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AIM AND SCOPE

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ORIGINAL ARTICLE

Observational Study

Management of restless legs syndrome in chronic liver disease: A challenge for the correct diagnosis and therapy

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Abstract

AIM

To investigate the association between restless legs syndrome (RLS) and well-defined chronic liver disease, and the possible therapeutic options.

METHODS

Two hundred and eleven patients with chronic liver disease, complaining of sleep disturbances, painful leg sensation and daily sleepiness, were included. Patients with persistent alcohol intake, recent worsening of clinical conditions, or hepatitis C virus were excluded. Diagnosis of RLS was suggested by the Johns Hopkins questionnaire and verified by fulfilling the diagnostic criteria by Allen. All patients were tested, both at baseline and during follow-up, with the Hamilton rating scale for depression, sleep quality assessment (PSQI), Epworth sleepiness scale (ESS), International Restless Legs Syndrome Study Group evaluation, and international RLS severity (IRLS) scoring system. Iron-free level, ferritin, folate, vitamin B12 and D-OH25 were detected. Neurological examinations and blood test

occurred at the beginning of the therapy, after 2 wk, and at the 28th, 75th, 105th, 135th, 165th and 205th day. Regarding therapy, pramipexole or gabapentin were used.

RESULTS

Patients were moderately depressed, with evident nocturnal sleep problems and concomitant daily sleepiness. Sleep problems and involuntary leg movements had been underestimated, and RLS syndrome had not been considered before the neurological visit. All (211/211) patients fulfilled the RLS diagnostic criteria. Twenty-two patients considered their symptoms as mild, according to IRSL, but 189 found them moderate to very severe. No correlation was found between ammonium level and ESS or PSQI. Augmentation was rather precocious in our patients (135th day), and more frequent (35%) than previous data (8.3%-9.1%). The dosage of dopamine agonists was found to be associated with augmentation and appears in range with the literature. Previous intake of alcohol and lower levels of vitamins have been related to the phenomenon in our study.

CONCLUSION

RLS is a common disorder, requiring rapid diagnosis and treatment. Further research is therefore fundamental.

Key words: Restless legs syndrome; Chronic liver disease; Dopamine agonist treatment; Augmentation

Core tip: The diagnosis of restless legs syndrome (RLS) relies on the presence of unpleasant sensation in the legs associated with the urge to move. Symptoms mostly begin during periods of rest or inactivity and worsen in the evening or night. Partial or total relief is related to movement. Chronic hepatic failure was recently described in association with RLS, but there are very limited studies, with no mention to treatment. We describe RLS syndrome associated with well-defined chronic liver disease along with therapeutic options, discussing risks, benefits and potential side effects, with a particular look at the augmentation phenomenon in hepatic failure.

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INTRODUCTION

Restless legs syndrome (RLS) is defined as a very sickening, bilateral (even if also unilateral) sensation, almost described as affecting a very limited zone, between the knees and ankles, sometimes involving thighs and feet and resulting in feelings of scrambles, creeps or crawls. The discomfort is experienced only during the rest phase and it is relieved by active movement of the legs. Patients describe the symptoms of RSL as unbearable, when they are strained to maintain the sit-down position, such as during long flights or social events. But, usually, sleep is the worst moment of the day and RLS can disturb their sleep for hours. The American patients' organization Restless Legs Syndrome Foundation reminds us that RLS is "the most common disorder you have never heard of" (http://www.rls.org).

RLS remains a clinical diagnosis based on confirming the four essential diagnostic features of RLS: (1) An urge to move the legs, usually but not always accompanied by or felt to be caused by uncomfortable and unpleasant sensations in the legs; (2) the urge to move, as any accompanying unpleasant sensation begins or worsens during periods of rest or inactivity, such as lying down or sitting; (3) the urge to move, as any accompanying unpleasant sensation is partially or totally relieved by movement, such as walking or stretching; and (4) the urge to move, as any accompanying unpleasant sensation during rest or inactivity only occurs or is worse in the evening or night compared to during the day[1,2]. Moreover, supportive criteria should be found in family history, response to dopaminergic therapy and the presence of involuntary, rhythmic muscular jerks in the lower limbs, including dorsiflexion or fanning of toes, flexion of ankles, knees and hips, the so-called periodic limb movements during sleep (PLMS)[1,3].

Helpful tools to make an accurate RLS diagnosis include the Johns Hopkins telephone diagnostic interview, medical history (evaluating for four essential diagnostic features of RLS and iron deficiency), and evaluating and ruling out mimics[4]. RLS frequently occurs in patients with kidney disease.

