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***Observational Study***

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

Moretti R *et al*. RLS and hepatic chronic disease

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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***

211 patients with chronic liver disease complaining sleep disturbances, painful leg sensation and daily sleepiness were included. Patients with persistent alcohol intake, recent worsening of clinical conditions, or HCV 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: 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. Iron free level, ferritin, folate, vitamin B12, D-OH25 were detected. Neurological examinations and blood test occurred at the beginning of the therapy, after two weeks, at 28th, 75th, 105th, 135th, 165th and 205th day. Regarding therapy, Pramipexole or Gabapentin were used.

***RESULTS***

Patients resulted 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. 22 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 resulted rather precocious in our patients (135th day), and more frequent (35%) that previous data (8.3%-9.1%). The dosage of dopamine agonists reported to be associated with augmentation appears in range with literature. Previous intake of alcohol, lower levels of vitamins have been related in our study to the phenomenon.

***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

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**Core tip:**The diagnosis of restless legs syndrome relies on the presence of unpleasant sensation in the legs associated with the urge to move. Symptoms mostly begins during periods of rest or inactivity and worsens in the evening or night. The 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 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 leg syndrome (RLS) is defined as a very sickening, bilateral (even if also unilateral) sensation, almost described affecting a very limited zone, between the knees and ankles, sometimes interesting thighs and feet and resulting like 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; any accompanying unpleasant sensation begins or worsens during periods of rest or inactivity such as lying down or sitting; (3) the urge to move; any accompanying unpleasant sensation is partially or totally relieved by movement, such as walking or stretching; (4) the urge to move; 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: dorsiflexion or fanning of toes, flexion of ankles, knees, and hips, so-called periodic limb movements during sleep (PLMS)[1,3].

Helpful tools to make an accurate RLS diagnosis include: (1) Johns Hopkins Telephone Diagnostic Interview; (2) Medical history (evaluating for four essential diagnostic features of RLS and iron deficiency); (3) 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 *i.v.* 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, a part hereditary neuropathic patients[2]. Some data seems to indicate that there is a considerably higher risk to develop RLS in migraneous patients, especially in those who experienced the dopaminergic anticipatory symptoms, such as nausea, somnolence, yawning[2]. RLS is also common during pregnancy, especially during the last trimester and iron deficiency may be a major cause. 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**

The 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 1st, 2008 and December, 1st 2015. They had been referred to the neurologist for three complaints: 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 HCV (to exclude HCV related peripheral complications).

All the other 211 patients have been followed up, by a neurologist at least for 24 months (Table 1).

According to the neurological exams the diagnosis of RLS was suggested by the Johns Hopkins Questionnaire[4] and verified by fulfilling the diagnostic criteria by Allen[1]. Only three patients mentioned a possible familiar history or RLS. Iron free level, ferritin level, folate and vitamin B12 and vitamin D-OH25 was measured in all patients (Table 2).

At baseline, patients were tested with: 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 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].

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].

IRLSSG[1] is based on the assessment of five questions, with the necessary fulfillment of three or more than them: (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) occurs only or are worse in the evening or night than during the day; (4) partially or totally relieved by repeated leg movements; and, (5) the occurrence of above features is not solely accounted for by another medical or behavioral condition.

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 was graded as mild (0–10), moderate (11–20), severe (21–30), and very severe (31–40).

Drugs used to treat RLS belong to many different pharmacological classes as the dopaminergic agents, opioids, benzodiazepines and anti-epileptic drugs. We decided to avoid the employment of opioids and benzodiazepine due to the hepatic conditions. Therefore, the first–choice drug is Pramipexole, a dopamine agonist[14] .

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

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

Another aim of this study was also to define the “augmentation phenomenon” in the liver patients. 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[13,11,18]. 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, any study has ever been conducted in hepatic patients to consider this phenomenon.

Titration, side effects, augmentation phenomenon and whichever LABS alterations have been checked and reported in our study.

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 the participation at the first visit.

**RESULTS**

Baseline characteristics of patients reported in Tables 1 and 2. A synopsis of test’s scores has been reported in Table 3.

Patients resulted 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.

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 non-steroidal anti-inflammatory 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 resulted moderately depressed to an objective test, such as 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: (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);(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 is 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 in the evening for the first two weeks. We then duplicated the dosage for two more weeks, up to 0.36 mg, once a day; this dosage was maintained till the up to 75th day. At the 75th day, we prescribed 0.7 mg daily which was then increased to 0.88 mg daily at 105th day. 41 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 later). The remaining 170 patients were prescribed 1.4 mg daily, which seemed quite appropriate in respect of their average BMI. At the following scheduled visit, at 165th day, we reported that 134 patients (65%) felt well with the 1.4 mg/daily dose (being the maximum allowed dosage of 2.1 mg daily). On the contrary, 36 patients (25%) reported the re-appearance 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 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 (Table 4).

