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Daytime dysfunction in children with restless legs syndrome

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ABSTRACT

We investigated daytime dysfunction in children with restless legs syndrome (RLS) and the effects of treatment primarily with iron supplements on RLS symptoms and daytime dysfunction. We recruited 25 children with RLS (male:female = 6:19, mean age at study onset: 12.3 years) for this prospective study, assessing their demographics, symptomatic characteristics, serum ferritin levels, and daytime functioning using the ADHD Rating Scale IV (ADHD-RS-IV), the Pediatric Symptom Checklist (PSC), and the Pediatric Quality of Life Inventory (PedsQL™). Children with RLS were compared with 28 controls (male:female = 10:18, mean age: 13.2 years) on these measures, pre- and post-treatment. Before treatment, ADHD-RS-IV (all ps < 0.05) and PSC scores ($p < 0.05$) were significantly higher and PedsQL™ scores (all ps < 0.05) significantly lower in the RLS group than in the control group. Eight and one of the RLS group had abnormally high PSC and ADHD-RS-IV scores, respectively. Following treatment, participants' daytime function had improved to levels similar to those of controls. Sixteen out of twenty-three cases were successfully treated primarily with iron supplement. Some children with RLS have daytime dysfunction; however, this can be treated with iron supplements.

1. Introduction

Restless legs syndrome (RLS) is a sensorimotor disorder characterized by an irresistible urge to move the legs. Following the establishment of the diagnostic criteria for child RLS in a workshop held at the National Institute of Health (NIH) in 2003 [1], a significant number of studies on child RLS have been conducted [2–4]. The Peds REST study, conducted in the United States (US) and the United Kingdom (UK), revealed that the prevalence of definite RLS was 1.9% in those aged 8 to 11 and 2.0% in those aged 12 to 17 [5]. In a study on children in Turkey, the prevalence of definite RLS was 1.7% in those aged 10 to 12 and 3.2% in those aged 13 to 19 [6]. These study results indicate that RLS is not a rare condition in childhood, despite a relatively lower rate in this age group compared with that in adults [7,8].

Recent studies have noted that symptoms of attention deficit hyperactivity disorder (ADHD) are frequently complicated by child RLS [5]. Moreover, RLS symptoms have been reported in 12–35% of children with ADHD [9,10]. These results suggest a possible pathological association between RLS and ADHD [11]. However, neither the type of children with RLS at risk of developing ADHD symptoms nor the severity profile of ADHD symptoms in children with RLS has yet been clarified. Moreover, the impact of RLS on children's daytime dysfunction remains unclear.

Considering these issues, we set out this study to evaluate daytime function in children with RLS using the following previously validated measures: the Japanese version of the ADHD Rating Scale IV (ADHD-RS-IV) to record participants' levels of ADHD symptoms [12,13]; the Japanese version of the Pediatric Symptom Checklist (PSC), an measurement of psychosocial problems in children [14,15]; and the Japanese version of the Pediatric Quality of Life Inventory (PedsQL™), version 4, which evaluates quality of life (QOL) in children [16,17]. We then analyzed the association between the diurnal distribution of RLS symptoms and these daytime function measures and how these scores changed from pre- to post-treatment. In addition, we discussed the effectiveness of iron treatment – which is reportedly effective for treating both RLS and ADHD in patients with low serum ferritin levels [4,18] – not only on reducing symptoms of child RLS but also reducing the above-indicated daytime dysfunctions.

2. Methods

This study was approved by the Ethical Committee of the Neuropsychiatric Research Institute, Tokyo, Japan. After receiving a thorough explanation about the purpose and procedure of the present study, all participants and their parents returned written informed consent for participation.