The prevalence of RLS, which is high in dialysis patients and which has been associated with increased risk for cardiovascular disease in the general population, could also play a role in the pathogenesis of hypertension during sleep in renal patients. It should be noted that intravenous iron treatment reduces the RLS symptoms in patients with end-stage renal disease[2]. RLS is common in rheumatologic disorders, such as rheumatoid arthritis or Sjögren's syndrome[1,2], but not in isolated peripheral neuropathy, as in hereditary neuropathic patients[2]. Some data seem to indicate that there is a considerably higher risk for developing RLS in migraneous patients, especially in those who experienced the dopaminergic anticipatory symptoms, such as nausea, somnolence and yawning[2]. RLS is also common during pregnancy, especially during the last trimester, and iron deficiency may be a major cause; the symptoms of RLS usually disappear soon after childbirth. An increased

prevalence of RLS has been described in patients with liver cirrhosis in the United States[5] and Japan[6]. Very recently, Goel *et al*[7] described in India RLS in a series of chronic hepatic failure patients.

MATERIALS AND METHODS

This study included 267 adult patients with chronic liver disease, referred to our Neurological Unit by the Liver Unit of the University of Trieste between June 1, 2008 and December 1, 2015. The patients had been referred to the neurologist for the three complaints of sleep disturbances, painful leg sensation, daily sleepiness not correlated to hepatic encephalopathy. Patients with chronic liver disease included primary liver tumor and liver cirrhosis. We excluded 13 patients with chronic and persistent significant alcohol intake (> 30 g/d in men and > 20 g/d in women; to avoid acute alcohol polyneuropathy, which might mimic some symptoms of RLS and low compliance), 25 patients with recent worsening of clinical condition (jaundice, ascites or encephalopathy, gastrointestinal bleeding, or hospitalization), and 12 patients with hepatitis C virus (HCV; to exclude HCV-related peripheral complications).

All the other 211 patients were followed up by a neurologist at least for 24 mo (Table 1). According to neurological exams, the diagnosis of RLS was suggested by the Johns Hopkins questionnaire[4] and verified by fulfilling the diagnostic criteria by Allen *et al*[1]. Only 3 patients mentioned a possible familiar history of RLS. Iron-free level, ferritin, folate, vitamin B12 and vitamin D-OH25 was measured in all patients (Table 2).

At baseline, patients were tested with the Hamilton rating scale for depression[9], sleep quality assessment (PSQI)[10], Epworth sleepiness scale (ESS)[11], International Restless Legs Syndrome Study Group (IRLSSG) evaluation[12], and international RLS severity (IRLS) scoring system[13].

The Pittsburgh sleep quality index (PSQI) is an effective instrument, employed to measure the quality and pattern of sleep in adults. It differentiates "poor" from "good" sleep quality by measuring the following seven areas (components): Subjective sleep quality; sleep latency; sleep duration; habitual sleep efficiency; sleep disturbances; use of sleeping medications; and, daytime dysfunction over the last month. A total score of 5 or greater is indicative of poor sleep quality[10].

The ESS questionnaire asks the subject to rate the probability of falling asleep on a scale of increasing probability from 0 to 3 for eight different situations that most people engage in during their daily lives, though not necessarily every day. The scores for the eight questions are added together to obtain a single number. A number in the 0-9 range is considered to be normal, while a number in the 10-24 range indicates that expert medical advice should be sought. For instance, scores of 11-15 are shown to indicate the possibility of mild to moderate sleep apnea, where a score of 16 and above indicates the possibility of severe sleep apnea or narcolepsy[10].

Table 1 Baseline general conditions of patients recruited

Characteristic	Hepatic failure, *n* = 211
Male/female	107/104
Age in year, mean and standard deviation	59 ± 4.7
(median range)	(36-74)
BMI, kg/m^2	25.43 ± 4.1
Cause of liver disease, *n*	211
Previous alcohol abuse	139
Hepatic venous outflow tract obstruction	14
Cryptogenic	12
Liver primary tumor	46
Child-Pugh class; number	211
A	132
B	54
C	25

BMI: Body mass index.

The IRLSSG[1] evaluation is based on the assessment of the following five questions, with the necessary fulfillment of three or more: (1) An urge to move the legs, usually accompanied by uncomfortable and unpleasant sensations in the legs; (2) which begins or worsens during periods of rest or inactivity; (3) which occurs only or is worse in the evening or night than during the day; (4) which is partially or totally relieved by repeated leg movements; and (5) for which the occurrence of the above features is not solely accounted for by another medical or behavioral condition.

