Magnesium Therapy for Periodic Leg Movements-related Insomnia and Restless Legs Syndrome: An Open Pilot Study

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Summary: Periodic limb movements during sleep (PLMS), with or without symptoms of a restless legs syndrome (RLS), may cause sleep disturbances. The pharmacologic treatments of choice are dopaminergic drugs. Their use, however, may be limited due to tolerance development or rebound phenomena. Anecdotal observations have shown that oral magnesium therapy may ameliorate symptoms in patients with moderate RLS. We report on an open clinical and polysomnographic study in 10 patients (mean age 57±9 years; 6 men, 4 women) suffering from insomnia related to PLMS (n=4) or mild-to-moderate RLS (n=6). Magnesium was administered orally at a dose of 12.4 mmol in the evening over a period of 4-6 weeks. Following magnesium treatment, PLMS associated with arousals (PLMS-A) decreased significantly (17±7 vs 7±7 events per hour of total sleep time, $p<0.05$). PLMS without arousal were also moderately reduced (PLMS per hour of total sleep time 33±16 vs 21±23, $p=0.07$). Sleep efficiency improved from 75±12% to 85±8% ($p<0.01$). In the group of patients estimating their sleep and/or symptoms of RLS as improved after therapy (n=7), the effects of magnesium on PLMS and PLMS-A were even more pronounced. Our study indicates that magnesium treatment may be a useful alternative therapy in patients with mild or moderate RLS- or PLMS-related insomnia. Further investigations regarding the role of magnesium in the pathophysiology of RLS and placebo-controlled studies need to be performed.

Key words: Restless legs syndrome; periodic leg movements during sleep; magnesium; therapy; polysomnography

PERIODIC LEG MOVEMENTS DURING SLEEP (PLMS) are repetitive movements of the lower extremities, which are often associated with arousals or awakening and may cause disturbed sleep. Patients with restless legs syndrome (RLS) complain about restlessness and paresthesias of the legs mainly during the evening and night, causing frequent awakenings and sleep disturbances.[1] Most patients with RLS have an elevated number of PLMS.

Pharmacologic treatment studies of RLS and PLMS have been performed with various drugs, including benzodiazepines, opioids, and dopaminergic agents. A treatment regimen with L-dopa has been established (eg, 2-4), though side effects (gastrointestinal symptoms, headache), which may reduce patients' compliance, are not uncommon. Further therapeutic problems may arise due to an end-of-the-dose rebound and augmentation of RLS symptoms in the afternoon.[5,6]

Clinical studies with magnesium in patients with RLS have not been performed until now, although there are some indications that magnesium may ameliorate symptoms of RLS. It has been reported that symptoms in pregnancy resembling RLS (eg, paraesthesia of the extremities, muscle twitches) were improved after treatment with magnesium.[7,8] In our sleep disorders department, we have seen an amelioration of typical RLS symptoms in some cases after magnesium therapy.

To pursue our anecdotal observations, we initiated an open pilot study on the effects of magnesium in 10 patients

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who suffered from PLMS-related insomnia with or without symptoms of a mild or moderate RLS.

PATIENTS AND METHODS

After medical and neurological examination (including ECG, EEG, and blood samples), patients were admitted to our sleep disorders department and underwent 2 consecutive nights of polysomnography before magnesium treatment. The study included patients with symptoms of RLS according to the criteria of The International Restless Legs Syndrome Study Group,[1] with a moderately (<30/hour) elevated PLMS-arousal index (PLMS-A-index = number of PLMS associated with arousal per hour total sleep time). Also included were patients with insomnia and elevated PLMS-A (≥5.0/hour) according to Coleman, 1982.[9]