Participants with RLS were 25 children 18 years of age or younger (6 boys, 19 girls; age range: 7–18; mean age: 12.3 years) who visited our

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outpatient clinic seeking for the treatment of the disorder between September 2009 and March 2011. RLS was diagnosed using the criteria for adult RLS in the International Classification of Sleep Disorders, Second Edition (ICSD2) for participants older than 12 years, and using the pediatric criteria for participants 12 years old or younger [1]. Participants' siblings with no symptoms of RLS were used as controls. Participants and controls were confirmed by attending physicians to be completely free of other mental, physical, and sleep disorders at the time of investigation.

All participants with RLS were diagnosed as having the disorder after detailed clinical interviews by at least two psychiatrists with expertise in sleep disorders followed by nocturnal polysomnographic (n-PSG) recordings and suggested immobilization tests (SIT). As a Japanese version of the International Restless Legs Syndrome Severity Scale (IRLS) for children [3] was not available at the time of the assessment, RLS symptoms were evaluated using the IRLS for adults (version 2.1) [19] after a thorough discussion of symptoms and daytime functioning with the participants and their parents. The ADHD-RS-IV, PSC, and PedsQL™ were completed by participants to evaluate their daytime functioning.

SITs and n-PSG recordings were performed as supportive measures for the diagnosis of RLS. SITs were performed between 21:00 and 22:00 on all the RLS participants, followed by n-PSG recordings between 22:00 and 06:00 before starting the treatment; both were conducted using Alice5 (Respironics, Inc., Murrysville, PA, USA) or Comet (Grass, Astro-Med, Inc., West Warwick, RI, USA) [20]. Sleep stages were scored according to the criteria of Rechtschaffen and Kales [21] and the American Sleep Disorders Association (ASDA) arousal criteria guidelines [22]. The periodic leg movement (PLM) index – that is, the number of PLMs per hour of sleep – was also calculated using the standard method [23].

The SIT was administered in order to measure both PLMs while awake (PLMW) and subjective discomfort due to RLS [24]. Leg movements during the SIT (SIT index) were scored according to the criteria defined by Michaud et al. [24]. During the SIT, leg discomfort was measured using a visual analog scale (VAS) [25].

Thus, the survey items in this study were as follows: gender; age of onset of subjective RLS symptoms; estimated duration of disease morbidity; presence/absence of family history of RLS; daytime function measures including the ADHD-RS-IV, PSC, and PedsQL™; serum ferritin level at the time of diagnosis; PSG variables including PLM index, SIT index, and SIT VAS max.

The Japanese version of the ADHD-RS-IV was scored using participants' parents' responses to 18 questions about their children's behavior. Parents responded to each question using the following scale: *never occurs* (0 points), *occurs sometimes* (1 point), *occurs frequently* (2 points), and *occurs very frequently* (3 points). We then calculated two subscale scores (Hyperactivity Disorder Rating Scale and Attention Deficit Rating Scale) and the total score of the ADHD-RS-IV from these results. Following the study by Takahashi et al. [26], we used the raw scores of the ADHD-RS-IV.

For the Japanese version of the PSC, participants' parents were asked to respond to 35 questions rating their child's level of psychosocial problems. Responses to each question were made using the following scale: *never occurs* (0 points), *occurs sometimes* (1 point), and *occurs frequently* (2 points); we then calculated the total PSC score. Regarding the PedsQL™ version 4, summary scores were compiled for the physical and psychosocial components of quality of life, which were formed from the 23 core scale items. Physical health scores were calculated from the 8 items relevant to physical function and psychosocial health scores from the 15 items representing affective, social, and school functions [16,17]. Responses to each item, which on the original scale range from 0 to 4, were converted into item scores of 0–100 (0 = 100; 1 = 75; 2 = 50; 3 = 25; 4 = 0) to adjust the range of possible scores from 0 (lowest QOL) to 100 (highest QOL). Then, summary scores for these two components (physical health and psychosocial health) and total scores were calculated by averaging the item scores.

