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CASE REPORTS

Therapeutic effectiveness of thalidomide in a patient with treatment-resistant restless legs syndrome

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Recent developments in the genetics of restless legs syndrome (RLS) revealed associations of disease risk with genetic loci containing the genes coding cereblon, the protein bound by thalidomide, and its endogenous substrate MEIS2, whose degradation is inhibited by the thalidomide-cereblon interaction. Therefore it was hypothesized that thalidomide may be a potential treatment option for RLS. Here we report on the therapeutic effect of thalidomide in a patient with otherwise treatment-resistant RLS who received 100 mg thalidomide off-label for 3 weeks. The female patient, severely affected by RLS before treatment, experienced significant amelioration of the symptoms, increased self-reported sleep quality, and better daytime functioning during thalidomide treatment. This therapeutic success warrants larger studies investigating the efficacy of drugs of the thalidomide class in RLS.

Keywords: restless legs syndrome, thalidomide, case report, treatment

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INTRODUCTION

Restless legs syndrome (RLS) is a common multifactorial disorder with both genetic and environmental causes contributing to its pathogenesis. It affects 5%–10% of European populations and often requires lifelong therapy. The current first-line treatment options for RLS include dopamine agonists and α2-δ ligands.[1] As a second-line alternative, opioids are frequently used in patients who are treatment-resistant. However, each line of therapy has its limitations: Dopaminergic treatment is limited by a specific adverse effect called augmentation, α2-δ ligands lack approval in many countries, and opioids have addictive potential. Therefore, additional therapeutic options are urgently needed.

A recent genome-wide association study revealed 19 genomic regions associated with RLS, among them the genetic loci of *CRBN* and *MEIS2*.[2] *CRBN* encodes cereblon, a component of the E3 ubiquitin ligase complex binding thalidomide.[3] This interaction inhibits the degradation of MEIS2, an endogenous substrate of cereblon.[4] Thalidomide is an effective hypnotic[5] and decreases spontaneous motor activity in mice.[6] Based on this background, we tried off-label therapy with thalidomide in a patient with treatment-resistant RLS.

REPORT OF CASE

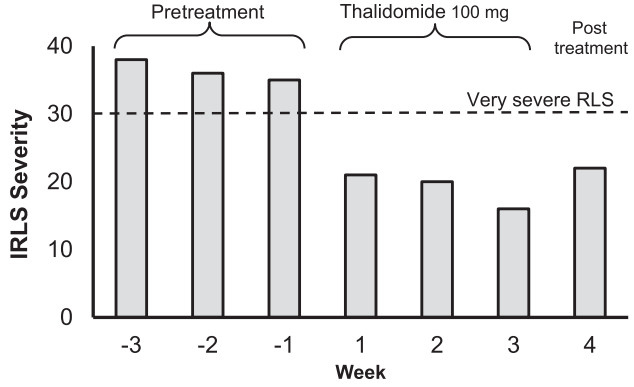
The female patient, aged 52 years, was diagnosed with RLS 20 years prior. Initial treatment response to L-Dopa/benserazide (up to 100/25 mg daily) was lost after < 1 year of therapy. Before age 52 years, she had tried pergolide (dose unknown), cabergoline (dose unknown), pramipexole (highest daily dose 0.54 mg between 18:00 and 22:00), ropinirole (dose unknown), rotigotine (3 mg), pregabalin (2 × 50 mg at 8:00 and 18:00), gabapentin (900 mg), tilidine (400 mg), and oxycodone/naloxone (35/17.5 mg controlled release daily), all without satisfactory therapeutic effect or with intolerable adverse effects (pregabalin and oxycodone/naloxone). Serum iron parameters were normal (ferritin 219 ng/mL, transferrin 205 mg/dL, transferrin saturation 39%), indicating sufficient iron stores and kidney function. The patient's RLS is familial, and she is a heterozygous carrier of the risk alleles of the lead single-nucleotide polymorphisms at both the *CRBN* and *MEIS2* loci (rs1848460 and rs996064, respectively).[2] Because of the treatment-resistant course of the disease, past hysterectomy, and absence of history of neuropathy or other risk factors for thalidomide adverse effects, it was decided to offer the patient an *Individueller Heilversuch* with thalidomide, meaning off-label experimental use in a single case, in agreement with the clinical ethics committee of the University Hospital Rechts der Isar of the Technical University Munich. The patient was informed and consented to the treatment.

First, a down-titration of her concomitant insufficient RLS medications was initiated to avoid unwanted drug interactions. Oxycodone/naloxone (30/15 mg controlled release daily) and pregabalin (100 mg daily) were completely stopped, and the daily dose of pramipexole was reduced from 0.54 mg–0.36 mg but could not be paused completely because of intolerable symptom rebound. In addition to pramipexole in reduced dosage, the patient kept on-demand tilidine drops

(maximum 10 drops, corresponding to 25 mg, daily) as her baseline medication. Pramipexole was taken daily throughout the observation period, whereas tilidine was used only 4 times during the pretreatment phase.