The IRLS score[11,12] consists of a set of 10 self-administered questions, each of which is scored on a scale extending from 0 to 4. The scores of individual questions are aggregated to yield a total score ranging from 0 to 40. Based on the IRLS score, RLS is graded as mild (0-10), moderate (11-20), severe (21-30), or very severe (31-40).

The drugs used to treat RLS belong to many different pharmacological classes, including the dopaminergic agents, opioids, benzodiazepines and antiepileptic drugs. We decided to avoid the employment of opioids and benzodiazepine due to the hepatic conditions. Therefore, the first-choice drug was pramipexole, a dopamine agonist[14] .

Neurological examinations and laboratory tests were performed at the beginning, after 2 wk, at the 28th, 75th, 105th, 135th and 165th day, and at the final day of the follow-up, the 205th day. If major side effects induced by the neurological therapy occurred, such as nausea, vomiting, somnolence, hypotension or optical illusions, the pramipexole was stopped.

The second-choice drug was gabapentin, due to its beneficial properties and to the limited hepatic side effects[15-18].

Another aim of this study was to define the augmentation phenomenon in the liver patients.

Table 2 Baseline metabolic parameters of 211 patients recruited

Labs parameter (normal values)	Average of 211 patients (range)
Hemoglobin (14-16 g/dL)	11.1 (7.5-12.3)
Platelets counts (150-400 × 1000/μL)	97 (65-423)
Serum protein (g/dL)	7.6 (3.4-10.1)
Serum bilirubin (0.1-1.3 mg/dL)	1.7 (0.9-12)
Alanine aminotransferase (8-55 IU/L)	77 (24-452)
Aspartate aminotransferase (8-48 IU/L)	71 (34-715)
International normalized ratio (INR)	1.8 (1.0-4.9)
Serum creatinine (0.6-1.2 mg/dL)	1.0 (0.6-2.1)
Serum albumin (3.7-5.0 g/dL)	3.5 (1.5-5.1)
Ammonium (40-80 μg/dL)	97 (45-134)
Folate (3.89-26.0 ng/mL)	2.3 (1.9-12.3)
Iron free level (40-150 μg/dL)	26.5 (12-89)
Ferritine (20-200 ng/mL)	235 (126-456)
Vitamin B12 (205-870 pg/mL)	189 (121-245)
Vitamin D-OH25 (30-100 ng/mL)	41 (12-130)

Augmentation is a characteristic phenomenon, well known in RLS patients, even if its mechanisms are not fully understood and most importantly, the possible inducing factors have not been identified[11,13,18]. It seems to be a pejorative condition of the earliest symptoms of RLS, or an expansion to other body parts, such as the trunk or upper limbs, compared with the initial benefits of the therapy[19]. It has been related to long-term duration of dopaminergic therapy, to higher dosage, and to the dopamine stimulation (up to 14.2%-73% with L-DOPA, and from 8.3 up to 70% with dopamine agonists)[19-22]. Opioid analgesics, such as tramadol, methadone and oxycodone, may be considered for RLS treatment; although, trials reviewing long-term efficacy are lacking. The potential for abuse and adverse effects including dizziness, nausea and constipation limit the usefulness of these medications. In addition, tramadol has been rarely associated with RLS symptom augmentation[23].

As far as we know, no study has ever been conducted in hepatic patients to consider this phenomenon.

Titration, side effects, augmentation phenomenon and whichever alterations in laboratory test findings were checked and are reported here.

All procedures complied with ethical standards for human investigations and the principles of the Declaration of Helsinki. All the patients gave written informed consent for participation at the first visit.

RESULTS

Baseline characteristics of patients are reported in Tables 1 and 2. A synopsis of the various test scores are reported in Table 3.

Patients were moderately depressed, with evident nocturnal sleep problems and a concomitant daily sleepiness. The most relevant aspect is that the sleep problem had been underestimated, and RLS syndrome had not been considered before the neurological visit, since 211/211 patients fulfilled the IRLSSG criteria for RLS.

Table 3 Synopsis of the tests at baseline

Test (range)	Results
Hamilton rating scale (0-66)	18.5 ± 4.5
PSQI (0-5)	3.4 ± 0.5
ESS (0-24)	11 ± 2.1
IRLSSG	Fulfillment of criteria: 211/211
IRSL (0-40)	0-10 (mild) = 22 11-20 (moderate) = 76 21-30 (severe) = 109 31-40 (very severe) = 4

ESS: Excessive diurnal sleepiness; IRLS: International RLS severity scoring system; IRLSSG: International Restless Legs Syndrome Study Group evaluation; PSQI: Depression, sleep quality assessment.