In this study, the scores of the daytime function measures were first compared between all the participants with RLS (before treatment) and the control children. Using information about the diurnal distribution of RLS symptoms obtained from each RLS affected participant or his or her parents, we classified RLS participants into two groups (only at nighttime; day and night) depending on the presence or absence of symptoms from daytime to 18:00 and the period after 18:00; this classification was created by Tzonova et al. [27]. Then, the daytime function measures were compared again among the only-at-nighttime group, the day-and-night group, and the control group.

Referring to Konofal et al.'s comparison of the mean serum ferritin levels between controls and children with ADHD [18], 40 ng/mL of serum ferritin was set as a cut-off value for starting the administration of iron supplements in this study. Following at least three months after dosage fixation of the treatment drugs, participants' treatment outcomes were evaluated by comparing the scores of the IRLS as well as those of the ADHD-RS-IV, PSC, and PedsQL™ before and after treatment. Post-treatment scores were also compared with those of the control group. In this study, 50% responder was determined when a patient showed 50% or more of the decrease in IRLS after treatments according to previous reports [28,29].

2.1. Statistics

Changes in the scores of daytime function measures before and after treatment in RLS children were analyzed using a paired *t*-test. The scores of the controls and RLS children both before and after treatment were compared using a one-way analysis of variance (ANOVA) with age and sex treated as random effects and group as a fixed effect.

To compare daytime functioning among the only-at-nighttime group (before treatment), the day-and-night group (before treatment), and the control group, ANOVA and subsequent Bonferroni–Dunn post-hoc analysis were used. The IRLS scores before treatment were also compared between the former two-patient groups using an unpaired *t*-test.

SPSS Statistics software version 11.5 J for Windows (SPSS Inc., Chicago, IL, USA) was used for all analyses. A p-value of less than 0.05 was considered to indicate a statistically significant difference.

3. Results

In RLS children the mean age of onset of the symptoms was 8.9 ± 3.1 years old, and the duration of disease morbidity at the time of the survey was 3.4 ± 2.9 years. Six RLS children (24%) had a family history of RLS in their first-degree relatives. The mean serum ferritin level of all the RLS children at the time of diagnosis was 29.7 ± 19.1 ng/mL. Regarding the diurnal distribution of RLS symptoms, 15 RLS children (60%) reported experiencing symptoms both during the day and at night, while 10 RLS children (40%) experienced symptoms only at night. The mean PLM index on the PSG was 4.5 ± 7.3 per hour. No RLS children had sleep apnea syndrome. The maximum VAS score on the SIT was 44.0 ± 36.3, and the SIT index was 2.5 ± 6.6 per hour (Table 1).

The RLS children before treatment showed higher values than did the controls for total scores of the ADHD-RS-IV ($p < 0.05$), total PSC scores ($p < 0.05$), and scores on the Attention Deficit ($p < 0.05$) and Hyperactivity Disorder Rating Scales ($p < 0.01$; Table 2). On the other hand, the total, physical summary scale, and psychosocial summary scores of the PedsQL™ in the RLS children before treatment were significantly lower compare with the controls ($p < 0.05$). Only one RLS affected child before treatment scored 25 points on the ADHD-RS-IV, which is the cut-off for abnormal values [30,31]. As for the PSC, eight RLS children (32%) scored over 17 points, which is the cut-off for abnormal values [14,15].

Table 1
Descriptive variables of the participating children with RLS.

Sex: male/female (n)	6/19
Age at time of investigation (y)	12.3 ± 3.8 (7–18)
Age at self-reported onset of RLS (y)	8.9 ± 3.1 (3–16)
Duration of RLS morbidity (y)	3.4 ± 2.9 (1–12)
Diurnal distribution of RLS symptoms Only during nighttime (n)	10 (40)
During both daytime and nighttime (n)	15 (60)
Weekly occurrence of RLS symptoms (days)	5.5 ± 1.5 (2–7)
IRLS total score (points)	20.2 ± 3.2 (15–27)
Family history of RLS (n)	6 (24.0)
Serum ferritin level (ng/mL)	29.7 ± 19.1 (3.6–87.2)
Polysomnographic variables	
PLMI on PSG (/h of sleep)	4.5 ± 7.3 (0–23.6)
SIT VAS max value (full.100 mm)	44.0 ± 36.3 (0–100)
SIT index (/h)	2.5 ± 6.6 (0–27)

