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Restless Legs Syndrome in Gun Factory Workers Exposed to Solvents

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Authors' contributions

This work was carried out in collaboration between all authors. Authors AE, ED, MS and NBM designed the study, wrote the protocol, and wrote the first draft of the manuscript. Authors AC, EB, TP, ME and YT managed the literature searches. Author NBM performed the analyses of the study. All authors read and approved the final manuscript.

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ABSTRACT

Background: Restless legs syndrome (RLS) is a sensorimotor disorder characterized by a complaint of an almost irresistible urge to move the legs.
Aims: We investigated whether long-term low-level exposures to solvents affects the development of restless legs syndrome.
Methods: 388 workers were questioned for RLS, psychological distress and somatic symptoms.
Results: The prevalence of RLS was not different in workers exposed to solvents than in those without (n: 192; 5.2% vs. n: 196; 5.6%, p = 0.8, respectively). Exposure to solvents was not associated with an increased risk of RLS. In solvent-exposed group, there was positive correlation between daytime sleepiness, frequent awakening, kicking during sleep, sleep duration, time spent in bed, apnea and snoring scores. Alcohol consumption were related to higher kicking during sleep and difficulty falling asleep scores. The RLS percentages were 7/173 (4.0%) for daytime working

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subjects; and 2/16 (12.5%) for shift-workers.
Conclusion: Chronic exposure to low doses of solvents doesn't affect the development of RLS.

Keywords: Solvents; restless legs syndrome; workers; exposure.

1. INTRODUCTION

Restless legs syndrome (RLS) is a sensorimotor disorder characterized by a complaint of an almost irresistible urge to move the legs [1]. RLS can occur as a primary disorder, with no apparent cause other than a possible genetic predisposition, or as a secondary condition, most commonly related to iron deficiency, pregnancy, or end-stage renal disease [2]. The prevalence of RLS in various regions in the world has been estimated between 2.5 and 29% [3].

Organic solvents are commonly used as mixtures rather than individual solvents in industry [4]. The health effects of long-term, low-level exposure to organic solvents have been studied for many years [5]. Exposure to solvents is an important health hazard in workplaces. Exposure to organic solvents has been reported to increase the risks for acute and chronic health effects among workers [6]. However, information on adverse health effects associated with long-term solvent exposure is still controversial [7].

When acute, high-dose organic solvent exposure occurs, neurologic dysfunction, including fatigue, headache, dizziness, giddiness, disorientation, confusion, hallucination, and/or seizure; other neurologic consequences; coma; or death are seen in the patients. Symptoms of raised intracranial pressure (ICP), such as headache, nausea, or vomiting, which may also be consistent with acute toxic exposure [8,9].

Long-term exposure to organic solvents mainly occur as exposure to the mixture of the solvents. Pure exposure is rarely seen. Exposure to low concentrations has not been found to cause changes in performances, but exposure to higher concentrations affects reaction times and the speed of perception. Moreover, toluene causes changes in subjective experiences and feelings. There are some results indicating that exposure to trichloroethylene and other solvents impairs memory and causes neurotic symptoms, that exposure to styrene causes disturbances in visuomotor accuracy and psychomotor performance, and that some performances of house painters exposed to different mixtures of solvents are impaired [10].

Long-term, low-dose exposure to organic solvents is related to neurologic dysfunction [8,9]. Symptoms referable to the Central Nervous System (CNS) are headache, confusion, disorientation, behavior changes, or memory problems that are seen as intermittent or of slow onset. Symptoms referable to the PNS, such as numbness in the feet and hands, pain, weakness, or difficulty walking that are also intermittent or of slow onset [8,9].

For solvents with high partition coefficients, increased solubility of a gas in the blood is associated with slowed onset of symptoms. The CNS, which is rich in both blood supply and lipid content, is a common target of solvent distribution. Effects consistent with known acute effects of the neurotoxin. Acute and chronic effects of toluene have been attributed to the metabolites benzyl alcohol and benzaldehyde, to free radicals, and to the parent compound [8,11]. Xylene can interact with membrane-bound integral proteins, and these interactions may be the critical factor in determining the anesthetic effects of xylene on the CNS [8].

