Original article

Restless legs syndrome: clinical experience with long-term treatment

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Abstract

Background and purpose: There are limited data on long-term treatment efficacy, and almost none on predictors of treatment response in patients with restless legs syndrome (RLS). To assess: (1) long-term efficacy of RLS treatment in a clinical setting, (2) predictors of a good treatment response, and (3) the value of the RLS-severity score according to the criteria of the International Restless Legs Syndrome Study Group (IRLSSG).

Patients and methods: Over three years 70 patients (36 men, 34 women; mean age: 59 years; range: 29–79) with RLS were prospectively assessed. Diagnosis of RLS was made according to international criteria Severity of RLS symptoms was were assessed at the outset by the IRLSSG rating scale. Treatment was chosen individually according to clinical judgement. After a mean follow-up time of 16 months (range: 1–106 months) evolution of symptoms was assessed by both overall clinical impression and IRLSSG rating scale. Clinical characteristics and treatment effect were compared between patients never treated for RLS before this study ('naïve'=N-pts) and those with previous treatment ('treated'=T-pts). Predictors of treatment response were sought for comparing patients with good treatment response (good, better or much better on follow-up) and those with bad (B-pts) treatment response.

Results: There were 40 N-pts and 30 T-pts. The mean IRLSSG score (hereinafter, IRLSSG) at baseline was 26 (range 12–38). No significant differences were found between N-and T-pts in age, gender, etiology and duration of RLS, positive family history, presenting sleep complaint, IRLSSG, or percentage of patients with periodic limb movements in sleep (PLMS) on polysomnography (PSG). At final follow-up 30 (76%) of 40 N-pts and 23 (77%) of 30 T-pts had a good (G-pts) treatment response. The mean IRLSSG at follow-up was 19 (range:1–36). There was a significant correlation between improvement of overall clinical impression (better or much better on final follow-up) and reduction of IRLSSG ($P<0.0001$). PLMS were more common in B- than G-pts (100 vs 58% of patients, $P=0.02$). In all other variables considered the two groups were similar.

Conclusion: (1) A good long-term treatment response can be obtained and maintained in a clinical setting in about 80% of RLS patients. (2) Patients with RLS and without PLMS may have a better long-term treatment response, and (3) the IRLSSG is a useful tool for assessment of evolution of RLS symptoms over time in individual patients.
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Keywords: Predictors; Polysomnography; Efficacy

1. Introduction

Restless legs syndrome (RLS) is a disorder characterized by unpleasant limb sensations occurring at rest in association with an irresistible urge to move and sleep disturbances. The estimated prevalence ranges from 5–10% in the general population [1,2]. The diagnosis of RLS is based primarily on the patient's history. Four diagnostic criteria were developed by the IRLSSG in 1995 [3]: (a) desire to move the limbs usually associated with paresthesias/dysesthesias, (b) motor restlessness, (c) symptoms are worse or exclusively present at rest with at least partial and temporary relief by activity and (d) worsening of symptoms in the evening/at night. More recently, the presence of periodic limb movements in sleep (PLMS) and treatment response to dopaminergic drugs were suggested as supportive diagnostic criteria. Treatment is

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currently based on four major classes of medications: dopaminergic agents, benzodiazepines, anticonvulsants, and opioids [4].

Several short-term studies have reported significant benefit of drug therapy in RLS. Little is known, however, about long-term treatment efficacy [5–8], and there are only very limited data on predictors of treatment response in RLS. A few authors noted that familial RLS patients required higher levodopa doses than did sporadic cases, and that patients with familial RLS were more likely to lose their initial benefit from dopaminergic drugs [9–10].

The aims of this study were: (1) to assess long-term treatment efficacy of RLS in a sleep clinic setting, that is outside a study protocol, (2) to identify predictors of a good long-term treatment response, and (3) to test the value of a new RLS severity score for assessing evolution of RLS symptoms.

2. Methods

Over three years we prospectively assessed 89 consecutive patients from the sleep clinic of the University Hospital in Bern, Switzerland with the diagnosis of RLS. We excluded seven patients not meeting the four international criteria for RLS, six patients not receiving any pharmacological treatment, and six patients without follow-up data. We report on 70 patients who: (1) satisfied the four minimal diagnostic criteria for RLS, (2) were seen at least twice (first visit: baseline; final visit: follow-up) in our clinic, and (3) rated the severity of their RLS-symptoms by completing an RLS-score questionnaire (see later). In 46 patients we obtained a baseline and one or more follow-up IRLSSG. A conventional PSG was obtained and scored according to international criteria in 44 of 70 patients. The degree of excessive daytime sleepiness (EDS) was estimated by the Epworth sleepiness score (ESS) [11], and considered excessive when the ESS was >10.

