due to their RLS symptoms. Lifetime rates were higher and associations of RLS and depression and panic disorder were comparable (see Table 2). Again, a higher rate of RLS patients attributing their major depressive episodes to a general medical condition (13.8% vs. 1.8%, OR=8.45, 95% CI=4.1–17.1) was found.

The analysis of age-of-onset characteristics of specific depressive disorders and panic disorder among RLS patients revealed that in most of the patients the psychiatric disorder appeared after the onset of RLS. This is the case in 76.7% of patients with major depression, 83.3% of patients with dysthymia, 63.6% of patients with GAD, and 60% of patients with panic disorder, all of whom describe the occurrence of RLS before the onset of the psychiatric disorders.

Eighty-two percent of RLS patients received pharmacological treatment of their RLS, most often with dopaminergic medication. Comparing the prevalence rates of depression and anxiety disorders of patients with (n=107) and without (n=23) pharmacological treatment of their RLS no significant group differences emerged. The 12-month prevalence rates for MDE were 8.7 % vs. 9.4% (OR=1.49; 95% CI=0.27–8.34), for dysthymia 8.7 vs. 4.7 (OR 0.47, 95% CI 0.08–2.65), for GAD 4.4 vs. 9.4 (OR=2.21, 95 % CI 0.27–18.32), and for panic disorder 8.7 vs. 8.4 (OR 1.35, 95 % CI 0.23–7.94). The lifetime prevalence rates for MDE were 8.7% vs. 26.2% (OR=4.04; 95% CI=0.87–18.74), for dysthymia 8.7 vs. 4.7 (OR 0.47, 95 % CI 0.08–2.65), for GAD 4.4 vs. 9.4 (OR=2.21, 95 % CI 0.27–18.32), and for panic disorder 8.7 vs. 12.2 (OR 1.91, 95 % CI 0.35–10.46).

Discussion

The main finding of our study is that RLS patients are at increased risk for DSM-IV depressive and anxiety disorders. The temporal relationship between depression, panic disorder and RLS suggests that in most cases RLS occurs as the primary condition. This

pattern of tempo tion that their mental disorder symptoms might be caused by their RLS symptoms.

Because it is well known that somatic disorders e. g. diabetes [3], cardiovascular disorders [12] or cancer [21] increase the risk of depression and some anxiety disorders [30], we allowed for this association in our analyses by comparing RLS patients with a subset of age-adjusted community respondents suffering from at least one somatic disorder. It should be noted that this control strategy is a strong test and although the control group was not specifically scrutinized for possible RLS symptoms the exclusion of control subjects with diseases known to be associated with the RLS obviously minimizes RLS-cases within the controls. Considering the older age of the RLS-patients and the sex difference in comparison to the controls we have statistically corrected for age and gender. Our finding, even in this strict comparison, that RLS patients have significantly higher rates of both depressive and anxiety disorders (particularly from the GAD and panic spectrum) is remarkable. It suggests that RLS patients are at an even higher risk of psychiatric disorder than patients with other somatic disorders. Although the patients' causal attribution suggests that some of this excess mental disorder morbidity might be explained by the direct or indirect effect of RLS, suggesting some pathophysiologic pathway, it is noteworthy that this relationship does not sufficiently explain the observed association. Furthermore, this association is also of strong clinical relevance because it is known that antidepressants can aggravate RLS [7, 14]. The importance of the need for specific treatment of the mental illness in RLS patients is also supported by the high number of the patients (38%) reporting suicidal thoughts due to their RLS symptoms. Taken together our results call for further studies on the role and efficacy of antidepressants in RLS-patients, particularly because some patients also experienced an improvement in their RLS symptoms with antidepressant treatment [5].

Possible mechanisms by which RLS increases the risk of specific depressive and anxiety disorders are not known at the moment. It could be that sleep disturbances may increase the risk of these disorders and it is well known that sleep disturbances can increase the risk of depressive disorders [4]. Furthermore, sleep deprivation can worsen panic disorder [19] and may, in susceptible subjects, trigger a panic disorder. However, currently used medication for the treatment of RLS such as dopaminergic, GABAA-ergic and opioidergic compounds may also influence the development of depression and anxiety disorders in susceptible RLS patients. Our own exploratory analysis could not detect any differences between treated and untreated RLS patients. However, as only 23 RLS patients did not receive pharmacological treatment, and the number of patients with specific depressive or anxiety disorders did not exceed three, this exploratory analysis lacks the power to detect subtle effects.

Because RLS is a highly familial disorder [26], the increased risk of specific depressive and anxiety disorders could have a genetic etiology as well, and it needs to be investigated whether both the neurological and psychiatric conditions segregate within the same families. Although the clinical association of RLS and depression and anxiety disorders had already been described in the 19th century, our study confirms this clinical observation using standardized diagnostic criteria for the first time. It should now be possible to explore the mechanisms involved in this specific comorbidity and to evaluate the implications for the treatment of these common neurological and psychiatric disorders. Our findings underline the need for further studies on the role and efficacy of antidepressants in RLS.