In the differential diagnosis of solvent exposure and related neuropathy , the list of the diseases are "Acute CNS symptoms (rapid onset), Cerebral anoxia, Cerebral ischemia, Drug overdose, Drug toxicity, Hyperglycemia or hypoglycemia, Metabolic derangements, Thyroid storm, Wernicke encephalopathy, Meningitis, Encephalitis, Central pontine myelinolysis Chronic CNS symptoms (slow onset), Dementia, Epilepsy, Multiple sclerosis, etc. [8]. In the present study, all partiicipants were regularly underwent physical examination via the Ocuupational physicians of the factory, therefore diffrential diagnosis were not performed by research team. The diagnosed neurological diseases, stroke or traumatic brain injury were not included to this study.

Preventive methods to avoid solvent exposure are reducing inhalation, ingestion, or dermatologic exposures may be accomplished by not eating or smoking in the workplace and

by improving use of personal protective equipments (PPE), including masks and breathing apparatuses. Other protective measures are wearing gloves made of latex, Vicryl, or other impermeable material to limit skin absorption and by showering and changing clothes on completion of job tasks [8].

In principle, one could expect a relationship between the exposure to solvents and the restless legs syndrome. Gun factory workers may be expose different harmful agents such as ammonia, cyanides, formaldehyde, nitrogen dioxide, isocyanates, ozone, phosgene, sulfur dioxide, phthalic anhydride, cadmium, chromium, nickel, beryllium and wood shavings [12]. Previous one study suggested that RLS symptoms fluctuated in correlation with serum ammonia level [13].

We investigated whether long-term low-level exposures to solvents affect the development of restless legs syndrome.

2. METHODS

2.1 Study Setting and Sample

The study was undertaken by Departments of Kirikkale University, Medical School between January to April 2007.

Our study was conducted on the workers of Gun Factory, Kırıkkale, Turkey. At that factory, gun parts are produced from raw materials in workshops. These parts are cleaned with solvents, and the workers are exposed to toluene, acetone, butanol, xylene, benzene and trichloroethylene during their work shift (continually 8 h/day, 5 days a week).

2.2 Data Collection and Management

The study was performed on a total of 388 male workers divided into two groups as the workers exposed to solvents only (n=192) (Chronic exposure duration was 17.74±7.79 years, ranged to 1 to 36 years); and those that were not exposed to solvents during their work in service areas such as security, office, and engineering departments (Control group) (n=196). Mean age of the solvent exposed group was 42.97±6.34; and mean age of the control group was 40.98±8.13.

We excluded workers such as welders, carpenters, lathe operators, because they did not exposed solvents in the factory; and because they exposed different harmful agents such as ammonia, cyanides, formaldehyde, nitrogen dioxide, isocyanates, ozone, phosgene, sulfur dioxide, phthalic anhydride, cadmium, chromium, nickel, beryllium and wood shavings [12].

Workers in the study and control groups were included into the study after signing an informed consent. In both groups, there was no history of stroke or traumatic brain injury or diagnosed neurological diseases.

The main exposure route for our study was inhalation the solvent concentration in the air of the factory was not measured at the current time. But there are measures to prevent the workers from the solvent's damage. Therefore, the solvent concentration in the air is thought that not too intense. This issue was limitation of our study.

We investigated the presence/or absence of RLS in solvent exposed group and control group. The criteria suggested by the The International Restless Legs Syndrome Study Group were used in the assessment for RLS: (a) the desire to move the limbs associated with paresthesias/ dysesthesias; (b) motor restlessness; (c) symptoms present exclusively or worse at rest (lying and sitting) with at least partial and temporary relief by activity; and (d) symptoms worse in the evening or at night [14]. Where necessary, the four screening questions were explained in detail to participants. Only those who gave a clear and distinct positive response to all four questions were classified as having RLS.

2.3 Instrumentations

2.3.1 Questionnaire

A detailed occupational history [The questions related to solvent exposure: Daily, weekly, and total exposure duration (years of solvent usage)], demographic characteristics and previous medical history; and questions about their smoking habits and alcohol consumption were asked.

The presence of RLS (according to the criteria), sleep conditions (Kicking during sleep (yes-no), Difficulty falling asleep (yes-no), Time to fall asleep (min), Sleep duration (hours), Time spent in bed (hours) were asked.

