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ORIGINAL ARTICLE

Leg movements during sleep in children treated with serotonergic antidepressants

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Abstract

Study Objectives: To evaluate leg movements during sleep (LMS) in children taking serotonergic antidepressants, compared to those of children with restless legs syndrome (RLS) and controls, and to assess the time structure of intermovement intervals (IMI).

Methods: Twenty-three children (12 girls, mean age 14.1 years) on antidepressants and with a total LMS index ≥ 15/h, 21 drug-naïve RLS children (11 girls, mean age 13.6 years) also with total LMS index ≥ 15/h, and 35 control children (17 girls, mean age 14.3 years) were recruited. LMS were scored and a series of parameters was calculated, along with the analysis of their time structure.

Results: Children taking antidepressants showed higher total and periodic LMS (PLMS) indexes than both controls and RLS children, as well as higher short-interval and isolated LMS indexes than controls. LMS periodicity was highest in children on antidepressants. In children taking antidepressants, a well-defined PLMS IMI peak corresponding to approximately 10–60 s, with a maximum at approximately 20 s was present, which was much less evident in RLS patients and absent in controls. A progressive decrease of PLMS during the night and more frequent arousals were found in children on antidepressants and with RLS.

Conclusions: Children taking serotonergic antidepressants show higher periodicity LMS than children with RLS or controls and have a higher number of PLMS through the night. Antidepressant-associated PLMS in children seem to have features similar to PLMS of adults with RLS. Whether this is a marker of an increased risk to develop RLS later in life needs to be determined.

Statement of Significance

The findings of this study show that serotonergic antidepressant use in children is associated with periodic leg movements during sleep (PLMS) with features similar to the typical PLMS of adults with restless legs syndrome (RLS). This is in contrast to PLMS of children with RLS, in whom the adult pattern starts developing during adolescence. Also, based on genetic findings reported in the earlier literature, we hypothesize that the antidepressant accelerated "maturation" of PLMS might indicate an increased susceptibility to develop RLS symptoms later in life. However, additional studies are needed with long-term prospective data to fully understand the clinical meaning of PLMS associated with antidepressant use.

Key words: periodic leg movements during sleep; antidepressants; restless legs syndrome; periodicity index; sleep-related movements; serotonergic antidepressants

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Introduction

Leg movements are commonly seen in pediatric polysomnography (PSG). When leg movements follow a specific pattern of periodicity they are called periodic leg movements (PLM) and occur more frequently during sleep (PLMS) [1, 2]. PLMS are identified by recording surface electromyography from the tibialis anterior (TA) muscles and are scored using one of the two current criteria established to score leg movements and PLMS [3, 4]. PLMS can occur in one leg or in both legs, can be associated with an arousal or an awakening, are accompanied by significant increases in heart rate [5] and blood pressure [6, 7], and can be seen in association with other comorbidities or medications [8, 9].

Restless legs syndrome (RLS) is the disorder most commonly associated with an elevated number of PLMS, but other conditions have also been studied, in particular narcolepsy [10–12], rapid eye movement (REM) sleep behavior disorder [13], pediatric seizure disorders [14], and a large number of other conditions [2]. PLMS can also be found as an incidental finding. Periodic leg movement disorder (PLMD) is diagnosed when PLMS are associated with night time or daytime symptoms such as sleepiness, fatigue, or hyperactivity, and not secondary to another disorder or medication use [15]. Scientific studies evaluating the contribution of PLMS to daytime symptoms are few and in many cases, patients with PLMS often have other comorbidities or take medications known to increase PLMS [14], in particular, serotonergic antidepressants [14, 16].