Continuous variables are expressed as mean ± SD
Parentheses for categorical variables indicate percentage, and those for continuous variables indicate range.
IRLS: International Restless Legs Syndromes Severity Scale
PLMI: periodic limb movement during sleep Index, PSG: polysomnogram
SIT: suggested immobilization test, VAS: visual analogue scale

Of all the RLS children, 23 received regular treatment for the disorder for three months or longer; their total IRLS scores after treatment were significantly lower than their scores before treatment ($p < 0.01$). Moreover, significant improvement was seen after treatment in ADHD-RS-IV total scores ($p < 0.05$) and scores of its both subscales (Hyperactivity Disorder Rating Scale, $p < 0.01$; Attention Deficit Rating Scale, $p < 0.05$); in the PedsQL™ total score ($p < 0.01$); and in the PSC scores (physical health summary score, psychosocial health summary score, and total score, $p < 0.01$). The one RLS child who had an abnormally high ADHD-RS-IV total score before treatment showed improvement with treatment such that it reached normal range, and of the eight participants who had abnormally high scores on the PSC before treatment, the scores of seven decreased to within the normal range after treatment. There were no significant differences in the daytime function scores between the RLS children after treatment and those in the controls, except that the Hyperactivity Disorder Rating Scale Scores were significantly lower in the former group than in the latter group ($p < 0.01$).

We compared IRLS scores before treatment between the two RLS symptom diurnal distribution groups before treatment and the daytime function measures between these two groups and the controls (Table 3). The results showed no significant difference in IRLS score between the two RLS groups ($t(1) = 1.11$, $p = 0.34$). However, there were significant differences in the scores of the Attention Deficit and Hyperactivity Disorder Rating Scales, as well as in the total score of the ADHD-RS-IV between these three groups (Attention Deficit Rating Scale: $F(2,17) = 7.9$, $p < 0.01$; Hyperactivity Disorder Rating Scale: $F(2,17) = 15.0$, $p < 0.01$; total score: $F(2,17) = 10.2$, $p < 0.01$). Post-hoc testing revealed that the scores of both Rating Scales and the total score of the ADHD-RS-IV in the day-and-night group before treatment were significantly higher than those in the control group (Hyperactivity Rating Scale: $p < 0.05$; Attention Deficit Rating Scale: $p < 0.05$; Total score: $p < 0.01$). The score on the Attention Deficit Rating Scale and the total score of the ADHD-RS-IV were also higher in the only-at-nighttime group before treatment compared with the controls ($p < 0.01$). Moreover, before treatment the Hyperactivity Disorder Rating Scale score was significantly higher in the day-and-night group than in the only-at-nighttime group ($p < 0.01$). For the PedsQL™, there were significant differences in the summary scores of the physical and psychosocial health components as well as in the total score between the RLS two groups before treatment and the controls (physical health summary score: $F(2,17) = 54.1$, $p < 0.01$; psychosocial health summary score: $F(2,17) = 56.9$, $p < 0.01$; total score: $F(2,17) = 70.8$, $p < 0.01$). Post-hoc testing revealed that the only-at-nighttime group before treatment clearly had lower summary scores of physical and psychosocial health and total score than did the other two groups ($p < 0.01$), with a significant but small difference in the physical health summary score between the only-at-nighttime and day-and-night groups ($p < 0.05$). The day-and-night group before treatment also showed lower values in these scores than the control group ($p < 0.01$). There was a significant difference in PSC score between the groups ($F(2,17) = 42.0$, $p < 0.01$), and the PSC scores in the only-at-nighttime group before treatment were higher than those in the day-and-night group before treatment ($p < 0.05$) and control groups ($p < 0.01$). The score in the day-and-night group before treatment was also higher than the score in the control group ($p < 0.01$).