Daytime sleepiness, Frequent awakenings, Snoring and Apnea were assessed by the Modified Sleep and Health Questionnaire as: 5-point frequency scale: (0) never;(1) rarely: less than once a week; (2) sometimes: once or twice a week; (3) frequently: three to four times a week; (4) almost always: five to seven times a week; and (5) not sure [15].

2.3.2 Mini-mental Status Examination (MMSE)

The MMSE was administered to assess cognitive functioning. This test explores cognitive domains: temporal and spatial orientation, short-term memory, computation, secondary memory, verbal attainment, and constructive ability. Healthy subjects have scores > 23. The main items were: Orientation (OR) (Total 10 points); Registration memory (RM) (Total 3 points); Attention and counting (AC) (Total 5 points); Recall (Total 3 points) (R); Language (Total 9 points) (L) [16].

2.3.3 Assessment of psychological status

Hospital Anxiety and Depression Scale (HAD Scale) was used. The participants were asked to fill out the self-reported Hospital Anxiety and Depression (HAD) scale questionnaire for the assessment of psychological distress. The scale consisted of 14 questions in which the overall severity of anxiety and depression was rated on 4-point, Likert-type scale (0 to 3). Seven questions were related to anxiety and seven to depression [17]. Psychological distress score was defined as the total HAD score. The reliability and validity of the scale were done by Aydemir and Guvenir in 1987. The cut off point was 10 for the anxiety subscale and 7 for the depression subscale [18].

All the steps of the study were planned and carried out according to the principles outlined in the Declaration of Helsinki [19]. The study was conducted without any financial support; or any funds. We conducted the study with our own personal support. Some of the data of this study including Total HAD and MMSE scores; and respiratory findings were presented before [20-22].

2.4 Data Analysis

SPSS 16.0 version was used. Independent samples t-test, Chi-Square and Spearman's correlation rho efficient tests were used.p value <0.05 was considered as statistically significant.

3. RESULTS

Demographic data and sleep characteristics of the study and control groups were presented on Table 1. There were no significant differences for Body-Mass Index (BMI), smoking, alcohol consumption, exercise and active hand of the workers ($p<0.05$) (Table 1).

RLS was present 10 workers (5.2%) in solvent exposed group; and 11 workers (5.6%) in the control group. There was no-significant difference between groups by Chi-Square test ($p=0.860$, $X^2=0.031$) (Table 1).

"Kicking during sleep", "Time to fall asleep", "Sleep duration", "Time spent in bed" and "Frequent awakenings" values were not different between two groups ($p>0.05$). The difference between daytime sleepiness between the study and control groups was statistically significant between solvent-exposed and non-exposed group by Chi-Square test ($p=0.008$, $X^2=7.121$) (Table 1).

People who complain of RLS (A total of 21 workers-10 workers in solvent-exposed group; and 11 in control group) had a higher percentage of complaints, namely morning headache, morning tiredness, Environmental adaptation and indecision compared to non-RLS workers of the study and control groups. Except indecision ($p=0.010$), the others did not reach statistically significant level ($p>0.05$) (Table 2).

HAD and MMSE results were not different between the solvent exposed workers and control group ($p>0.05$) (Table 3).

The RLS percentages were 7/173 (4.0%) for daytime working subjects; and 2/16 (12.5%) for shift-workers (work schedule changes daytime and/or night in different weeks of the month).

In solvent-exposed group, correlation analysis were performed by Spearman's correlation rho efficient test:

- RLS scores were lower in smoking workers ($p=0.013$, $r=-0.231$). Exercise was also related to lower RLS scores ($p=0.049$, $r=-0.184$).
- Frequent awakening ($p=0.004$, $r=0.264$), apnea ($p=0.033$, $r=0.200$) and alcohol consumption ($p=0.000$, $r=0.346$) were related to lower "kicking during sleep" scores".