Previous studies have demonstrated that not all leg movements are equal. Patients with RLS and patients with narcolepsy have PLMS that differ in the intermovement interval (IMI) [17] or, more specifically, in their time structure [10, 18]. Another study has confirmed that the analysis of IMI can help identify PLMS that are responsive to dopaminergic medication from those not responding to dopaminergic treatment [19]. Furthermore, analysis of PLMS across the lifespan has shown that leg movements in young children have low periodicity and do not approach the periodicity of adults until the adolescent years [20, 21]. IMI seems to be more appropriate to describe the real degree of periodicity [22] of leg movements during sleep (LMS). Studies specifically assessing this aspect are still few, but they support the findings of leg movements with low degree of periodicity in young children that changes to a periodic pattern during adolescence [12, 21, 23].

Studies on adults and children taking antidepressants have shown an increase in PLMS [16], in particular, selective serotonin receptor inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors but not bupropion, which is a dopamine reuptake inhibitor [24, 25]. We hypothesize that since SSRIs decrease dopamine levels [26], the PLMS seen in association with serotonergic antidepressants will show characteristics consistent with a response to dopaminergic inhibition. Hence the aims of this current study are: (1) to evaluate the PSG characteristics of LMS in children taking antidepressants, (2) to compare LMS in children taking antidepressants with those of children with RLS and controls, and (3) to specifically assess the time structure of IMI in the same groups of subjects.

Methods

Subjects

For this study, 23 children (12 girls and 11 boys, mean age 14.1 years, SD 2.94) on serotonergic antidepressants for depression, anxiety, or both were consecutively recruited at the Seattle Children's Hospital, Seattle, WA, USA. None of the children had another medical or psychiatric disorder. All children had a total LMS index ≥ 15/h at PSG recording, which had been ordered because of snoring, fatigue, or sleepiness. Nine of them were taking sertraline (75–200 mg/day), six escitalopram and one citalopram (10–30 mg/day), five fluoxetine (10–30 mg/day), one duloxetine (30 mg/day), and one trazodone (100 mg/day). Treatment duration ranged between 2 and 12 months. A positive family history for RLS was reported for two children while, for another, a family history positive for PLMD was reported; however, none of the children in this group was diagnosed with RLS.

A second sample of 21 drug-naïve RLS children with a total LMS index ≥ 15/h was selected from our database (including children recruited by the authors at their respective centers, who have been successfully used for previous studies [12]) of age and sex matched with the above group (11 girls and 10 boys, mean age 13.6 years, SD 2.96). RLS was diagnosed following standard criteria, including a careful exclusion of mimics [27]. None of these children had another medical or psychiatric disorder.

Finally, another age- and sex-matched group of 35 control children (17 girls and 18 boys, mean age 14.3 years, SD 2.79) was selected from the same database. None of these children was taking drugs or was affected by another medical, psychiatric, or sleep disorder other than snoring. In all three groups, physical and neurological examinations were done. In the control group, no selection was made based on the amount of LMS.

The sex composition and age of the groups were not statistically significant (chi-square = 0.107, NS) and (Kruskal–Wallis analysis of variance [ANOVA] $H_{2,79}$ = 1.492, NS), respectively. All children had an apnea-hypopnea index < 1/h. In addition, sleep apnea was ruled out in each case, independently, by two different sleep experts. No sample size/power analysis was possible because this was a convenience sample. The study was approved by the local ethics committee and all subjects or their parents/guardians had provided informed written consent.

Polysomnographic recording

All subjects underwent a routine full-night PSG recording in the sleep lab, including electromyogram of the submentalis and both TA muscles and electrocardiogram. Sleep stages and arousals were visually scored following standard criteria [28]. Leg movements activity during sleep was detected and scored according with the most recent criteria by the World Association of Sleep Medicine [22], followed by the calculation of a series of parameters including:

1. Total LMS index, n/hour;
2. PLMS index, n/hour, LMS included in regular and non-interrupted sequences of at least four with onset-to-onset IMI 10–90 s;
3. PLMS/arousal index, n/hour, an arousal event, and an PLMS event were considered to be associated with each other when there was less than 0.5 s between the end of one event and the onset of the other event, regardless of which was first;
4. Short-interval LMS (SILMS) index, n/hour, LMS with preceding IMI < 10 s;
5. Isolated LMS (ISOLMS) index, n/hour, LMS with IMI >90 s, and LMS with IMI 10–90 s not meeting all the criteria for PLMS;

6. Percentage of bilateral PLMS, PLMS formed by two to four monolateral LMS from the two legs overlapping each other within 0.5-s windows with a combined total duration < 15 s;
7. Periodicity index, PLMS/total LMS ratio;
8. PLMS duration, s;
9. SILMS duration, s;
10. ISOLMS duration, s;
11. PLMS index in REM sleep, n/hour;
12. PLMS index in non-rapid eye movement sleep (NREM) sleep, n/hour.