All the patients pointed out that their involuntary leg movements had not been considered previously, or had been interpreted as neuropathic pain and therefore treated with nonsteroidal antiinflammatory drug. Of the 211 RLS patients, 22 considered their symptoms as mild, according to IRSL, but 189 found them moderate to very severe (Table 3).

Patients were moderately depressed according to an objective test, such as the Hamilton scale. Symptoms included depressed mood, insomnia, work and activities production, retardation as slowness of thought and speech, anxiety and somatic symptoms, insight and diurnal variation, and not in the more psychiatric-related scores, such as feelings of guilt, suicide thoughts, agitation, genital symptoms, hypochondriasis, loss of weight, depersonalization and derealization, paranoid symptoms, obsession and compulsive symptoms.

A Spearman's rank correlation analysis showed the following: (1) A positive correlation between IRLSSG fulfillment criteria and poor nocturnal sleep quality (PSQI: $r = 0.89$, $P < 0.01$); (2) a positive correlation between IRLSSG fulfillment criteria and excessive diurnal sleepiness (ESS: $r = 0.92$, $P < 0.01$); (3) a positive correlation between IRLSSG fulfillment criteria and Hamilton's score ($r = 0.76$, $P < 0.05$); and, (4) a positive correlation between the four levels of IRSL and PSQI (IRSL 0-10 *vs* PSQI: $r = 0.71$, $P < 0.05$; IRSL 11-20 *vs* PSQI: $r = 0.78$, $P < 0.05$; IRSL 21-30 *vs* PSQI: $r = 0.83$, $P < 0.01$; IRSL 31-40 *vs* PSQI: $r = 0.89$, $P < 0.01$). There was no correlation found between ammonium level and ESS or PSQI.

At the beginning, all patients were prescribed pramipexole at an average dosage of 0.18 mg, to be taken in the evening for the first 2 week. We then duplicated the dosage for 2 more weeks, up to 0.36 mg, once a day; this dosage was maintained till the 75th day. At the 75th day, we prescribed 0.7 mg daily, which was then increased to 0.88 mg daily at the 105th day. Forty-one patients reported side effects at the 135th day, such as persistent nausea, optical illusions and visual hallucinations, and decided to stop the pramipexole therapy (see below). The remaining

Table 4 Synopsis of pramipexole titration

Patients	Baseline	75th day	105th d	135th day	165th day	205th day
211	0.18 mg					
211		0.7 mg				
211			0.88 mg			
170				1.4 mg		
134					1.4 mg	
36					0.88 mg	
110						1.4 mg
60						0.7 mg

Table 5 Synopsis of gabapentin titration

Patients	45th day	75th day	105th day	135th day	165th day	205th day
41	100 mg					
41		300 mg				
35			300 mg			
6			400 mg			
30				300 mg		
11				500 mg		
27					300 mg	
14					600 mg	
16						300 mg
25						600 mg

Table 6 Results for pramipexole therapy during follow-up of 170 patients

Test (range)	135th day	165th day	205th day
Hamilton rating scale (0-66)	9.2 ± 0.1 (-9.3 ± 3.0; < 0.01)	8.7 ± 1.3 (-9.8 ± 1.7; < 0.01)	9.0 ± 1.1 (-9.5 ± 0.2; < 0.01)
PSQI (0-5)	2.2 ± 0.7 (-1.2 ± 0.2; < 0.05)	1.9 ± 0.7 (-1.32 ± 0.2; < 0.05)	2.3 ± 0.7 (-1.1 ± 0.2; < 0.05)
ESS (0-24)	8. 3 ± 0.7 (-7.1 ± 0.4; < 0.01)	8. 5 ± 0.4 (-7.3 ± 0.7; < 0.01)	8 .7 ± 1.1 (-7.7 ± 0.2; < 0.01)
IRSL (0-40)	0-10 (mild) = 51	134	110
	11-20 (moderate) = 100	12	45
	21-30 (severe) = 19	14	15
	31-40 (very severe) = 0	0	0

Within-group analysis was done by comparing results at each day's visit *vs* baseline. ESS: Excessive diurnal sleepiness; IRLS: International RLS severity scoring system; PSQI: Depression, sleep quality assessment.