Table 1 12-month prevalence rates and odds ratio of depressive disorders, panic attacks and anxiety disorders in RLS patients and the GHS-MHS control group (* $p < 0.05$) (RLS restless leg syndrome; MDE major depressive episode; GAD generalized anxiety disorder; w weighted; OR odds ratio; CI confidence interval)

	RLS (n = 130)			Controls (n = 2265)			RLS vs. Controls		RLS > 65 years (n = 108)		
	N	%	95% CI	N	%w	95% CI	OR	95% CI	N	%	95% CI
# Any MDE	23	17.7	12.0–25.3	222	8.7	7.5–10.1	2.55*	1.5–4.4	9	8.3	4.5–15.3
MDE	12	9.2	5.3–15.6	197	7.7	6.6–9.0	1.31	0.6–2.5	6	5.6	2.5–11.9
Dysthymia	7	5.3	2.5–10.9	107	3.8	3.0–4.7	1.09	0.4–2.6	3	2.8	0.9–8.3
Panic Attack	14	10.7	6.4–17.4	111	4.1	3.3–5.1	2.85*	1.4–5.4 ^a	4	3.7	1.3–9.5
# Any Panic Disorder	11	8.5	4.7–14.7	57	2.1	1.6–2.1	4.65*	2.1–10.1 ^a	0	0.0	
Panic Disorder	11	8.5	4.7–14.7	55	2.0	1.5–2.7	5.22*	2.4–11.3 ^a	0	0.0	
# Any GAD	11	8.5	4.7–14.7	63	2.3	1.7–3.1	3.52*	1.7–7.1	2	1.9	0.4–7.2
GAD	11	8.5	4.7–14.7	60	2.3	1.7–3.0	3.66*	1.8–7.4	1	0.9	0.1–6.4
Pattern of comorbidity											
Anxiety & Depression	13	10	5.8–16.5	134	4.8	4.0–5.8	2.08*	1.0–4.0	4	3.1	1.3–9.5
Panic & Depression	4	3.1	1.1–8.0	32	1.2	0.8–1.7	3.57*	1.0–11.8	0	0.0	

Including patients with the disorder due to a general medical condition according to DSM-IV

^a OR adjusted for mean control group = 5.4 for panic attack (95% CI = 2.5–11.7), 9.5 for panic attack due to medical condition (95% CI = 4.2–21.1), and 10.1 for panic disorder (95% CI = 4.5–22.4)

Table 2 Lifetime prevalence rates and odds ratio of depressive disorders, panic attacks and anxiety disorders in RLS patients and the GHS-MHS control group (* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$) (RLS restless leg syndrome; MDE major depressive episode; w weighted; OR odds ratio; CI confidence interval)

	RLS (n = 130)			Controls (n = 2265)			RLS vs. Controls		RLS > 65 years (n = 108)		
	N	%	95% CI	N	%w	95% CI	OR	95% CI	N	%	95% CI
# Any MDE	48	36.9	29.0–45.6	393	15.2	13.7–16.8	3.30***	2.1–5.0	21	19.4	13.0–28.1
MDE	30	23.0	16.6–31.2	348	13.4	11.9–14.9	1.93**	1.2–3.0	17	15.7	10.0–23.9
Dysthymia	7	5.3	2.5–10.9	108	3.8	3.1–4.7	1.10	0.4–2.5	4	3.7	1.3–9.5
Panic Attack	20	15.38	10.1–22.7	193	7.2	6.2–8.4	2.11**	1.2–3.6 ^b	8	7.4	3.7–14.2
# Any Panic Disorder	15	11.4	7.0–18.3	92	3.4	2.7–4.2	3.64***	1.8–6.9 ^b	5	4.6	1.9–10.7
Panic Disorder	15	11.4	7.0–18.3	87	3.2	2.5–4.0	4.13***	2.1–8.0 ^b	5	4.6	1.9–10.7
Pattern of comorbidity											
Anxiety & Depression	25	19.2	13.3–27.0	173	6.0	5.1–7.1			9	8.3	4.3–15.3
Panic & Depression	9	6.9	3.6–12.8	47	1.6	1.2–2.3	4.57***	1.9–10.7	2	1.9	0.4–7.2

Including patients with the disorder due to a general medical condition according to DSM-IV

^b OR adjusted for mean control group = 4.6 for panic attack (95% CI = 2.2–9.5), 8.5 for panic attack due to medical condition (95% CI = 3.9–18.3), and 9.1 for panic disorder (95% CI = 4.2–19.5)

Acknowledgement

This work was supported by a Habilitations Förderpreis grant from the Bavarian Ministry of science, culture and art.

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