All sleep leg movement onset-to-onset IMIs, from each recording, were counted, in each subject, for 2-second classes ($0.5 < IMI \leq 2$, $2 < IMI \leq 4$, $4 < IMI \leq 6$, …, $98 < IMI \leq 100$) and group grand averages were obtained, which were used for statistical analysis. Finally, hourly, night-distribution histograms of the number of PLMS, during the first eight recording hours, were obtained for each group of subjects.

Statistical analysis

The nonparametric Kruskal–Wallis ANOVA was used for between-group comparisons, followed by post hoc comparisons by the Mann–Whitney test. Frequencies were compared with the chi-square test.

Subsequently, in the group of children on antidepressants, we checked for possible simultaneous associations of age, sex, family history of RLS/PLMD, and duration and type of treatment, used as independent factors/predictors, with PLMS index, total LMS index, or Periodicity index, considered as dependent variables, by means of the General Regression Models module offered by the commercially available software STATISTICA v.6, StatSoft Inc. This module allows to build models for designs with categorical predictor variables, as well as with continuous predictor variables. For each dependent variable, the statistical significance of the association of each independent factor was obtained by considering the effect of the other independent factors.

Results

Table 1 shows the comparison between sleep staging parameters found in the three age groups of children. Children on serotonergic antidepressants had longer sleep latency and higher number of stage shifts than both controls and RLS children; in addition, they had decreased sleep efficiency and sleep stage N2, with respect to controls only. Arousals were also highest in children on antidepressants and lowest in controls; all between-group comparisons showed statistically significant differences.

The same groups were also compared for their LMS parameters (Table 2) and children taking antidepressants showed higher PLMS (especially during NREM sleep), PLMS/arousal, and total LMS indexes than both controls and RLS children, as well as higher SILMS and ISOLMS indexes than controls. Periodicity index was highest in children on antidepressants, followed by those with RLS and, then by controls. We also performed a post hoc power analysis based on the total PLMS index values found in the three groups of children (with their sample size), characterized by an effect size $f = 0.557$, and we found that the differences between our groups could have been detected with a power of 95% at a significance level $\alpha = 0.005$.

The analysis of the distribution of IMIs (Figure 1) showed the presence, in children taking antidepressants, of two well-defined peaks, the first between 2 and 10 s, with a maximum at around 4 s, and the second, corresponding to PLMS, between approximately 10 and 60 s, with a maximum at around 20 s. This second peak was much less evident in RLS patients and not evident at all in controls, while the peak at around 4 s was very similar in children on antidepressants and those with RLS, but lower in controls. The differences between the groups were generally highly significant in correspondence of the 10–60 s peak.

Figure 2 shows an example of the PSG appearance of LMS in a representative case of a child on an antidepressant and another child with RLS. In the first case, clearly periodic activity is evident with all IMI ranging approximately 10–30 s, while in the second case (RLS) leg movements appear to be separated by more irregular IMI and often shorter than 10 s.