170 patients were prescribed 1.4 mg daily, which seemed quite appropriate in respect of their average body mass index. At the following scheduled visit, on the 165th d, we reported that 134 patients (65%) felt well with the 1.4 mg/daily dose (the maximum allowed dosage being 2.1 mg daily). On the contrary, 36 patients (25%) reported the reappearance of unpleasant sensations in their legs and feet, with the urgency to rise up and move, during night and early morning (augmentation phenomenon). These patients were treated with 0.88 mg daily. At the 205th day, 110 patients (52%) continued to feel good with the 1.4 mg daily dosage; on the other hand, 60 patients (48%) reported the augmentation symptoms

Table 7 Results for gabapentin therapy during follow-up of 41 patients

Test (range)	135th day	165th day	205th day
Hamilton rating scalec(0-66)	9.7 ± 0.4 (-9.8 ± 0.2; < 0.01)	9.7 ± 0.5 (-9.8 ± 0.3; < 0.01)	10.0 ± 0.7 (-9.9 ± 1.2; < 0.01)
PSQI (0-5)	2.7 ± 0.7 (+ 0.7 ± 0.2; NS)	2.9 ± 0.3 (+0.5 ± 0.2; NS)	3.0 ± 0.5 (+0.6 ± 0.3; NS)
ESS (0-24)	9 9 ± 0.7 (-0.7 ± 1.0; NS)	9. 5 ± 0.4 (-0.5 ± 0.1; NS)	12 .7 ± 1.1 (-3.3 ± 0.1; < 0.05)
IRSL (0-40)	0-10 (mild) = 21	18	17
	11-20 (moderate) = 14	19	22
	21-30 (severe) = 6	4	2
	31-40 (very severe) = 0	0	0

Within-group analysis was done by comparing results at each day's visit *vs* the 45th day results. ESS: Excessive diurnal sleepiness; IRLS: International RLS severity scoring system; NS: Nonsignificant; PSQI: Depression, sleep quality assessment.

and were titrated to 0.7 mg daily (Table 4).

The 41 patients who abandoned pramipexole, after 2 wash-out weeks, were administered gabapentin at 100 mg daily for 10 d, then 200 mg daily for 20 d, and then 300 mg for 40 d. At the 105th day, 6 patients (14%) required 400 mg daily. At the 135th day, 11 patients (27%) needed 500 mg gabapentin daily. At the 165th day, 14 patients (34%) needed gabapentin up to 600 mg daily, and at the 205th day, 25 patients (61%) needed 600 mg gabapentin (Table 5).

Considering the 170 patients who completed the 205 d of follow-up with pramipexole, the results were rather satisfactory (Table 6), with an evident and constant amelioration of depression, of sleep quality and of daily sleepiness, as far as Wilcoxon signed rank test within-group comparison (*vs* baseline) showed. At the final visit, their subjective feeling of the intensity of RLS disturbances was perceived as mild to moderate in 155 patients and severe in 15 of them. Nobody declared a very severe score (Table 6).

The 41 patients who abandoned pramipexole, due to side effects, were treated with gabapentin (Table 5). According to a Wilcoxon signed rank test, there was a slight worsening of nocturnal sleep quality, significantly evident at the 205th day (Table 7) according to reporting of an increase in daily sleepiness. The quality of RLS disturbances was perceived at final visit as mild to moderate in 29 patients and severe in 2 of them. All the 41 patients who took gabapentin reported abdominal weight gain (5.2 ± 1.1 kg, range: 2.4-7.6) at the final visit.

We have determined the onset of augmentation symptoms in 170 patients who carried on with pramipexole. Logistic regression analysis to identify factors associated with the augmentation was performed with independent variables, including age, body mass index, IRLS alcohol abuse, iron-free levels, folate, vitamin B_{12} and D-OH25, alanine and

Table 8 Analysis of factors for association with the presence of augmentation

Factor	*n*	Univariate		Multivariate	
		OR (95%CI)	*P* value	OR (95%CI)	*P* value
Age	170	1.07 (0.7-1.2)	0.24	1.1 (0.9-1.3)	0.20
BMI	170	1.3 (0.9-1.5)	0.45	1.6 (1.0-1.9)	0.40
IRLS	170	1.5 (1.1-2.2)	0.36	1.7 (1.2-2.2)	0.57
Alcohol abuse	139	2.3 (0.9-4.1)	< 0.001	3.75 (2.7-6.2)	< 0.001
Daily pramipexole	170	3.6 (2.1-6.8)	< 0.001	7.2 (4.1-15.2)	< 0.001
Treatment duration, > 75 d/< 75 d	170	2.3 (1.3-4.2)	0.036	6.6 (3.1-11.2)	0.01
ALT	170	1.3 (0.9-1.6)	0.21	3.1 (1.7-3.9)	0.54
AST	170	1.6 (0.8-1.7)	0.50	2.7 (0.7-4.2)	0.76
Iron-free level	170	2.9 (0.9-4.1)	0.01	5.05 (1.1-12.2)	0.06
Vit. B12	170	4.25 (1.3-9.7)	0.01	6.9 (4.7-7.6)	0.01
Folate	170	4.1 (3.1-13.6)	0.01	5.7 (4.2-8.2)	0.01
Vit. D-OH25	170	4.8 (3.4-12.9)	0.01	5.67 (2.4-8.9)	0.01