Clinical assessment included age, gender, etiology and duration of RLS, presenting sleep complaint (insomnia, EDS), heredity, and previous treatment for RLS. All patients were seen by at least one of the two senior authors of the paper (MG, CB). The presence of PLMS during conventional PSG was assessed using standard international criteria. Severity of RLS symptoms was estimated by IRLSSG at study outset. After a treatment follow-up time of 1–106 months (mean: 16 months) evolution of symptoms was re-assessed by both overall clinical impression (much better, better, unchanged, or worse as compared to study outset) and IRLSSG. Follow-up was at least >6 months in 51 patients (73%), in 34 patients (49%) follow-up was >12 months. The overall clinical impression was determined by the treating physician, blinded to the results of the IRLSSG, based on the follow-up examination in our outpatient clinic. Treatment of RLS was chosen individually and independently from the study protocol according to clinical judgment (age, associated sleep disturbances, co-morbid illnesses, and previous

treatment). Pharmacological RLS treatment included levodopa and dopamine agonists (pergolide, and pramipexole), benzodiazepines (clonazepam), anticonvulsants (gabapentin), opioids, or combinations of the above. Clinical characteristics and treatment efficacy were compared between 40 N-pts (naïve) and 30 T-pts (with previous treatment). Predictors of treatment response were searched for comparing patients with good treatment response (G, much better or better on follow-up) and those with bad treatment response (B, unchanged or worse on follow-up). The following variables were considered as potential predictors of treatment response: gender, etiology of RLS, duration of RLS, heredity, presenting sleep complaint (insomnia or EDS), and presence of PLMS during baseline PSG.

2.1. Assessment of severity of RLS symptoms by the IRLSSG

The clinician rated the overall clinical evolution of RLS symptoms at follow-up visit as unchanged, worse, better or much better. Long-term treatment response was considered good in patients who were better or much better at final follow-up clinic visit compared to baseline visit. Patients independently rated the severity of RLS symptoms using a rating scale specifically developed by the IRLSSG, [12]. The following ten questions are assessed in the IRLSSG: RLS discomfort in legs or arms; need to move around; relief of discomfort by moving around; severity of sleep disturbance; severity of tiredness or sleepiness; severity of the RLS as a whole; frequency of symptoms; severity of symptoms on an average day; impact of symptoms on ability to carry out daily affairs; and severity of mood disturbance. For each question there were five possible answers, rated from 0 to 4 points. A score of 0 points indicates the absence of RLS symptoms; a score of 40 points indicates the maximal severity of RLS symptoms.

2.2. Statistical analysis

Values are given as mean, standard deviation, and range. Comparisons of gender, etiology, duration, sleep disturbance, familiarity, and long-term treatment response between groups were done with χ^2 test; comparisons of age, ESS, PLMS and IRLSSG with Mann–Whitney U test. The evolution of intraindividual IRLSSG over time was analysed using the Wilcoxon matched-pairs signed-rank test. Comparisons of score-intervals and subjective outcome were performed with Kruskal-Wallis one-way ANOVA. Statistical significance was set at $P < 0.05$.

3. Results

3.1. Clinical characteristics

The study group consisted of 36 men and 34 women (mean age of 59 ± 14 years; range 29–79 years) with a mean

duration of RLS symptoms of 12 years (range 1–55 years). There were **57** (81%) patients with idiopathic RLS and **13** patients with secondary RLS (among those five had a peripheral polyneuropathy, two a myelopathy, and one a Friedreich ataxia). Family history was positive in 20 (30%) patients. In 54 (77%) patients the main sleep complaint was insomnia. The mean ESS was 7 (range: 0–23). Twenty (29%) patients had an ESS ≥ 10 and 16 of them had an ESS > 10. An ESS ≥ 10 was significantly more common in patients with idiopathic RLS than in those with secondary RLS (26 vs 0%; $P = 0.04$). The ESS was also higher in patients with idiopathic RLS than in those with secondary RLS ($P = 0.05$).

Of the 30 T-pts, eight had previously attempted use of 2 drugs for RLS, eight had attempted 3 drugs, and five more than 3 drugs. Compared to the 40 N-pts, T-pts were older (62 vs 56 years; $P = 0.08$) and had a higher IRLSSG at baseline (28 vs 24; $P = 0.06$).