The assessment of the hourly distribution of PLMS during the night (Figure 3) disclosed that both groups of children taking antidepressants and with RLS show a decrease as sleep progresses; however, children on antidepressants have a generally higher number of PLMS than both RLS children and controls, throughout the night. Also, the slope of the decrease

Table 1. Sleep parameters found in the three groups of subjects

	1. Controls (n = 35)		2. Antidepressants (n = 23)		3. RLS (n = 21)		Kruskal–Wallis ANOVA		Mann–Whitney test, P<		
	Mean	SD	Mean	SD	Mean	SD	$H_{2,79}$	P<	1 versus 2	2 versus 3	1 versus 3
Time in bed, min	515.7	55.16	519.0	40.38	513.9	68.25	0.21	NS			
Sleep period time, min	483.0	47.74	474.6	39.48	478.9	62.57	0.34	NS			
Total sleep time, min	451.6	61.97	406.1	76.21	433.4	85.33	5.02	NS			
Sleep latency, min	18.5	15.64	43.9	25.44	26.5	30.28	15.16	0.0005	0.00001	0.01	NS
Stage R latency, min	122.3	60.36	141.4	85.61	151.3	97.72	1.56	NS			
Stage shifts/hour	7.3	3.97	15.1	5.94	11.2	5.19	26.53	0.0001	0.000002	0.025	0.002
Awakenings/hour	2.3	2.13	5.1	3.81	3.5	2.96	11.12	0.004	0.002	NS	0.04
Sleep efficiency, %	87.7	9.28	78.2	13.12	84.6	13.45	7.75	0.02	0.005	NS	NS
Stage W, %	6.5	8.98	14.8	12.44	9.6	12.33	5.62	NS			
Stage N1, %	5.6	2.96	10.4	9.43	6.6	5.54	4.01	NS			
Stage N2, %	48.2	8.29	40.6	11.20	43.4	11.26	8.85	0.012	0.009	NS	0.03
Stage N3, %	22.3	4.74	20.0	7.83	24.3	8.77	2.060	NS			
Stage R, %	17.4	5.11	14.2	6.72	16.1	7.81	1.808	NS			
Arousals/hour	6.2	4.47	19.4	13.60	11.1	5.22	33.918	0.0001	0.000001	0.01	0.00012

Table 2. Leg movement activity during sleep parameters found in the 3 groups of subjects

	1. Controls (n = 35)		2. Antidepressants (n = 23)		3. RLS (n = 21)		Kruskal–Wallis ANOVA		Mann–Whitney test, $P<$		
	Mean	SD	Mean	SD	Mean	SD	$H_{2, n=79}$	$P<$	1 versus 2	2 versus 3	1 versus 3
PLMS index, n/hour	1.51	1.62	14.50	17.73	5.90	4.69	42.09	0.0001	0.000001	0.0065	0.0002
PLMS/arousal index, n/hour	0.2	0.30	1.5	1.43	0.7	0.56	30.165	0.000001	0.000001	0.01	0.00012
SILMS index, n/hour	3.18	2.57	7.75	7.54	6.36	4.74	15.56	0.0004	0.005	NS	0.0002
ISOLMS index, n/hour	8.23	3.15	15.59	7.65	13.90	5.16	28.11	0.0001	0.00001	NS	0.00002
Total LMS index, n/hour	12.92	6.09	37.84	25.78	26.16	11.66	41.67	0.0001	0.000001	0.04	0.000005
Bilateral PLMS, %	30.91	23.80	32.99	21.74	28.49	21.94	0.57	NS			
Periodicity index	0.102	0.098	0.374	0.189	0.211	0.137	32.02	0.000001	0.00011	0.0042	0.0025
PLMS duration, s	2.69	1.00	2.70	0.81	2.76	1.27	0.01	NS			
SILMS duration, s	2.55	0.78	3.09	0.84	2.72	1.00	4.97	NS			
ISOLMS duration, s	3.04	0.78	3.47	1.09	3.01	0.99	1.34	NS			
REM PLMS index, n/hour	0.54	1.66	4.31	5.46	3.28	5.77	16.08	0.001	0.0053	NS	0.045
NREM PLMS index, n/hour	1.70	1.96	16.17	19.81	6.70	5.63	41.69	0.000001	0.00013	0.005	0.0002

PLMS, periodic leg movements during sleep; SILMS, short-interval leg movements during sleep; ISOLMS, isolated leg movements during sleep; LMS, leg movements during sleep.