Table 2
Comparison of daytime function measures between children with RLS and controls.

		Children with RLS Before/after treatment		Controls	Remarks
IRLS		20.0 ± 3.2	5.8 ± 4.9	–	a)**
ADHD	Attention	5.8 ± 3.2	4.2 ± 0.4	3.5 ± 0.3	a)*, b)*
	Hyperactivity	2.4 ± 2.1	0.5 ± 0.6	1.0 ± 0.2	a)**, b)**, c)**
	Total	8.2 ± 5.3	4.7 ± 2.5	4.6 ± 0.8	a)*, b)*
Peds QL	Physical	78.8 ± 6.0	88.4 ± 6.1	92.1 ± 0.9	a)**, b)*
	Psychosocial	68.1 ± 10.9	82.3 ± 7.4	83.5 ± 1.3	a)**, b)*
	Total	70.7 ± 8.9	83.8 ± 6.7	87.2 ± 1.1	a)**, b)*
PSC	Total	15.9 ± 8.6	7.8 ± 3.8	6.3 ± 0.8	a)**, b)*

IRLS: International Restless Legs Syndromes Severity Scale;
ADHD: Attention Deficit Hyperactivity Disorder Rating Scale IV;
Attention: Attention Deficit Rating Scale; Hyperactivity: Hyperactivity Disorder Rating Scale;
Peds QL: The Pediatric Quality of Life Inventory ver. 4;
Physical: physical health summary score; Psychosocial: psychosocial health summary score
PSC: Pediatric Symptom Checklist.
Values are expressed as mean ± SD.
a) before treatment vs. after treatment
b) before treatment vs. control
c) after treatment vs. control
** $p < 0.01$.
* $p < 0.05$.

Of the 23 RLS children who received treatment, iron treatment alone was initiated for 16 children with serum ferritin levels of less than 40 ng/mL at the time of RLS diagnosis. If a RLS child did not show clear improvement in RLS symptoms two months after starting the treatment, treatment content was changed to a combination of iron supplementation with clonazepam (CNZP) and/or pramipexole (PPX). Meanwhile, RLS children who had initial serum ferritin levels of higher than 40 ng/mL ($n = 7$) received either CNZP or PPX, but no iron supplement.

Table 4 shows the rates of 50% responders to the treatments, which was calculated from the IRLS score at three months or later following dosage fixation divided by the IRLS score before treatment; this table also shows the participants who showed a complete remission of RLS symptoms. Of the 16 RLS children who received the treatment with the iron preparation alone, 8 (50%) were 50% responders. Of these, four (50%) showed a complete remission of RLS symptoms with no recurrence at the final follow-up observation conducted three or more months after completing treatment. The remaining eight RLS children did not experience adequate improvement with iron treatment alone and, therefore, received the combination treatment. Of these, six continued to receive the two-drug combination therapy during the follow-up period; five of these RLS children (83.3%) then became 50% responders. Two RLS children, who did not show sufficient improvement of RLS symptoms even with the two-drug combination therapy, received a three-drug combination (iron, CNZ, and PPX), after which both became 50% responders.

In five of the seven RLS children with initial serum ferritin levels over 40 ng/mL, CNZP alone was regularly administered for three months or longer. Four of these RLS children (80%) became 50% responders under this treatment. The remaining two RLS children received PPX alone; of these RLS children, one was judged to be a 50% responder (50%). Two of five RLS children treated with CNZP alone (40%) and

Table 3
Comparison of IRLS score and daytime function measures between two RLS symptom diurnal distribution groups before treatment and controls.