In 44 (63%) patients a conventional PSG was recorded. These patients complained significantly more often of EDS (36 vs 0%; $P < 0.001$; mean ESS 9 vs 5; $P = 0.01$) and had significantly less previous treatment for RLS than patients without PSG (68 vs 38%; $P = 0.02$; Table 1). PLMS index > 10 was found in 30 (68%) of the 44 patients. There were no differences in demographic data between patients with or without periodic leg movements (PLMS).

Additional sleep diagnoses (more than one possible in each patient) were made in 20 patients and included sleep apnea syndrome ($n = 10$, apnea-hypopnea index > 10/h of sleep), fragmentary NREM myoclonus ($n = 3$, [18]), primary snoring ($n = 2$), confusional arousals ($n = 2$), REM sleep behavior disorder ($n = 2$), sleep paralysis ($n = 1$), sleepwalking ($n = 1$), bruxism ($n = 1$), and nocturnal leg cramps ($n = 1$).

Table 1
Clinical and demographic characteristics in RLS patients with and without PSG

	With PSG	Without PSG
Number of pts	44	26
Female:Male	20:24	14:12
Age (years)	29–78 (57)	34–79 (61)
RLS duration (years)	1–55 (13)	2–37 (11)
Positive family history (%)	8 (26%)	10 (38%)
Idiopathic RLS (%)	35 (80%)	22 (85%)
EDS (%)	**16/44 (36%)** [*]	**0/26** [*]
Mean ESS (range)	**9** (0–23) [**]	**5** (0–11) [**]
'Naïve' at baseline (%)	**68%** [†]	**38%** [†]
Treatment response (%)		
Much better	34%	31%
Better	41%	46%
Unchanged/worse	25%	23%
IRLSSG at baseline	25	27
IRLSSG at follow-up	17	21

Naïve patients, never treated for RLS before study begin; EDS, excessive daytime sleepiness; ESS, Epworth sleepiness score; IRLSSG, International RLS Study Group Rating Scale; *, $P < 0.001$; **, $P = 0.01$; †, $P = 0.02$.

3.2. RLS treatment during study period[1]

Over the three years, levodopa was tried in 48 patients (69% of 70 patients), pramipexole in 27 patients (39%), pergolide in 26 patients (37%), clonazepam in 21 patients (30%), gabapentin in 17 patients (24%), and opioids in 11 patients (16%). At study end 22 of 27 patients (81%) on pramipexole, 15/21 (58%) on pergolide, 12/21 (57%) on clonazepam, 7/17 (41%) on gabapentin, 18/48 (38%) on levodopa and 4/11 (36%) on opioids had good symptom control. Thirteen (19%) patients were on a combination therapy of two drugs an one patient had three drugs.

3.3. Long-term treatment response: results and prediction

At final follow-up 53 (76%) of 70 patients achieved good control of their RLS symptoms (G-pts; clinical impression much better or better, Table 2 and Fig. 1). Out of these 53 patients 21 (40%) had tried one drug, 18 (34%) two drugs, 8 (15%) three drugs, and 6 (11%) four or more drugs. At baseline, G-pts, had less frequently a PLMS-Index > 10 than B-pts (58 vs 100%; $P = 0.02$). G-pts tended also to be older than B-pts (60 vs 54 years; $P = 0.08$). No significant differences were found between the two groups in gender, etiology and duration of RLS, familiarity, presenting sleep complaint, IRLSSG at follow-up, and percentage of patients with PLMS at baseline (Table 2). There was also no difference in the percentage of patients previously treated for RLS. Overall 30 (76%) of 40 N-patients and 23 (77%) of 30 T-patients had a good treatment response.

3.4. International RLS study group rating scale (IRLSSG)

In 46 patients we were able to re-assess the IRLSSG (Fig. 2) to a mean time interval of 10 ± 7 months (range 2–30) after the first (baseline) assessment. The mean IRLSSG was 26 (range 12–38) at baseline and 19 (range 1–36) at follow-up. Overall clinical impression was much better in 37%, better in 33%, and unchanged in 30%. There was a significant correlation between improvement of overall clinical impression (much better or better on final follow-up) and reduction of IRLSSG ($P < 0.0001$, Kruskal-Wallis test).

4. Discussion

To our best knowledge this is the first study assessing both long-term efficacy of treatment and predictors of treatment response in a large group of RLS patients outside a study protocol. The attempt of this analysis to reflect

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[1] Since patients were on a variable number of drugs, the numbers exceed the total number of patients.