- As sleep duration (p=0.000, r=0.334), time spent in bed (p=0.000, r=0.368), apnea (p=0.000, r=0.324), alcohol consumption (p=0.001, r=0.305) and MMSE scores (p=0.003, r=0.272) increased, "difficulty falling asleep" values also increased.
- Longer sleep duration was related to higher difficulty falling asleep (p=0.000, r=0.334), time spent in bed (p=0.000, r=0.858) and apnea (p=0.000, r=0.336) scores. Older workers (p=0.050, r=0.183) sleep duration was also higher. Workers with frequent awakenings had lower sleep duration scores (p=0.002, r= –0.281).
- Higher difficulty falling asleep (p=0.000, r=0.368), sleep duration (p=0.000, r=0.858), apnea (p=0.000, r=0.402), total MMSE scores (p=0.002, r=0.292) were related to higher time spent in bed scores. Older workers' "time spent in bed "scores was also higher.
- Higher snoring scores were related to higher daytime sleepiness (p=0.009, r=0.244), frequent awakenings (p=0.001, r=0.299), apnea(p=0.009, r=0.243), and total HAD scores (p=0.017, r=0.249); and lower MMSE scores (p=0.001, r= ─0.308).
- Higher frequent awakenings scores were related to higher kicking during sleep (p=0.004, r=0.264),, daytime sleepiness (p=0.009, r=0.244), snoring (p=0.001, r=0.299), and apnea scores (p=0.035, r=0.198); and lower sleep duration scores(p=0.009, r=0.244).
- Higher apnea scores were related to higher kicking during sleep (p=0.033, r=0.200), difficulty falling asleep (p=0.000, r=0.324), sleep duration (p=0.000, r=0.336), time spent in bed (p=0.000, r=0.402), daytime sleepiness (p=0.047, r=0.186), snoring (p=0.009, r=0.243), and frequent awakenigs scores (p=0.035, r=0.198). Different from the literature, in solvent exposed group, higher apnea scores were related to lower BMI scores (p=0.001, r= ─0.316).

4. DISCUSSION

RLS may cause severe sleep disturbances, poor quality of life, depressive and anxious symptoms, and may be a risk factor for cardiovascular disease [23]. Exposure to solvents is an important health hazard in workplaces has been reported to increase the risks for acute and chronic health effects among workers [6]. In the present study, we investigated the relationship between exposure to solvent and RLS; and according to our knowledge, this is the first study evaluating restless legs syndrome in workers exposed solvents. RLS was present 10 workers (5.2%) in solvent exposed group; and 11 workers (5.6%) in the control group. There was no-significant difference between groups.

Sleep parameters of both group was also evaluated. The results showed that daytime sleepiness scores were significantly higher in solvent exposed workers. Whereas "Kicking during sleep", "Time to fall asleep", "Sleep duration", "Time spent in bed" and "Frequent awakenings" values were not different between two groups.

People who complain of RLS (5.2% of solvent exposed workers and 5.6% of non-exposed workers) had more complaints of indecision significantly. Morning headache and morning tiredness values were also higher in workers with RLS, but no-significance was detected.

In the present study, total HAD scores were not different between solvent exposed and non-exposed group. In the literature, a population-based survey demonstrates significantly higher anxiety and depression symptoms in RLS patients compared with contemporaneous control subjects, and a correlation of the intensity of these symptoms with the severity of RLS [23]. Other studies also indicated association between psychological indices and RLS symptoms [24]. It is important to realize the severity and presence of depression in persons with RLS. Treatment for depression in RLS patients should focus on achieving and maintaining remission of depressive symptoms using a variety of methods including antidepressants that do not exacerbate RLS symptoms, cognitive behavior therapy, and social support, providing an active clinical approach to managing depression in this group [25]. Cho et al. reported that RLS has a considerable impact on the QoL [26]. The QoL impairment relates to the degree of depression with RLS.

In solvent-exposed group, correlation test results showed that:

- RLS scores were lower in smoking workers. Ishaq et al reported that RLS was also significantly associated with increasing age, high body mass index,

and smoking status in Rheumatoid arthritis patients [27]. Sevim et al investigated the prevalence, risk factors, and clinical presentation of restless legs syndrome (RLS) in a Turkish population [28]. Of the 3,234 participants, 103 (3.19%) experienced RLS. RLS was found to be more common among women, cigarette smokers, and individuals residing in high altitudes. The discrepancy in RLS prevalence studies (including the authors') suggests that prevalence varies among different races, thus supporting a genetic predisposition.