The 41 patients who abandoned Pramipexole, after two wash-out weeks, were administered Gabapentin, 100 mg daily for ten days, then 200 mg daily for twenty days, and then 300 mg for forty days. At 105th day, 6 patients (14%) required 400 mg daily; at 135th day, 11 patients (27%) needed 500 mg Gabapentin daily, at 165th day, 14 patients (34%) needed Gabapentin up to 600 mg daily, and at 205th day, 25 patients (61%) needed 600 mg Gabapentin (table 5).

Considering the 170 patients who completed the 205 days 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). At the final visit, their subjective feeling of the intensity of RLS disturbances is 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 205th day (Table 7) reporting an increase of daily sleepiness. Quality of RLS disturbances is 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 weight abdominal gain (5.2 ± 1.1 kilos-range 2.4-7.6) at the final visit.

We have testified the onset of augmentation symptoms in 170 patients, who carried on Pramipexole. Logistic regression analysis to identify factors associated with the augmentation were performed with independent variables, including age, BMI, IRLS alcohol abuse, iron-free levels, folate, vitamin B12 and D-OH25 levels, alanine and aspartate aminotransferase, treatment duration of Pramipexole, 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. The daily Pramipexole dose, the duration of the treatment, a previous alcohol abuse, the iron-free levels as well as the lower levels of B12, D-OH25, and folate were significantly associated with augmentation at univariate analysis (Table 8). On the other hand, the abuse of alcohol, the dose of Pramipexole and its duration, the level of vitamin B12 and DOH25 and of folate, on 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 as well have RLS. The presence of RLS was not associated with gender and cause or severity of the liver disease 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 electrolyte altered 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, reduce 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 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 (DAT)[28] with increased concentration of the extracellular dopamine with a four times increase in the amplitude of the circadian variation of extracellular dopamine (night-day difference)[29]. These same findings have confirmed in RLS patients[2] . The CSF of these patients has significantly more 3-O-methyldopa (3-OMD), 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 than night[30] and this finding isconsistent with the larger circadian extracellular dopamine pattern 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, 32,33,34]. Our study confirms an effective and rapid benefit by the use of dopamine agonist (as well recognized and reported in Literature[3,32,33]. On the other hand, RLS 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 which in turn often leads to increasing postsynaptic desensitization and augmentation of the RLS[2,32,34,35,36]. 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%) that previously described by Ferini-Strambi (8.3%)[20]and by Takahashi (9.1%)[22].The dosage of dopamine agonists reported to be associated with augmentation appears in range with Literature[14,19,20,21,22]. Previous intake of alcohol, lower levels of vitamins have been related in our study to the phenomenon.

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 leg syndrome (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; any accompanying unpleasant sensation begins or worsens during periods of rest or inactivity such as lying down or sitting; (3) the urge to move; any accompanying unpleasant sensation is partially or totally relieved by movement, such as walking or stretching; (4) the urge to move; 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, 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, it has been described in India RLS in a series of chronic hepatic failure patients. Data in hepatic patients is limited.

***Research objectives***

According to the neurological exams the diagnosis of RLS was suggested by the Johns Hopkins Questionnaire and verified by fulfilling the diagnostic criteria by Allen. Iron free level, ferritin level, folate and vitamin B12 and vitamin D-OH25 was measured in all patients. Drugs used to treat RLS belong to many different pharmacological classes as the dopaminergic agents, opioids, benzodiazepines and anti-epileptic drugs. We decided to avoid the employment of opioids and benzodiazepine due to the hepatic conditions. Therefore, the first–choice drug is Pramipexole, a dopamine agonist. The second-choice drug is Gabapentin, due to its beneficial properties and to the limited hepatic side-effects. Neurological examinations and LABS occurred at the beginning, after two weeks, at 28th day, at 75th day, at 105th, 135th, 165th and at the final day of the follow-up, at 205th day. Another aim of this study was also 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: 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, 25 patients with recent worsening of clinical condition and 12 patients with HCV. All the other 211 patients have been followed up, by a neurologist at least for 24 mo. At baseline, patients were tested with: 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. Titration, side effects, augmentation phenomenon and LABS alterations whichever have been checked and reported in our study. The first–choice drug is Pramipexole, a dopamine agonist. If major side effects induced by the neurological therapy occurred, such as nausea, vomiting, somnolence, hypotension, or optical illusions, pramipexole was stopped. The second-choice drug is Gabapentin, due to its beneficial properties and to the limited hepatic side-effects. Another aim of this study was also to define the “augmentation phenomenon” in the liver patients.

