Journal of the Neurological Sciences 336 (2014) 232–236

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Daytime dysfunction in children with restless legs syndrome

Naomichi Furudate [a,b], Yoko Komada [a,c], Mina Kobayashi [a,b,c], Shun Nakajima [a,b,c], Yuichi Inoue [a,b,c,*]

[a] Department of Somnology, Tokyo Medical University, Tokyo, Japan
[b] Department of Psychiatry, Tokyo Medical University, Tokyo, Japan
[c] Japan Somnology Center, Neuropsychiatric Research Institute, Tokyo, Japan

ARTICLE INFO

Article history:
Received 4 September 2013
Received in revised form 28 October 2013
Accepted 1 November 2013
Available online 11 November 2013

Keywords:
Restless legs syndrome
Children
Attention deficit hyperactivity disorder
Psychosocial problems
Quality of life
Iron

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

* Corresponding author at: Department of Somnology, Tokyo Medical University, 6-1-1 Shinjuku, Shinjuku-ku, Tokyo 160-8402, Japan. Tel.: +81 3 3351 6141; fax: +81 3 3351 6208.
E-mail address: inoue@somnology.com (Y. Inoue).

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http://dx.doi.org/10.1016/j.jns.2013.11.001

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].