- Exercise was related to lower RLS scores. Ghorayeb and Tison reported that RLS is often accompanied by pain or other unpleasant sensations, it either occurs or worsens with rest particularly at night, and improves with activity [29]. The relation between exercise and RLS may be explained as: "Daily activity, including moderate aerobic exercise and lower-body resistance training, can significantly reduce the symptoms of restless legs syndrome. Swim, go for a walk, take the stairs, or spend a few minutes doing jumping jacks. Keep in mind that excessive exercise—like training for a marathon—can actually make restless legs syndrome worse." [30].
- Daytime sleepiness Frequent awakening, kicking during sleep, sleep duration, time spent in bed, apnea and snoring scores usually shows positive correlation with each other.
- Different from the literature, in solvent exposed group, higher apnea scores were related to lower BMI scores. This may be due to solvent's effects on central nervous system and/or peripheral respiratory system.
- Older workers' "time spent in bed "scores was also higher. By ageing, sleeping problems were seen more.

The pathophysiology of RLS includes an altered brain-iron metabolism, abnormal opioid systems, a dopaminergic dysfunction, a probable role of pain control systems and a genetic susceptibility with nine loci and three polymorphisms in genes serving developmental functions. The most robust and consistent observation is reduced CNS iron stores, even in the setting of normal systemic iron studies [31]. RLS treatment begins with the elimination of triggering factors and iron supplementation when deficient. Mild or intermittent RLS is usually treated with low doses of l-DOPA or codeine; the first-line treatment for moderate to severe RLS is dopaminergic agonists (pramipexole, ropinirole, rotigotine). In severe, refractory or neuropathy-associated RLS, antiepileptic (gabapentin, pregabalin) or opioid (oxycodone, tramadol) drugs can be used [31].

In the present study, in solvent exposed group, no depressive complaints were detected in workers. Because of this reason, medical treatment were not recommended; only relaxative measures were recommended to these workers. As activity causes to decrease RLS, our solvent exposed worker's RLS percentages were detected as lower (5.2%) due to their work's active environment.

In our study, alcohol consumption were related to higher kicking during sleep and difficulty falling asleep scores. Aldrich and Shipley reported that periodic leg movements contribute to sleep disturbance in a significant proportion of alcohol users [32]. Alcohol use may increase the frequency of periodic leg movements in susceptible individuals. On the other hand, subjects with symptoms related to periodic leg movements may be using alcohol to relieve symptoms, or the movements may be secondary to alcohol-induced sleep disturbance.

In the present study, MMSE results were not different between the solvent exposed workers and control group. Whereas in Maliutina and Taranenko's study [33], cognitive functions were investigated in workers exposed to methanol and formaldehyde. Montreal scale (MCA) was used to evaluated the cognitive functions. Moderate cognitive disorders of multifunctional type were seen in the study group. In Sabbath, et al. [34] study, a total of 2,143 retirees in the GAZEL cohort underwent cognitive testing. Lifetime exposure to chlorinated solvents, petroleum solvents, and benzene was assessed using a job exposure matrix. Thirty-three percent of participants were exposed to chlorinated solvents, 26% to benzene, and 25% to petroleum solvents. Their results showed that highexposure to solvents was significantly associated with poor cognition; for example, those highly exposed to chlorinated solvents were at risk of impairment on the Mini-Mental State Examination. In our study, solvent exposure was low dose and long-term; and the reason for the normal cognitive functions in our workers maybe related to exposure dose of the solvents being low.