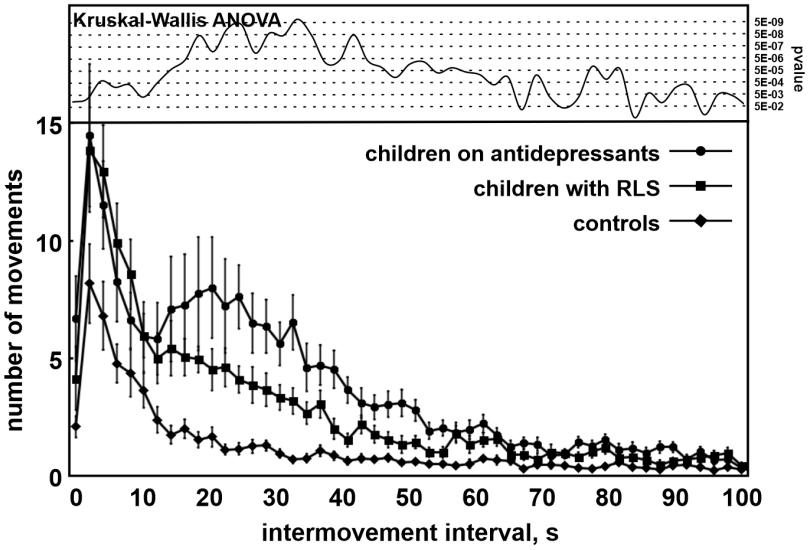

Figure 1. Distribution of intervals between consecutive leg movements during sleep in children taking serotonergic antidepressants, with RLS, and controls. Data are shown as mean (circles, squares, and diamonds) and standard errors (whiskers). The $H_{2,79}$ values obtained with the Kruskal–Wallis ANOVA, comparing the three groups and computed for all points of the graphs, are shown on the top, along with their significance level (p value).

seems to be more pronounced in children antidepressant (slope = −1.77) or with RLS (slope = −1.11) than in controls (slope = −0.20), but the difference did not reach statistical significance.

Finally, Table 3 reports the analysis of the effect of some independent factors on PLMS index, Periodicity index, or total LMS, used as dependent variables, in the group of children taking antidepressants. Among the factors tested, age was found to be significantly associated with increased PLMS index and Total LMS index, with a "large" correlation coefficient (following the indications by Cohen [29], correlations 0.10, 0.30, and 0.50 are considered to correspond to small, medium, and large sizes, respectively). Among the three antidepressants tested (the remaining were taken by only one child each), fluoxetine was found to be positively associated with PLMS index and Total LMS index, also with a large correlation coefficient value.

Discussion

In agreement with our original hypothesis, this study demonstrates that children taking serotonergic antidepressants show higher periodicity leg movements than children with RLS and controls and have a higher number of PLMS throughout the night, when compared to the other two groups.

All the antidepressants used by the children in this study increase serotonin levels. Four belong to the selective serotonin reuptake inhibitors (sertraline, escitalopram, citalopram, and fluoxetine), one is a serotonin/norepinephrine receptor inhibitor (duloxetine), and one has serotonergic and histaminergic properties (trazodone). Serotonin has been implicated in many different functions including behavior, mood regulation, cognitive function, motor activity, and sleep/wake cycle. There is an important relationship between serotonin and dopamine. Serotonergic projections from the raphe nuclei are known to