At commencement of the study, it was uncertain whether magnesium would be effective in RLS- and/or PLMS-related insomnia. Therefore, patients with severe RLS according to clinical judgement, or with a PLMS-A index higher than 30/hour, were not included because of ethical considerations. Patients with abnormal ECG, EEG, or pathologic blood cell counts indicating anemia were also excluded. Because of the risk of magnesium accumulation, patients with elevated serum creatinine indicating renal failure were not included. Further exclusion criteria were the intake of hypnotics, particularly of benzodiazepines, or other psychotropic drugs during the 4 weeks before examination. Patients with diseases known to cause symptomatic RLS (uremia, chronic bronchitis, iron deficiency, pregnancy) were also excluded. Thirteen patients diagnosed with insomnia and elevated PLMS or with RLS were entered into the study. Three patients were excluded from the evaluation for the following reasons: one patient was given doxepin additionally by her general practitioner during the treatment period; the second patient discontinued therapy because of lack of subjective benefits; and the third patient had taken magnesium only irregularly. Data from 10 patients were evaluated statistically (6 men, 4 women; mean age 57.4±9.4 years; duration of symptoms 6.1±5.8 years). Four patients suffered from insomnia and had an elevated PLMS-A index but did not fulfill RLS criteria.[1] One of these patients, a 63-year-old woman, had a history of alcohol abuse, but was abstinent for 4 weeks before treatment. She also had clinical signs of polyneuropathy, which was untreated before and during the magnesium-treatment period. Six patients had symptoms of mild or moderate RLS. Serum magnesium level was in the normal range in all patients (0.822±0.098 mmol/l), except for the 63-year-old female patient reported above (magnesium level 0.683 mmol/l).

Polysomnographic assessments included EEG (C3-A2, C4-A1), EOG, submental EMG, ECG, and superficial EMG of both anterior tibialis muscles for recording of PLMS.

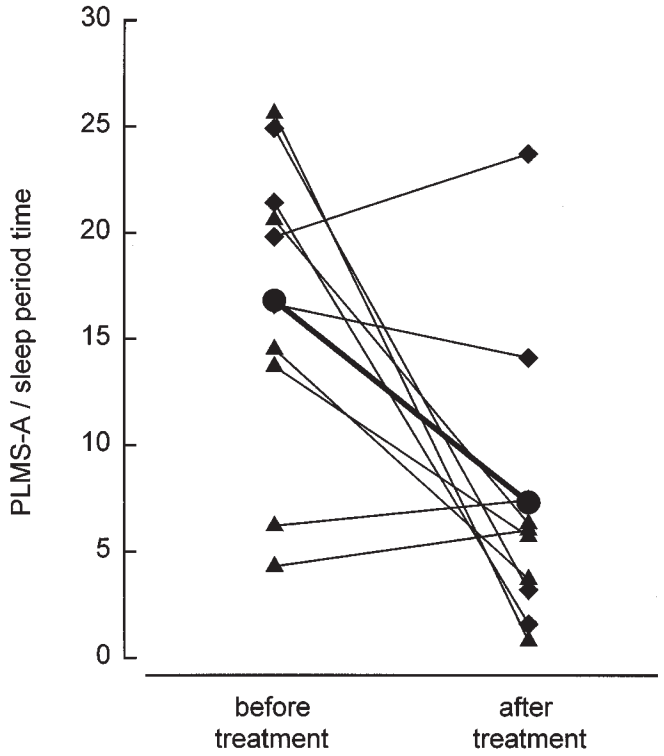

Figure 1.—Changes of the PLMS-A index (periodic leg movements during sleep with arousal/total sleep time) before and after magnesium treatment. Triangles indicate RLS patients (n=6), diamonds indicate patients with PLMS-related insomnia (n=4), and closed circles indicate mean values.

Each patient was monitored to exclude sleep-related respiratory disturbances by oronasal air flow, thoracic and abdominal efforts, and transcutaneous oxymetry during 1 of the 2 nights. After polysomnography, patients were given 12,4 mmol magnesium (magnesiumoxide) in the evening over a period of 4-6 weeks (mean 5.1 weeks). After the treatment period, patients were readmitted to the sleep laboratory for 1 night of clinical assessment and polysomnography with repeated PLMS recordings. Subjective sleep quality regarding the 2 weeks before polysomnography was assessed by the Pittsburgh Sleep Quality Inventory (PSQI).[10] Following the night of polysomnography, subjective sleep quality was measured with the SF-A ("Schlaffragebogen A")[11] at 07:00, and was evaluted for the items "quality of sleep" (range: 1 = very bad sleep to 5 = very good sleep) and "refreshing value of sleep" (range: 1 = no refreshing value to 5 = good refreshing value). Patients were also asked to estimate their symptoms (sleep disturbances and/or RLS) after therapy in terms of improved ("responders") and unchanged or worsened ("nonresponders").