Table 2
Clinical and demographic characteristics of the study population

	All pts	G-pts	B-pts	N-pts	T-pts
Number of pts	70	53	17	40	30
Female:male	34:36	26:27	8:9	19:21	15:15
Age (years)	29–79 (59)	29–79 (60)	29–76 (54)	29–79 (56)	34–78 (62)
Duration of RLS (years)	1–55 (12)	1–55 (12)	2–30 (11)	1–55 (13)	1–40 (10)
Positive family history (%)	30	26	35	23	37
Idiopathic RLS (%)	81	81	82	80	83
Insomnia (%)	77	77	76	75	80
Mean ESS (range)	7 (0–23)	7 (0–23)	7 (2–21)	7 (0–19)	8 (0–23)
PSG	$n=44$	$n=33$	$n=11$	$n=30$	$n=14$
PLMS (%)	68%	58%[*]	100%[*]	73%	57%
Follow-up time (months)	16 (1–106)	17 (1–106)	13 (1–41)	17 (1–54)	15 (1–106)
'Naïve' at baseline (%)	57%	57%	59%	100%	0%
Treatment response (%)					
Much better	33%	43%		38%	27%
Better	43%	57%		38%	50%
Unchanged/worse	24%		100%	24%	23%
IRLSSG at baseline	26	25	27	24	28
IRLSSG at follow-up	19	**15**[**]	**30**[**]	19	18

G-pts, patients with good treatment response (much better or better on follow-up); B-pts, patients with bad treatment response (unchanged or worse on follow-up); N-pts, naïve patients (never treated for RLS before study begin); T-pts, treated patients (patients with previous treatment for RLS); ESS, Epworth sleepiness score; PLMS, periodic limb movements in sleep.*, B-pts had significantly more PLMS at baseline than G-pts ($P=0.02$).**, G-pts had a significantly lower IRLSS at follow-up than B-pts ($P<0.0001$).

a 'real life' situation is further emphasized by the fact that (1) secondary forms of RLS (19% of patients) were not excluded; (2) the presence of PLMS was not required for inclusion in the study (PLMS-Index $<10/h$ in 32% of our patients), and (3) patients with associated sleep disorders (29%) were also included.

4.1. Long-term treatment efficacy

Our results confirm that even in sleep centers the long-term control of RLS may be difficult. After a mean follow-up time of 16 months (≥ 12 months in 49% of patients) treatment response was considered good (RLS symptoms were better or much better compared to onset of study) in 76% of patients. Surprisingly, no difference was found in the treatment outcome of N-patients and T-patients (RLS). Our results concerning long-term control of RLS are inferior to most percentages reported in controlled, short-term studies, but similar to those found in other surveys of non-selected RLS patients treated for longer periods of time [13]. In a two-year follow-up study with levodopa [5], 26 (87%) of 30 patients continued treatment, although 9 (31%) required higher doses. In a study with pergolide a near complete control of symptoms was obtained in 9 (45%), and a moderate control in 10 (50%) of 20 patients studied for an average duration of two years [6]. In an open follow-up of a controlled study pergolide was continued by 22 (79%) of 28 patients for at least one year [7]. Over a period of 15 to 24 months tramadol was found to achieve a clear amelioration of symptoms in 11 (91%) of 12 patients [8]. More recently, in a retrospective study of 49 patients over 27 months,

pramipexole was found to be completely effective in controlling RLS in 67% of patients [15].

In most of our RLS patients (48/70=69%) treatment was started with levodopa. This preference reflects the treatment strategy for RLS of most physicians at the time this study began [14]. In addition, levodopa was (and still is) the only drug accepted for RLS treatment in Switzerland. However, only 18 of the 48 patients (38%) were still on levodopa at the end of the study. Similarly, in a study of RLS treatment with standard and sustained-release levodopa, efficacy was found to persist up to one year in only 40% of 23 patients [16]. The percentage of patients remaining until the end of observation on pramipexole (87%) and, to a greater extent, pergolide (58%) was, conversely, higher in our
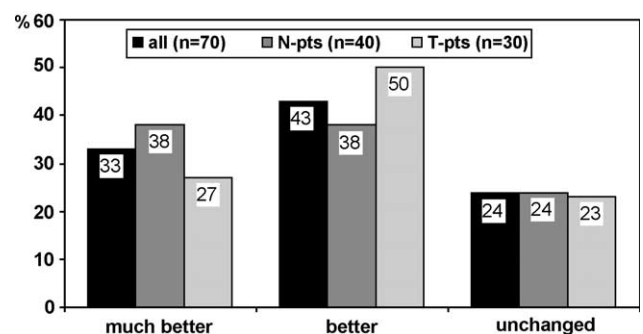