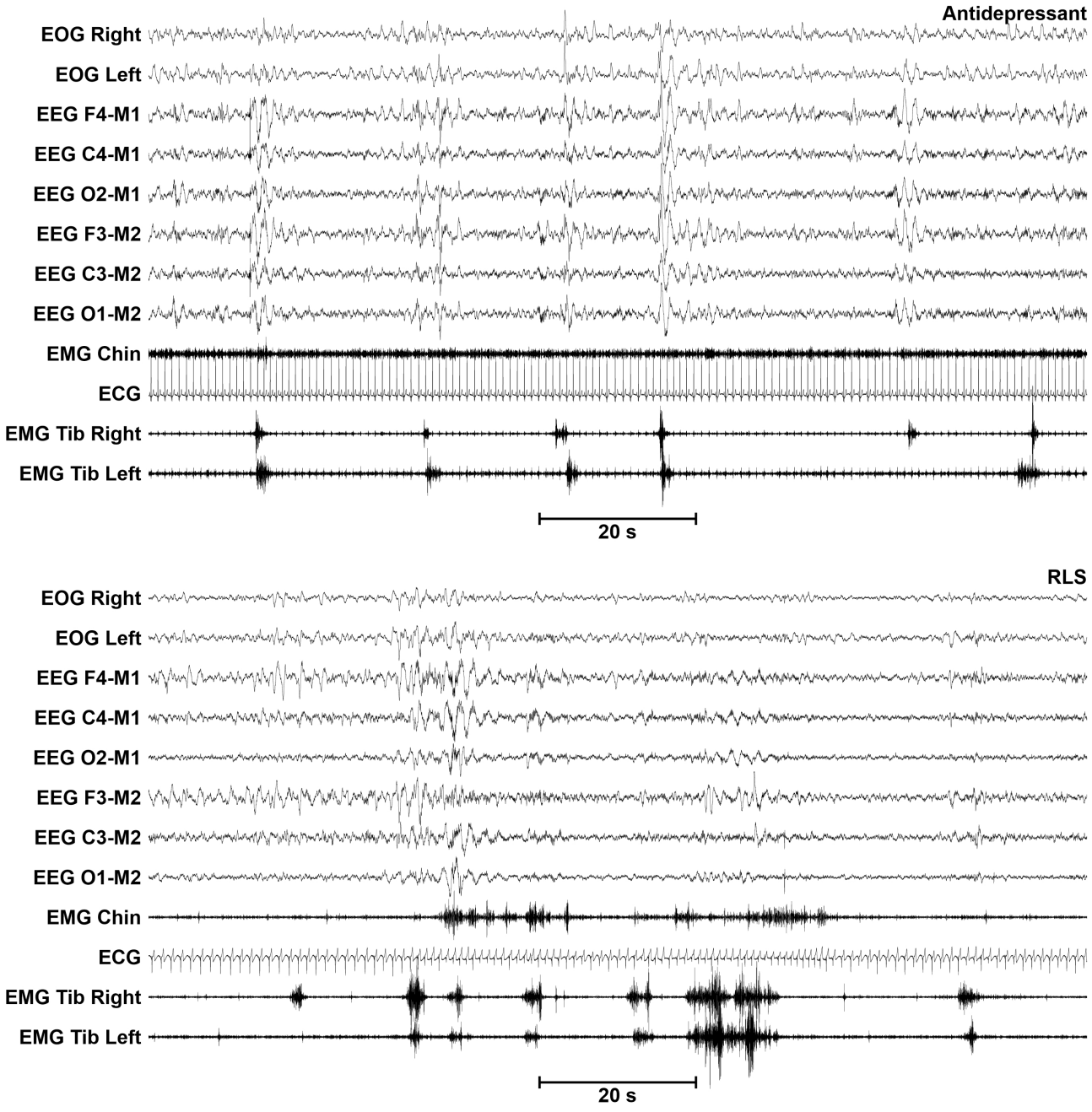

Figure 2. PSG appearance of leg movements during sleep in representative cases of a child on a serotonergic antidepressant (upper panel) and a child with RLS (lower panel).