		Distribution of RLS symptoms		Controls	Statistics
		Only at nighttime	Both nighttime and daytime		
IRLS		21.4 ± 0.87	19.7 ± 0.7	–	NS
ADHD	Attention	6.4 ± 0.66	5.2 ± 0.5	3.5 (0.3)	b)**, c)*
	Hyperactivity	1.6 ± 0.34	3.0 ± 0.28	1.0 (0.2)	a)**, c)**
	Total score	8.0 ± 0.9	8.2 ± 0.7	4.6 (0.8)	b)**, c)**
Peds QL	Physical	76.1 ± 1.5	80.4 ± 1.2	92.1 (0.9)	a)*, b)**, c)**
	Psychosocial	59.6 ± 2.2	73.3 ± 1.7	83.5 (1.3)	a)**, b)**, c)**
	Total score	63.7 ± 1.76	75.1 ± 1.5	87.2 (1.1)	a)**, b)**, c)**
PSC		20.5 ± 1.4	12.5 ± 1.1	6.3 (0.8)	a)*, b)**, c)**

IRLS: International Restless Legs Syndromes Severity Scale
ADHD: Attention Deficit Hyperactivity Disorder Rating Scale — IV
Attention: Attention-Deficit Rating Scale, Hyperactivity: Hyperactivity Disorder Rating Scale,
Peds QL: The Pediatric Quality of Life Inventory ver.4
Physical: physical health summary score, Psychosocial: psychosocial health summary score
PSC: Pediatric Symptom Checklist
NS: not significant
Values are expressed as mean ± SD.
a) only at nighttime vs. during both nighttime and daytime
b) only at nighttime vs. control
c) during both nighttime and daytime vs. control
** $p < 0.01$.
* $p < 0.05$.

one of two RLS children treated with PPX alone (50%) showed a complete remission of RLS symptoms with the regular administration of these drugs.

4. Discussion

In this study, we investigated ADHD scores in children diagnosed with RLS before treatment and the change in the scores following RLS treatment. Moreover, we aimed to identify the impact of RLS in the affected children on other daytime functioning measures. We found that, although their ADHD scores before treatment were significantly higher in comparison with the control group, only one RLS participant showed a pathologically high ADHD-RS-IV score [30,31]; the other participants scored within the normal range even before treatment. Thus, pathological ADHD symptoms secondary to RLS were relatively rare among Japanese children with RLS in the present study. However, the fact that hyperactivity scale scores before treatment were higher in the day-and-night group than in the only-at-nighttime group might indicate that ADHD scores increase depending on the existence of RLS symptoms during the daytime, although they mostly remained within the normal range.

Interestingly, RLS symptoms were observed during the daytime in more than half of the children with RLS before treatment. Generally, the more severe the RLS, the earlier in the day the symptom occurs [32,33]. However, we found no difference in IRLS scores, which measure RLS severity, between the only-at-nighttime and the day-and-night groups before treatment. Therefore, the daytime occurrence of RLS symptoms did not seem to depend on the aggravation of the disorder. The reason for this phenomenon is unclear. However, considering that a decrease in central nervous system dopamine receptor function at night may contribute to the concentrated occurrence of RLS symptoms during the night in adults [33], this diurnal change in dopamine receptor function possibly remains immature in RLS children due to their less-developed central nervous systems.

Of note is that the children with RLS before treatment in this study had significantly higher PSC scores than did the control group. Furthermore, more than one-third of them scored above the cut-off for psychosocial problems before treatment. This suggests that a certain number of children with RLS could develop psychosocial problems rather than ADHD-like symptoms. In addition, the physical, psychosocial, and total PedsQL™ scores were significantly lower in the RLS children before treatment than those in the control group. In the RLS children who

Table 4
Treatment outcome of the participating RLS children (n = 23).