Sleep recordings were analyzed visually by experienced raters according to Rechtschaffen and Kales.[12] PLMS were scored according to standard criteria[9]—ie, they

Table 1.—Values are mean ± standard deviation (SD). Significance is indicated by asterisk (*) and bold type. TST = total sleep time.

	All Patients n = 10		Responders n = 7		All patients n = 10	Responders n = 7
	before treatment	after treatment	before treatment	after treatment	p-value	p-value
PLMS-index	33 ±16	21 ± 23	33 ± 10	12 ± 11	0.069	**0.008***
PLMS-A-index	16.8 ± 7,2	7.3 ± 6,9	17.9 ± 7.6	3.9 ± 2.2	**0.018***	**0.007***
total PLMS	245 ± 127	157 ± 171	240 ± 86	93 ± 84	0.066	**0.016***
total PLMS with arousal	100 ± 44	47 ± 49	105 ± 44	28 ± 15	**0.022***	**0.012***
sleep efficiency (%)	75 ± 12	85 ± 8	76 ± 13	87 ± 7	**0.008***	**0.011***
total sleep time (min)	359 ± 55	405 ± 41	359 ± 60	422 ± 31	**0.015***	**0.009***
sleep period time (min))	443 ± 47	453 ± 32	438 ± 56	467 ± 13	0.641	0.247
number of stage shifts	161 ± 50	156 ± 35	172 ± 54	163 ± 37	0.806	0.737
number of awakenings	31 ± 19	25 ± 9	33 ± 23	24 ± 10	0.363	0.312
latency to stage 2 (min)	31 ± 49	17 ± 12	38 ± 57	13 ± 11	0.398	0.282
REM latency (min)	94 ± 52	79 ± 33	96 ± 45	76 ± 35	0.393	0.405
awake / TST (%)	19 ± 11	11 ± 5	18 ± 11	10 ± 6	**0.029***	0.080
stage 1/TST (%)	12 ± 5	13 ± 6	12 ± 6	13 ± 7	0.515	0.766
stage 2/TST (%)	52 ± 8	54 ± 6	51 ± 9	54 ± 7	0.224	0.420
stage 3 and 4/TST (%)	1 ± 2	2 ± 4	2 ± 2	3 ± 5	0.423	0.430
time in REM/TST (%)	17 ± 7	20 ± 3	17 ± 6	20 ± 4	0.226	0.292

were scored only if they were part of a series of four or more consecutive movements lasting at least 0.5 seconds with an intermovement interval of 4 to 90 seconds. Two indices were calculated: (1) the PLMS index, which gives the number of PLMS per hour of total sleep time (TST); and (2) the PLMS-A index, which considers only PLMS associated with arousal per hour of TST. Statistical analysis was performed by using Student's *t* test for dependent samples.

RESULTS

Periodic Leg Movements During Sleep and Sleep Parameters

Magnesium treatment had a distinct effect on PLMS which was most visible on PLMS associated with arousals (see Fig. 1 and Table 1). After therapy, patients' sleep improved, as indicated by the increase in sleep efficiency of nearly 10% (p=0.008) and the increase in total sleep time (TST) by an average of 46 minutes (p=0.015). The effects of treatment regarding PLMS and PLMS-A were even more pronounced in the group of patients with subjective improvement of sleep and/or RLS symptoms after therapy ("responders," n=7; see Table 1). Sleep-period time, the number of stage shifts, and the number of awakenings during sleep were not significantly influenced by medication. Latency to stage 2 and to the first REM period were markedly, though not significantly, diminished.