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BMI: Body mass index; CI: Confidence interval; IRLS: International restless leg syndrome severity; OR: Odds ratio; Vit.: Vitamin.

aspartate aminotransferases, treatment duration of pramipexole, and daily pramipexole doses. Univariate and multivariate logistic regression analyses were performed, and the Wald test was used to assess the significance of each variable, as reported in Table 8. Daily pramipexole dose, duration of treatment, previous alcohol abuse, iron-free levels as well as lower levels of B_{12}, D-OH25 and folate were significantly associated with augmentation in univariate analysis (Table 8). On the other hand, abuse of alcohol, dose of pramipexole and its duration, level of vitamin B12 and D-OH25 and of folate, in the multivariate regression analysis, seemed to be significantly associated with augmentation (Table 8).

DISCUSSION

In this study, we found that patients with chronic liver disease, such as liver cirrhosis or primitive tumors, who were referred for sleep disorders might have RLS as well. The presence of RLS was not associated with sex, and cause or severity of the liver disease was in line to what has been demonstrated by Goel *et al*[7]. As previously reported[3], many causative factors can induce RLS in hepatic chronic disease patients, such as low iron levels, high ferritin levels and associated low folate and vitamin B12 levels. It has also been described that the increased prevalence of RLS in chronic medical conditions (such as renal failure and, limited to few studies, hepatic failure) might be related to altered electrolyte levels, such as diuretic-induced hypokalemia, dilutional and diuretic-induced hyponatremia, hypocalcemia, or hypomagnesemia. Furthermore, it is possible that vitamin D deficiency, reduced physical activity, reduced muscular tone and increased serum levels of endotoxins and inflammatory cytokines (due to porta-systemic shunting resulting in low-grade inflammation) account for this phenomenon.

In particular, iron deficiency (present in all our patients) has been associated with dopamine pathology in RLS[24]. More specifically, it has been hypothesized that brain iron deficiency produces a dopaminergic pathology, resulting in the RLS symptoms[2]. Cerebral spinal fluid (CSF), autopsy and brain imaging studies clearly showed the expected brain iron deficiency, particularly affecting the dopamine-producing cells in the substantia nigra and their terminal fields in the striatum. A low content of iron in the brain is a well-established finding of RLS[24,25]. The dopamine pathology was, however, elusive and only recently has it been more clearly identified.

Animal and cellular iron deficiency studies have shown an increased activity of tyrosine hydroxylase in the substantia nigra[26] and decreased D2 receptors in the striatum[26]. These variations were associated with a decreased function of the cell membrane dopamine transporter[28] with increased concentration of the extracellular dopamine, with a 4-times increase in the amplitude of the circadian variation of extracellular dopamine (night-day difference)[29]. These same findings have been confirmed in RLS patients[2]. The CSF of these patients has significantly more 3-O-methyldopa, that correlates with the CSF homovanillic acid and RLS severity, indicating that increased dopamine production is proportional to the severity of RLS symptoms[30]. Moreover, the CSF tetrahydrobiopterin is significantly increased in the morning compared to night[30], and this finding is consistent with the larger circadian extracellular dopamine pattern observed in the iron-deprived rat.

As pointed out by Salas *et al*[2], RLS, unlike Parkinson's disease, is a hyper-dopaminergic condition with an apparent postsynaptic desensitization that overcompensates during the circadian low point of dopaminergic activity in the evening and night. This overcompensation leads to the RLS symptoms that can be easily corrected by adding dopamine stimulation at that time. The primary finding from multiple studies indicates that the iron deficiency affects dopaminergic function, by increasing tyrosine hydroxylase, which then increases extracellular dopamine[2,32-34]. Our study confirms an effective and rapid benefit by the use of dopamine agonist (as well-recognized and reported in the literature[3,32,33]).

On the other hand, RLS is a hyperdopaminergic condition, with an apparent postsynaptic desensitization that overcompensates during the circadian low point of dopaminergic activity in the evening and night. This overcompensation leads to the RLS symptoms that in turn often lead to increasing postsynaptic desensitization and augmentation of the RLS[2,32,34-36]. In fact, patients with RLS with mood and stress states may be at greater risk of developing compulsive behaviors while receiving standard dosage treatment of dopamine agonists (but

also of other drugs, such as tramadol[22]).