	50% responder	Complete disappearance	Daily dose of treatment drug
Patients with <40 ng/mL ferritin level (n = 16)			
Fe treatment (N)			
Fe alone	8/8 (100%)	4/8 (50.0%)	Fe: 56.25 mg/day(50–100 mg)
Fe + CNZP	3/4 (75.0%)	1/4 (25.0%)	Fe: 50 mg/day (50 mg) CNZP: 0.3 mg/day (0.1–0.5 mg)
Fe + PPX	2/2 (100%)	0/2 (0%)	Fe: 50 mg/day (50 mg) PPX: 0.093 mg/day (0.0625–0.125 mg)
Fe + PPX + CNZP	2/2 (100%)	0/2 (0%)	Fe: 50 mg/day (50 mg) PPX: 0.093 mg/day (0.0625–0.125 mg) CNZP: 0.21 mg/day (0.125–0.3 mg)
Patients with ≧40 ng/mL ferritin level (n = 7)			
CNZP alone	4/5 (80.0)	2/5 (40.0%)	CNZP: 0.47 mg/day (0.1–1.0 mg)
PPX alone	1/2 (50.0%)	1/2 (50.0%)	PPX: 0.14 mg/day (0.031–0.25 mg)

Daily dose of drugs are shown as mean (range).
Fe: sodium ferrous citrate; PPX: pramipexole; CNZP: clonazepam.
50% responder: Patients in whom IRLS score after treatment decreased to 50% or less of the value before treatment.
Complete disappearance: Patients who showed a complete disappearance of RLS symptom after treatment.

received treatment, the scores of the PSC and PedsQL™ after treatment had clearly improved, reaching levels quite similar to those of the control group. Thus, the diagnosis and treatment of RLS is thought to be important for solving the secondary daytime dysfunctions caused by this disorder.

Overall, our RLS children responded well to small doses of the therapeutic drugs including iron, clonazepam, or pramipexole, or some combination of these drugs. In particular, 50% of participants with initial serum ferritin levels less than 40 ng/mL became 50% responders after iron treatment alone, and a complete remission of symptoms was observed in four RLS children even after discontinuing the iron treatment. This finding is quite consistent with the results of previous studies [4,34]. Therefore, iron supplementation treatment should be given top priority as a therapeutic tool for childhood RLS, especially for patients with low serum ferritin levels. Iron deficiency in children is easily overlooked as they often have naturally low serum ferritin levels [4,11,18]. Thus, we want to emphasize the necessity of checking serum ferritin levels before deciding a treatment plan for children with RLS.

This study has some limitations. First, as mentioned above, we used the adult version of the IRLS because the pediatric version of the scale has not yet been established in Japan. It is possible that the IRLS scale does not precisely measure the severity of RLS in children. However, we believe that our measurement data was consistent with participants' actual symptoms, because we carefully interviewed participants and their parents regarding their RLS symptoms and the consequences thereof. Second, this was not a randomized controlled study; therefore, a placebo effect [35] might be implicated in the effectiveness of the drugs. Third, since patients from a single institution were included in this study, our study sample might not be representative of children with RLS in general. Fourth, a serum ferritin level of 40 ng/mL was tentatively defined as the cut-off level for initiating iron supplement treatment in this study. However, it is possible that we should have increased the dose of iron preparation for those participants who did not initially respond to iron monotherapy. In addition, we could not follow up on serum ferritin levels in the children with RLS. Finally, although our control subjects did not have any RLS-related symptoms, sibling controls might not be ideal because they possibly have a genetic predisposition to the disorder.

In the present study, ADHD scores RLS children increased depending on the severity of their daytime RLS symptoms, but only one RLS child had a pathologically high ADHD score. Meanwhile, the RLS participants reported psychosocial problems or deteriorated QOL. Many of the RLS children showed lower serum ferritin levels, and RLS symptoms were improved by treatment primarily with iron supplements in more than half of the affected children, leading to normalized daytime functioning. These findings encouraged us to emphasize the necessity of early diagnosis and treatment of child RLS. Future research should aim to establish an appropriate cut-off serum ferritin level for initiating iron supplement treatment for children with RLS.

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