***Research results***

Patients included in the study fulfilled the IRLSSG criteria for RLS; they resulted 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: (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; (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 in the evening for the first two weeks. Titration was standard: we duplicated the dosage for two more weeks, up to 0.36 mg, till the up to 75th day. At the 75th day, we prescribed 0.7 mg daily which was then increased to 0.88 mg daily at 105th day. 41 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 BMI. At 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 two wash-out weeks, were administered Gabapentin, at increasing dosages.

Considering the 170 patients who completed the 205 days 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). At the final visit, their subjective feeling of the intensity of RLS disturbances is 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 weight abdominal gain at the final visit.

As far as augmentation phenomenon, a Logistic regression analysis to identify factors associated with the augmentation were performed with independent variables, including age, BMI, IRLS alcohol abuse, iron-free levels, folate, vitamin B12 and D-OH25 levels, alanine and aspartate aminotransferase, treatment duration of Pramipexole, daily Pramipexole doses. Univariate and multivariate logistic regression analyses were performed and the Wald test was used to assess the significance of each variable. The daily Pramipexole dose, the duration of the treatment, a previous alcohol abuse, the iron-free levels as well as the lower levels of B12, D-OH25, and folate were significantly associated with augmentation at univariate analysis (Table 8). On the other hand, the abuse of alcohol, the dose of Pramipexole and its duration, the level of vitamin B12 and DOH25 and of folate, on 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 as well have RLS. The presence of RLS was not associated with gender and cause or severity of the liver disease in line to what has been demonstrated by the few other studies. As previously reported, in our study 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. Our study confirms an effective and rapid benefit by the use of dopamine agonist (as well recognized and reported in Literature. On the other hand, RLS 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 which in turn often leads 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%) that previously described by 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 in range with Literature. Previous intake of alcohol, lower levels of vitamins have been related in our study to the phenomenon.

***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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**Table 1 Baseline general conditions of patients recruited**

|  |  |
| --- | --- |
| Characteristic | Hepatic failure (*n* = 211) |
| Male/female | 107/104 |
| Age(yr and standard deviation);median (range) | 59 ± 4.7(36–74) |
| BMI kg/m2 | 25.43 ± 4.1 |
| Cause of liver disease; number | 211 |
| Previous alcohol abuse | 139 |
| Hepatic venous outflow tract obstruction | 14 |
| Cryptogenic | 12 |
| Liver primary tumour | 46 |
| Child-Pugh class; number | 211 |
| A | 132 |
| B | 54 |
| C | 25 |

BMI: Body mass index.

**Table 2 Baseline metabolic parameters of 211 patients recruited**

|  |  |
| --- | --- |
| Labs parameter (normal values) | Average: 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) |

**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 |

PSQI: Depression, Sleep Quality Assessment; ESS: Excessive diurnal sleepiness.

**Table 4 Synopsis of pramipexole titration**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Patients** | **baseline** | **75th day** | **105th day** | **135th day** | **165th day** | **205th day** |
| 211 | 0.18 mg |  |  |  |  |  |
| 211 |  | 0.7 |  |  |  |  |
| 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 (170 patients) (within group analysis has been done comparing results at each day visit *vs* baseline)**

|  |  |  |  |
| --- | --- | --- | --- |
| **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 *P* < 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 |

PSQI: Depression, Sleep Quality Assessment; ESS: Excessive diurnal sleepiness.

**Table 7 Results for gabapentin therapy during follow up (41 patients) (within group analysis has been done comparing results at each day visit** ***vs* 45th day results)**

|  |  |  |  |
| --- | --- | --- | --- |
| Test (range) | 135th day | 165th day | 205th day |
| Hamilton Rating Scale(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 |

PSQI: Depression, Sleep Quality Assessment; ESS: Excessive diurnal sleepiness.

**Table 8 Analysis of factor for association with the presence of augmentation**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  |  | **Univariate** |  | **Multivariate** |  |
|  | ***n*** | **Odds ratio (95%CI)** | ***P* value** | **Odds ratio (95%CI)** | ***P* value** |
| Age | 170 | 1.07 (0.7-1.2) | 0.24 | 1.1 (0.9-1.3) | 0.2 |
| BMI | 170 | 1.3 (0.9-1.5) | 0.45 | 1.6 (1.0-1.9) | 0.4 |
| 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) | 0.5 | 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 OH 25 | 170 | 4.8 (3.4-12.9) | 0.01 | 5.67 (2.4-8.9) | 0.01 |

BMI: Body mass index; IRLS: International restless leg syndrome severity.