modulate dopaminergic neurons. The projections from the raphe nuclei extend to the substantia nigra, ventral tegmental area, nigro-striatal pathway, and mesolimbic dopaminergic system [30]. Deficiency in serotonin then results in hyperactivity of the dopamine system (e.g. impulsive behaviors) [31]. Electrophysiologically, a decrease in serotonin increases the discharge rate of dopaminergic neurons in the ventral tegmental area, demonstrating the inhibitory control of serotonin on dopamine [32]. Both serotonin agonists and selective serotonin reuptake inhibitors are capable of inhibiting the activity of dopaminergic neurons but not everywhere and not at the same rate. Experiments using fluvoxamine, paroxetine, and sertraline showed a dose-dependent inhibition of some dopaminergic neurons, but not all [33], demonstrating that the modulation of dopaminergic activity by the serotonergic system is complex, and very likely complicated by the various receptor subtypes present in the dopaminergic nuclei. The role of dopaminergic pathways in the emergence of PLMS has been postulated to be localized in the hypothalamic A11 projections to the spinal cord [34]. These projections also receive modulatory fibers from serotonergic, adrenergic, and gamma aminobutyric acid (GABA) ergic pathways [35].

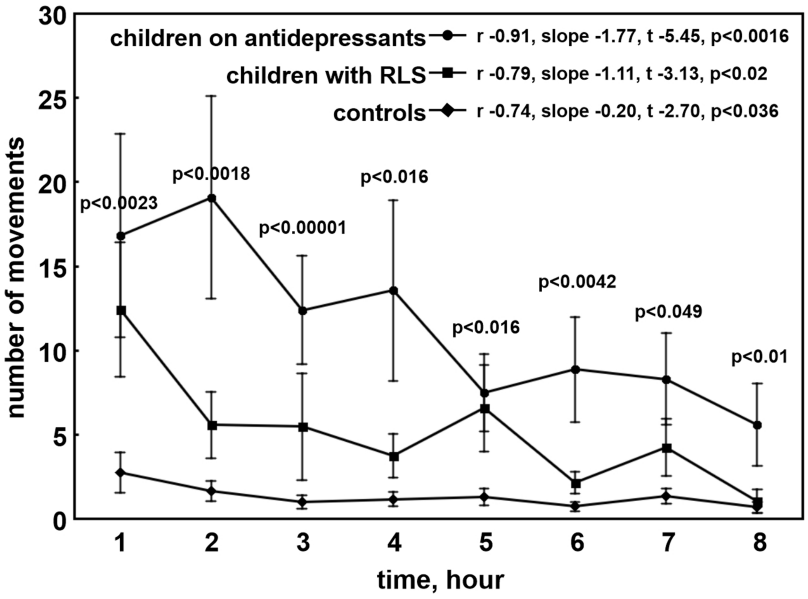

Figure 3. Number of PLMS recorded during the first 8 h of sleep in children taking serotonergic antidepressants, with RLS, and controls. Data are shown as mean (circles, squares, and diamonds) and standard errors (whiskers). The *p* values obtained with the Kruskal–Wallis ANOVA, comparing the three groups and computed for all points of the graphs, are also shown.

Table 3. Association between PLMS index, Periodicity index, or total LMS and age, sex, RLS family history, and antidepressant treatment type and duration, in the group of 23 patients taking antidepressants

	PLMS index		Periodicity Index		Total LMS index	
Factor	Partial correlation	P<	Partial correlation	P<	Partial correlation	P<
Age	0.536	0.032	0.422	NS	0.515	0.041
Sex, male	–0.361	NS	–0.141	NS	–0.194	NS
RLS/PLMD family history	0.358	NS	0.173	NS	0.373	NS
Sertraline	–0.246	NS	–0.069	NS	–0.158	NS
Escitalopram/citalopram	–0.269	NS	0.157	NS	–0.494	NS
Fluoxetine	0.596	0.015	0.309	NS	0.516	0.041
Treatment duration	–0.233	NS	0.320	NS	–0.431	NS

PLMS, periodic leg movements during sleep; LMS, leg movements during sleep.