Fig. 1. Assessment of RLS evolution by overall clinical impression. A good long-term treatment efficacy (much better or better on final follow-up) of RLS symptoms was achieved in 76% of N-pts (naïve patients, never treated for RLS before study began) after a mean follow-up time of 17 months, and in 77% of T-pts (treated patients, patients with previous treatment for RLS) after a mean follow-up time of 15 months.
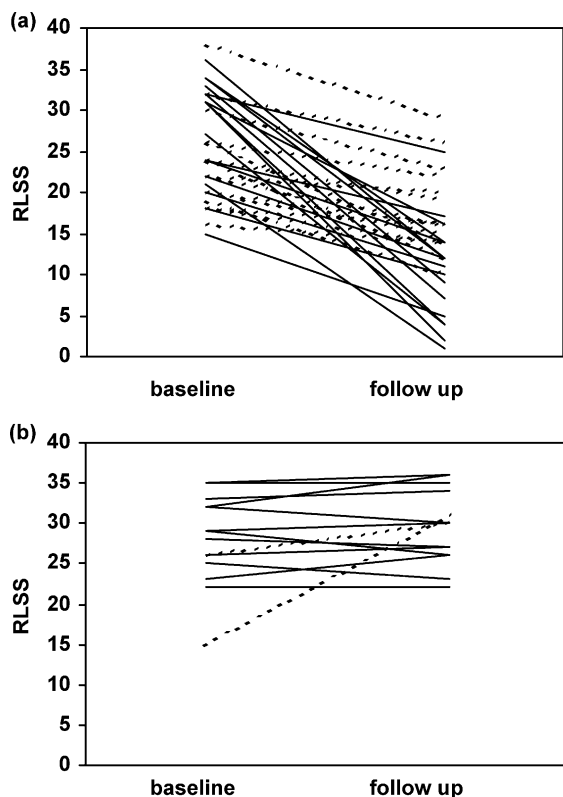
Fig. 2. Assessment of RLS evolution by IRLSSG rating scale. (a) much better/better at follow up (n = 32). (b) unchanged/worse at follow up (n = 14). Evolution of RLS symptoms as assessed by the IRLSSG rating scale (0–40) in (a) 32 pts with a much better (black lines) or better (broken lines) overall clinical impression, and (b) 14 pts with an unchanged (black lines) or worse (broken lines) overall clinical impression. Clinical improvement of RLS and reduction of IRLSS rating scale were correlated (P < 0.0001).

study. These observations are in accord with the few reports on the long-term control of RLS with dopamine agonists [7,17]. It is, however, noteworthy, that in two of our patients treatment with dopamine agonists (pramipexole and pergolide) had to be discontinued because of the appearance of 'sleep attacks' (one of these two patients has previously been reported in detail) [19]. Obviously, the design of our study calls for great caution when interpreting the long-term efficacy of different drugs. A direct comparison between levodopa and dopamine agonists in RLS patients is needed to clarify this important issue.

4.2. Predictors of long-term response

Prediction of a good long-term response was difficult in this study. Patients with (G-pts) and without (B-pts) good treatment response were similar in age, gender, etiology of RLS (idiopathic vs secondary), duration of RLS, main sleep complaint (insomnia vs EDS) and positive family history. Patients without PLMS at baseline had, however, a better outcome than patients with PLMS (P = 0.02). Although the absence of PLMS is often considered to indicate the presence of less severe RLS, there was no difference in

the IRLSSG in patients with and without PLMS in this study. This observation suggests the existence of a subgroup of RLS patients with mild and/or infrequent PLMS, in whom treatment with dopaminergic drugs is helpful.

There are only very limited data in the literature concerning predictors of treatment outcome. Few authors noted that familial RLS patients required higher levodopa doses than did sporadic cases, and that patients with familial RLS were more likely to lose their benefit from dopaminergic drugs [9,10].

4.3. International RLS study group rating scale (IRLSSG)

The IRLSSG rating scale is a recently developed and validated RLS severity scale [12]. In this study we found a significant correlation between an improvement in the overall clinical impression (much better or better on final follow-up) and a reduction in the IRLSSG (P < 0.0001). The IRLSSG appears, therefore, to be a reliable instrument for assessing intra-individual changes in RLS severity over time.

Our study suffers from several limitations including uncontrolled study conditions and lack of objective (PSG) data at final follow-up. However, for a variety of reasons previously discussed, our data may reflect better 'true' effects and limitations of current treatment strategies in RLS patients.

In conclusion, we demonstrated that a good long-term treatment response can be obtained and maintained in about 80% of patients with RLS in a clinical setting. Patients without PLMS may have a better long-term treatment response. Finally, the IRLSSG represents a useful tool for monitoring changes in severity of RLS symptoms in individual patients over time.

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