The patient was observed for 3 weeks with weekly visits at the neurologist (coauthor JW) after the reduction of her RLS therapy. Questionnaires evaluating the severity and consequences of the disease (the International Restless Legs Syndrome [IRLS] Study Group severity scale,[7] the RLS-6 scale,[8] the Epworth Sleepiness Scale,[9] and the Sleep Scale from the Medical Outcomes Study by RAND Health Care) were filled in weekly.[10] In addition, the patient was continuously monitored with a single actigraph (MicroMini-Motionlogger, Ambulatory Monitoring Inc., Ardsley, NY) attached to the wrist of her nondominant arm, recording activity and illumination. The patient reported her bedtimes using an event button. The reduction of her medication did not have beneficial effects on her symptoms. The patient had very severe RLS during that time (weekly RLS severity of 38, 36, and 35 out of maximum 40 points on the IRLS rating scale[7]; **Figure 1**). The RLS symptoms were accompanied by daytime sleepiness and insufficient sleep seemingly because of RLS, indicated by the RLS-6, Epworth Sleepiness Scale, and MOS sleep scale scores (**Table 1**). Disrupted sleep was supported by estimates of sleep parameters derived from the actigraphy data, showing prolonged nocturnal awakenings (mean wakefulness after sleep onset, 88.5 minutes during the baseline period) and prolonged sleep latency (mean sleep latency 43.6 minutes during the baseline period).

Figure 1—RLS severity.



RLS severity according to the IRLS rating scale during the 3 weeks leading up to the novel treatment (weeks –3 to –1) and during the treatment period with a 100 mg daily dose of thalidomide (weeks 1 to 3). IRLS = International Restless Legs Syndrome; RLS = restless legs syndrome.

After the medication withdrawal period, 100 mg thalidomide was administered once a day at 8:00 PM for 3 weeks. Potential adverse reactions to the treatment were evaluated weekly by in-person interview by a neurologist including physical and neurological examination, clinical blood sampling, and electrocardiogram. The patient reported no adverse reactions to the drug, and the laboratory parameters were within the normal range. No pathological changes were noticed in the electrocardiogram. The IRLS rating scale showed a substantial improvement of RLS symptoms (weekly scores 21, 20, and 16). Thalidomide ameliorated daytime sleepiness and self-reported sleep parameters, supported by a modest improvement of the actigraphy-based parameters, including mean wakefulness after sleep onset (45.0 minutes during treatment) and mean sleep latency (34.4 minutes during treatment). In interviews, the patient expressed improved sleep adequacy and was generally content with the thalidomide treatment period.

The patient was unavailable for further continuous observation in the following weeks. Retrospectively, the patient reported that the symptoms worsened again as soon as the night

Table 1—Mean RLS and sleep-related questionnaire data during baseline observation period and treatment with 100 mg thalidomide.

	Baseline			100 mg Thalidomide		
	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
IRLS rating scale	38.0	36.0	35.0	21.0	20.0	16.0
Epworth Sleepiness Scale	17.0	15.0	16.0	4.0	7.0	3.0
RLS-6 questionnaire						
Item 1: satisfaction with sleep	10.0	7.0	8.0	5.0	3.0	2.0
Item 2: symptom severity when falling asleep	10.0	8.0	6.0	3.0	3.0	2.0
Item 3: symptom severity during the night	10.0	7.0	7.0	2.0	3.0	1.0
Item 4: symptom severity at rest	10.0	10.0	10.0	9.0	3.0	4.0
Item 5: symptom severity when active	10.0	8.0	9.0	7.0	3.0	2.0
Item 6: daytime sleepiness or tiredness	10.0	8.0	5.0	2.0	1.0	1.0
Sleep Scale from the Medical Outcomes Study						
Subscale: sleep adequacy	100	80	100	40	30	20
Subscale: somnolence	60	27	33	20	33	20
Subscale: sleep disturbance	93	47	60	31	46	44

The data were collected once a week during an in-person interview with a neurologist. IRLS = International Restless Legs Syndrome; RLS = restless legs syndrome.

after the thalidomide treatment was stopped. She restarted pregabalin (75 mg daily) and continued pramipexole (0.18 mg twice daily) treatment shortly after thalidomide was discontinued. In a telephone consultation at age 55 years, the patient reported no change in symptom characteristics.

DISCUSSION

This is the first time a drug of the thalidomide class has been shown to provide short-term alleviation of RLS symptoms. The interpretation of the patient data is limited by the lack of polysomnography to assess periodic leg movements during sleep and to exclude other sleep disorders, and by the short follow-up period. However, despite the effect on periodic leg movements during sleep remaining unknown, the sleep questionnaires suggest that treating the patient's RLS with thalidomide ameliorated her sleep quality, resulting in better daytime functioning.

Thalidomide has a history of severe teratogenic adverse effects[11] and may potentially worsen neuropathy.[12] Therefore, it requires great caution when used and its prescription must be avoided in premenopausal women. However, existing thalidomide analogs[13] or new thalidomide derivatives under development may be less likely to have these adverse effects. Hence, the therapeutic potential of thalidomide shown here warrants novel molecules of the same class to be studied. By inhibiting MEIS2 degradation and thereby potentially compensating for reduced MEIS1, thalidomide use could be the first therapy to treat a symptom of idiopathic RLS by targeting the underlying molecular mechanism. However, the efficacy in RLS first needs to be confirmed in controlled clinical trials. Beyond RLS, our case report highlights the potential of genome-wide association studies in identifying new treatment targets in common disorders.

ABBREVIATION

IRLS, International Restless Legs Syndrome
RLS, restless legs syndrome

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DISCLOSURE STATEMENT

All authors have seen and approved the manuscript. Work was performed at Klinikum Rechts der Isar, Technische Universität München, Munich, Germany. The authors declare no conflicts of interest. The authors report the off-label use of thalidomide for the treatment of restless legs syndrome. The off-label use was performed in agreement with the clinical ethics committee of the University Hospital Rechts der Isar of the Technical University Munich.