It appears evident that RLS remains a still confounding, not immediately recognized condition requiring rapid diagnosis and treatment. Augmentation seems rather precocious in our patients (135th day) and more frequent (35%) than previously described by Ferini-Strambi (8.3%)[20] and by Takahashi *et al*[22] (9.1%). The dosage of dopamine agonists found to be associated with augmentation in this study appears in range with the literature[14,19-22]. Previous intake of alcohol and lower levels of vitamins have been related to the phenomenon in our study.

RLS is a major cause of insomnia, and the structure of sleep of sufferers may be severely impaired. Sleep disruption has, in consequence, a great impact on health and daytime functioning of RLS patients. Despite the fact that RLS is a very common disorder, it is frequently undiagnosed in primary care, and therefore inadequate therapy may be prescribed.

Additional neurophysiologic studies and more extended clinical trials are strenuously needed to explain some crucial pathologic mechanisms of the syndrome, in order to better employ common therapeutic agents and to find novel ones.

ARTICLE HIGHLIGHTS

Research background

Restless legs syndrome (RLS) remains a clinical diagnosis based on confirming the four essential diagnostic features of RLS, including: (1) An urge to move the legs, usually but not always accompanied by or felt to be caused by uncomfortable and unpleasant sensations in the legs; (2) the urge to move, as any accompanying unpleasant sensation begins or worsens during periods of rest or inactivity, such as lying down or sitting; (3) the urge to move, as any accompanying unpleasant sensation is partially or totally relieved by movement, such as walking or stretching; and (4) the urge to move, as any accompanying unpleasant sensation during rest or inactivity only occurs or is worse in the evening or night compared to during the day. Chronic medical situations (dialysis, end-stage renal disease and rheumatologic disorders) have a higher prevalence of RLS.

Research motivation

An increased prevalence of RLS has been described in patients with liver cirrhosis in the United States and Japan. Very recently, RLS has been described in India in a series of chronic hepatic failure patients. Data in hepatic patients are limited.

Research objectives

According to neurological exams, the diagnosis of RLS was suggested by the Johns Hopkins questionnaire and verified by fulfillment of the diagnostic criteria by Allen. Iron-free level, ferritin, folate and vitamin B12 and vitamin D-OH25 were measured in all patients. Drugs used to treat RLS belong to many different pharmacological classes, such as the dopaminergic agents, opioids, benzodiazepines and antiepileptic drugs. We decided to avoid the employment of opioids and benzodiazepine due to the hepatic conditions. Therefore, the first-choice drug was pramipexole, a dopamine agonist. The second-choice drug was gabapentin, due to its beneficial properties and to the limited hepatic side effects. Neurological examinations and laboratory tests were performed at the beginning, after 2 wk, at the 28th, 75th, 105th, 135th and 165th day, and at the final day of the follow-up, the 205th day. Another aim of this study was to define the augmentation phenomenon in the liver patients.

Research methods

The study included 267 adult patients with chronic liver disease, referred to our Neurological Unit by the Liver Unit of the University of Trieste, for three complaints, including sleep disturbances, painful leg sensation, and daily sleepiness not correlated to hepatic encephalopathy. Patients with chronic liver disease included primary liver tumor and liver cirrhosis cases. We excluded 13 patients with chronic and persistent significant alcohol intake, 25 patients with recent worsening of clinical condition, and 12 patients with hepatitis C virus infection. All the other 211 patients were followed up by a neurologist for at least 24 mo. At baseline, patients were tested with the Hamilton rating scale for depression, sleep quality assessment (PSQI), Epworth sleepiness scale (ESS), International Restless Legs Syndrome Study Group (IRLSSG) evaluation, and international RLS severity (IRLS) scoring system. Alterations in titration, side effects, augmentation phenomenon and laboratory test findings were checked and reported. The first-choice drug was pramipexole, a dopamine agonist. If major side effects induced by the neurological therapy occurred, such as nausea, vomiting, somnolence, hypotension or optical illusions, the pramipexole was stopped. The second-choice drug was gabapentin, due to its beneficial properties and to the limited hepatic side effects. Another aim of this study was to define the augmentation phenomenon in the liver patients.