Clinical Response

Seven out of 10 patients reported improvement of RLS symptoms and/or insomnia (5 patients with RLS and 2 patients with PLMS-related insomnia). In the Pittsburgh

Sleep Quality Inventory, 7 patients evaluated their sleep as better after therapy (13±4 vs 8±3; p=0.015); the decrease of the score from all patients was not significant, however (12±5 vs 10±4). Data from the SF-A revealed, in 7 patients, improvement or no change of sleep quality (2.3±0.6 vs 2.7±0.6; p=0.062). These patients felt more refreshed in the morning during therapy (3.0±1.1 vs 3.5±0.8; p=0.020). The mean SF-A scores of the 10 patients did not change markedly (score for "quality of sleep" 2.5±0.8 vs 2.6±0.5; score for "refreshing value of sleep" 3.1±1 vs 3.2±0.8). Change of symptoms as estimated by the patients (unchanged, improved, worsened) and decrease or increase of the PLMS-A index were parallel in 8 subjects. One subject experienced improvement of RLS, although his PLMS-A index was slightly higher after treatment (4.3 vs 6.0). One subject with PLMS stated no change, but his PLMS-A index was slightly lower (16.6 vs 14.1) after magnesium treatment.

Adverse Effects

No major side effects were reported. Some patients described occasional mild diarrhea. A reduction of the magnesium dosage was not necessary in any of the patients. Magnesium levels after treatment were slightly but not significantly higher than before treatment (0.823±0.123 vs 0.905±0.085 mmol/l).

DISCUSSION

To our knowledge, the present study is the first report on a significant therapeutic effect of magnesium on symptoms of RLS and PLMS-related insomnia. We found a clear reduction of periodic leg movements associated with arousal during sleep, and a significant improvement of sleep efficiency and of total sleep time. The effect of magnesium on PLMS-A was even more pronounced in the group of the seven patients with subjective improvement of sleep and/or RLS symptoms.

The extent of PLMS reduction in our study is comparable to previous pharmacological studies using dopaminergic drugs on PLMS. For example, in a study on bromocriptine for RLS, Walters et al described an increase in sleep efficiency from 55% to 70%, and a reduction in the total number of PLMS without arousal from 278 to 193 after therapy.[13] Recently, Trenkwalder et al reported on idiopathic RLS and RLS in uremic patients, and found a decrease of the PLMS-A index from 40 to 29/hour in patients with idiopathic RLS after L-dopa therapy.[4] Theoretically, our results could be influenced by a placebo effect. Such an effect seems unlikely, however, since—to our knowledge—significant treatment effects of placebo on RLS were not yet observed (eg, 4,14). A further bias of our data on PLMS could be due to a "first-night" or adaptation effect (ie, some reduction of PLMS in the second and following nights compared with the first night spent in the sleep laboratory), but this also seems unlikely. Previous studies have shown that, although there is a considerable variation of leg movements from one night to the next, this variation occurs with a random character.[15,16]

The mechanism of action of magnesium intake to improve symptoms of RLS and PLMS can presently only be speculated upon. One possible explanation may be a direct effect of magnesium on the nervous system. The depressing effect of magnesium on neuronal excitability has long been known, and is explained by its physiological calcium antagonism.[17] At the CNS level, magnesium seems to have a regulatory role in the function of several transmitters—among others, of acethylcholine and gamma-aminobutyric acid (GABA).[18] Also known is a direct effect of magnesium on the function of N-methyl-D-aspartate (NMDA) receptors.[19] Besides the effects of magnesium on the nervous system, it is also conceivable that by applying magnesium, we compensated a pre-existing magnesium deficit, at least in some of our patients. Though serum magnesium level was normal in all but one of our patients, one cannot rule out this possibility, since in case of a magnesium deficiency, serum magnesium level only weakly correlates with intracellular magnesium content.[20] A possible correlation between depletion of magnesium stores in the body and PLMS and/or RLS may be a subject for further studies. This could be investigated, for example, by means of magnesium-loading tests.

There are no known major side effects of magnesium therapy among patients with intact renal function and without serious bowel disease leading to increased resorption of magnesium. To our knowledge there exist, however, only few studies applying magnesium over several months, and only one case over 2 years.[21] In these studies, no side effects of the magnesium therapy were reported.

In summary, this open, unblinded study demonstrated significant improvement of sleep and PLMS after magnesium treatment. To evaluate whether magnesium might be a treatment alternative for RLS- and/or PLMS-related insomnia, double-blind placebo controlled studies should be performed.

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