Previous studies have confirmed a causal relationship between SSRIs and PLMS [16, 25, 36]. In a study using sertraline, 18% of participants showed elevated PLMI [37]. Although not fully understood, the mechanism of emergence of PLMS in patients taking antidepressants may be secondary to an increase in serotonin resulting in a decrease in dopamine signals in predisposed individuals. Indeed, not all subjects taking serotonergic antidepressants show increased PLMS and, although this effect might be transient and limited in duration [16], the genetic predisposition of each individual might play an important role [38]. It should be mentioned here that not only PLMS have been reported as a side effect of antidepressant drugs but are also clinically relevant for RLS [39], even if the relationship between RLS and depression is certainly complex and bidirectional [40, 41]. Also, patients with RLS are often on antidepressants. It has been reported that 28.5% of RLS patients who take medications are on antidepressants [42]; the analysis of this group of subjects would constitute a fascinating topic for future research.

Of pathogenic and clinical interest is the finding in one study that PLMS decreased significantly in children with iron therapy, whether they were on serotonergic antidepressants or not [43]. Moreover, the dopaminergic antidepressant, bupropion, is not associated with increased PLMS and may actually reduce PLMS and symptoms of RLS, as indicated by several reports in both adults [25, 44–46] and children [24]. Further studies are needed to clarify these important aspects and, if confirmed, antidepressant-induced PLMS might be considered to be also a marker of increased risk to develop RLS in future years, independently from the use of drugs, in consideration of the strictly entangled genetic bases of PLMS and RLS that is becoming clearer with recent genome-wide analyses [47, 48].

It should finally be considered that, in adults, it has already been reported that antidepressants are associated with a generalized increase in motor activity during sleep, including REM sleep without atonia [49] and bruxism [42], as well as an increased leg motor activity, as discussed above and confirmed also in children by our findings. Moreover, even if previous data on sleep arousals during long-term treatment with serotonergic antidepressants are scarce, there is evidence of an increased arousal level in the resting electroencephalography [50, 51], which seems to agree with our finding of an increased number of arousals in children taking antidepressants. This supports the diffuse effect of antidepressants on dopamine, mediated by the increased serotonergic activity that is not limited at the level

of the A11 hypothalamic nucleus. Indeed, they may also modulate the activity of glutamatergic subcoeruleus nucleus neurons controlling muscle atonia, through gamma aminobutyric acid GABAergic and glycinergic motoneurons [52], or the complex mechanism generating bruxism in which several brainstem areas, including the reticular pontis oralis, pontis caudalis, and parvocellularis, and neurotransmitters, such as serotonin, dopamine, GABA, and noradrenaline, play important roles [53].

Fluoxetine, rather than the other SSRIs tested in this study, was found to be positively associated with increased PLMS and total LMS. It should be noticed that most SSRIs, including citalopram, escitalopram, and sertraline, have half-lives close to 24 h, while fluoxetine has a half-life of 1–4 days. In addition, fluoxetine has the highest inhibitory constant for inhibition of monoamine uptake among the SSRIs used by the children recruited for this investigation [54]. It should also be considered that, in this study, the statistical power to exclude that the other drugs have a similar but less evident effect, as already shown in adult studies, was limited. A larger number of subjects taking each different serotonergic antidepressant might have allowed detection of a statistically significant effect size for all or most of them. This needs to be assessed in future studies; however, these findings parallel those on chin tone involvement, more evident with fluoxetine, recently reported by our group [55], and point to a generalized increase in motor activity in children taking serotonergic antidepressants. Finally, it cannot be excluded that a differential effect of the different antidepressants might exist between children and adults or be based on dosage. High doses of serotonergic medications result in serotonin syndrome, which is characterized by very high motor tone [56].

Some other limitations of this study should also be acknowledged to correctly consider its value: single-center experience, limited number of patients, and incomplete representation of clinically relevant antidepressants.

Conclusion

Our findings demonstrate that serotonergic antidepressants use in children is associated with PLMS that have adult features, similar to those usually seen in adults with RLS and rarely seen in children with RLS until late adolescence. This antidepressant accelerated "maturation" of PLMS in selected children (we only recruited children with increased LMS) might indicate an increased susceptibility to develop RLS symptoms in the future and deserves additional studies to be better interpreted. Long-term prospective data need be obtained with the aim to fully understand their clinical meaning.

Disclosure Statement

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