Table 1. Demographic and descriptive data

		Solvent exposed group		Control group		p
		Mean	**Std. dev.**	**Mean**	**Std. dev.**	
Age		42,97	6,347	40,98	8,13	p=0.008*, t= –2.682
Cigarette pocket year		8,74	11,87	8,51	11,13	P=0.850, t= –0.189
Body-Mass Index		25,87	2,65	26,02	2,45	p=0.572*, t=0.565
		n	**%**	**n**	**%**	
Smoking	Yes	144	75.0	140	71.4	P=0.427**
	No	48	25.0	56	28.6	X2=0.631
Alcohol consumption	No consumption	173	90,1	169	86,7	P=0.266**
	< 2 per week	14	7.3	18	9,2	X2=1.237
	2-5 per week	4	2.1	6	3,1	
	>5 per week	1	0.5	2	1,0	
Exercise	2-7 per week (regular)	29	15.1	40	20.5	P=0.195** X2=3.269
	Occasional	55	28.6	62	31.8	
	Rare	108	56.2	93	47.7	
Active hand	Right	96	92.3	102	93.6	p=0.925**
	Left	8	7.7	7	6.4	X2=0.009
Sleep charasteristics		**Mean**	**Std. dev.**	**Mean**	**Std. dev.**	
Time to fall asleep (min)		20,46	12,973	20,62	12,596	p=0.906*, t=0.118
Sleep duration (hour)		7,27	1,066	7,23	1,027	p=0.715*, t=-0.366
Time spent in bed (hours)		7,73	1,990	7,65	1,414	p=0.696*, t=-0.392
		n	**%**	**n**	**%**	
Restless leg syndrome	Present	10	5.2	11	5.6	p=0.860**
	Absent	182	94.8	185	94.4	X2=0.031
Kicking during sleep	Present	15	7.8	13	6.6	p=0.800**
	Absent	177	92.2	183	93.4	X2=0.064
Daytime sleepiness	[0] never;	70	36.5	97	49.5	
	[1] rarely: less than once a week	75	39.1	67	34.2	
	[2] sometimes: once or twice a week	31	16.1	22	11.2	p=0.008 X2=7.121
	[3] frequently: three to four times a week	11	5.7	7	3.6	
	[4] almost always: five to seven times a week	3	1.6	3	1.5	
	[5] not sure	2	1.0	0	0.00	
Nocturnal awakenings	[0] never;	87	45,3	101	51,8	
	[1] rarely: less than once a week	64	33,3	61	31,3	
	[2] sometimes: once or twice a week	21	10,9	21	10,8	p=0.101 X2=2.682
	[3] frequently: three to four times a week	15	7,8	9	4,6	
	[4] almost always: five to seven times a week	4	2.1	3	1,5	
	[5] not sure	1	0.5	0	0.00	

**p value shows the results of Independent samples t-test*
***p value shows the results of Chi-Square test*

Table 2. In all workers (Solvent exposed and non-exposed), prevalance of morning headache, indecision, environmental adaptation and morning tiredness in RLS and non-RLS workers*

	RLS group n (%)	Non-RLS group n (%)	p
Morning headache	9/21 (45.0%)	95/367 (25.9%)	0.060
Morning tiredness	8/21 (40.0%)	91/367 (24.8%)	0.100
Environmental adaptation	3/21 (14.3%)	23/367 6.3%)	0.100
Indecision	6/21 (28.6%)	41/366 (11.2%)	0.010

**p value shows the results of Chi-square test*

Table 3. HAD and MMSE results

HAD and MMSE results	Solvent exposed group		Control group		p
	Mean	Std. dev.	Mean	Std. dev.	
Anxiety score	5,99	3,362	6,24	3,542	p=0,495*, t=0.684
Depression score	6,24	3,238	6,58	3,264	p=0.320*, t=0.995
Total HAD score	12,1030	5,69727	12,9024	6,10161	p=0.220*, t=1.228
Total MMSE score	28,89	1,571	28,75	1,574	p=0.407*, t=-0.830

**p value shows the results of Independent samples t-test*

In our study, the relationship between workschedule and RLS were analyzed. The RLS percentages were 7/173 (4.0%) for daytime working subjects; and 2/16 (12.5%) for shift-workers (work schedule changes daytime and/or night in different weeks of the month). Simon reported that shift work disorder (SWD) occurs when individuals are unable to successfully synchronize their internal clocks with a work schedule that requires them to stay awake when it is dark and sleep when it is light [35]. When assessing for SWD, clinicians should take a thorough sleep history and have the patient maintain a sleep diary. Clinicians should also be aware of conditions that commonly occur in conjunction with this illness, including sleep apnea, restless legs syndrome, depressive and anxiety disorders, and chronic fatigue.

5. CONCLUSION

Present results suggest that the chronic exposure to low doses of solvents does not affect the development of restless legs syndrome. RLS in solvent-exposed workers may be related to shift-working; and sleep problems due to shift working. In solvent exposed workers, sleep related items and problems (Daytime sleepiness, Frequent awakening, kicking during sleep, sleep duration, time spent in bed, apnea and snoring scores) were usually seen together. To prevent and treat RLS, activity measures and some medications can be recommended for needed patients.

ETHICAL APPROVAL

All authors hereby declare that all study was conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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