Research results

Patients included in the study fulfilled the IRLSSG criteria for RLS; they were moderately depressed, with evident nocturnal sleep problems and a concomitant daily sleepiness. Of the 211 RLS patients, 22 considered their symptoms as mild, according to IRSL, but 189 found them moderate to very severe. A Spearman's rank correlation analysis showed the following: (1) a positive correlation between IRLSSG fulfillment criteria and poor nocturnal sleep quality (PSQI); (2) a positive correlation between IRLSSG fulfillment criteria and excessive diurnal sleepiness (ESS); (3) a positive correlation between IRLSSG fulfillment criteria and Hamilton's score; (4) a positive correlation between the four levels of IRSL and PSQI; and (5) no correlation between ammonium level and ESS or PSQI. At the beginning, all patients were prescribed pramipexole at an average dosage of 0.18 mg, to be taken in the evening for the first 2 week. Titration was standard; we duplicated the dosage for 2 more weeks, up to 0.36 mg, till the 75th day. At the 75th day, we prescribed 0.7 mg daily, which was then increased to 0.88 mg daily at the 105th day. Forty-one patients reported heavy side effects at the 135th day and decided to stop the pramipexole therapy. The remaining 170 patients were prescribed 1.4 mg daily, which seemed quite appropriate in respect of their average body mass index. At the 205th day, 110 patients (52%) continued to feel good with the 1.4 mg daily dosage; on the other hand, 60 patients (48%) reported the augmentation symptoms and were titrated at 0.7 mg daily. The 41 patients who abandoned pramipexole, after 2 wash-out weeks, were administered gabapentin, at increasing dosages. Considering the 170 patients who completed the 205 d of follow-up with pramipexole, the results were rather satisfactory, with an evident and constant amelioration of depression, of sleep quality and of daily sleepiness, as far as Wilcoxon signed rank test within-group comparison (*vs* baseline) showed. At the final visit, their subjective feeling of the intensity of RLS disturbances was perceived as mild to moderate in 155 patients and severe in 15 of them. Nobody declared a very severe score. The 41 patients who abandoned pramipexole, due to side effects, were treated with gabapentin, reporting a slight worsening of nocturnal sleep quality and an increase of daily sleepiness. All the 41 patients who took gabapentin reported abdominal weight gain at the final visit. As far as the augmentation phenomenon was concerned, a logistic regression analysis to identify factors associated with the augmentation were performed with independent variables, including age, body mass index, IRLS alcohol abuse, iron-free levels, folate, vitamin B12 and D-OH25 levels, alanine and aspartate aminotransferase, treatment duration of pramipexole, and daily pramipexole doses. Univariate and multivariate logistic regression analyses were performed and the Wald test was used to assess the significance of each variable. Daily pramipexole dose, the duration of the treatment, previous alcohol abuse, iron-free levels as well as lower levels of B12, D-OH25 and folate were significantly associated with augmentation in univariate analysis. On the other hand, abuse of alcohol, dose of pramipexole and its duration, level of vitamin B12 and D-OH25 and of folate, in the multivariate regression analysis, seemed to be significantly associated with augmentation.

Research conclusions

In this study, we found that patients with chronic liver disease, such as liver cirrhosis or primitive tumors, who were referred for sleep disorders might have

RLS as well. The presence of RLS was not associated with sex, and cause or severity of the liver disease was in line with what has been demonstrated by the few other studies. As previously reported, in our study, many causative factors induce RLS in hepatic chronic disease patients, such as low iron levels, high ferritin levels, and associated low folate and vitamin B12 levels. Our study confirms an effective and rapid benefit for the use of dopamine agonist (as is well-recognized and reported in the literature). On the other hand, RLS is a hyperdopaminergic condition with an apparent postsynaptic desensitization that overcompensates during the circadian low point of dopaminergic activity in the evening and night. This overcompensation leads to the RLS symptoms that in turn often lead to increasing postsynaptic desensitization and augmentation of the RLS. In fact, patients with RLS with mood and stress states may be at greater risk of developing compulsive behaviors while receiving standard dosage treatment of dopamine agonists (but also of other drugs, such as tramadol). Augmentation seems rather precocious in our patients (135th day), and more frequent (35%) than previously described by the most important study on the topic (8.3%-9.1%). The dosage of dopamine agonists reported in our study to be associated with augmentation appears to be in range with the literature. Previous intake of alcohol and lower levels of vitamins were related to the phenomenon in our study.

Research perspectives

It appears evident that RLS remains a still confounding, not immediately recognized condition requiring rapid diagnosis and treatment. Despite the fact that RLS is a very common disorder, it is frequently undiagnosed in primary care, and therefore inadequate therapy may be prescribed. Additional neurophysiologic studies and more extended clinical trials are strenuously needed to explain some crucial pathologic mechanisms of the syndrome, in order to better employ common therapeutic agents and to find novel ones.

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