

## A case of restless legs syndrome in a child presenting with growing pains

Dong Soon Kim, M.D., Hong Beom Shin, M.D.\* and Young Min Ahn, M.D.

Department of Pediatrics, Eulji General Hospital, School of Medicine, Eulji University, Komoki Sleep Center\*, Seoul, Korea

### = Abstract =

Restless legs syndrome (RLS) is a common neurological sleep disorder in adults characterized by the following diagnostic criteria: an urge to move that is usually associated with unpleasant sensations and symptoms that are worse at rest, relieved by movement, and most severe at night. The definite diagnosis of RLS in children is stricter and consists of self-description of leg discomfort or the presence of 2 of 3 supportive criteria combined with 4 essential criteria for diagnosis in adults. RLS in childhood has often been misdiagnosed as growing pains or a part of normal development. As a result, physicians have often missed the chance for proper management. We diagnosed a case of RLS in a 5-year-old boy presenting with growing pains, whose mother was found to have had RLS since childhood. We confirmed RLS by using a polysomnograph, in which the indices of periodic limb movement syndrome (PLMS) and periodic limb movement during wakefulness (PLMW) were recorded to be compatible with RLS criteria. The patient's ferritin level was low normal, and his symptoms improved after taking iron supplements. (*Korean J Pediatr* 2008;51:1222-1227)

**Key Words :** Restless legs syndrome, Growing pains, Iron deficiency anemia, Ferritin, Polysomnograph

### Introduction

Restless legs syndrome (RLS) is a sensorimotor disorder that often has a profound impact on sleep<sup>1)</sup>. The etiology is unknown, but is related to iron deficiency anemia (IDA) and family history.

There are four essential criteria for diagnosis of RLS in adults<sup>1)</sup>. First, there should be an urge or unpleasant sensation to move the legs; second, those urges begin or worsen during periods of rest or inactivity; third, the urges are partially or totally relieved by movement; and fourth, they worsen in the evening or night. Criteria for the diagnosis of definite RLS in children are stricter. First, the child must meet all the essential criteria for RLS in adults. In addition, they should relate a description, in his or her own words, that is consistent with leg discomfort or meet two out of three supportive criteria. Supportive criteria include: (a) sleep disturbance for age, (b) a biological parent or sibling

with definite RLS, and (c) the child has a polysomnographically documented periodic limb movement (PLM) index of 5 or more per hour of sleep<sup>1)</sup>.

Attention-deficit/hyperactivity disorder (ADHD) and PLM occur frequently in RLS children<sup>1,2)</sup>.

Recent questionnaire surveillance reported that the prevalence of RLS in children and adolescents was about 2% in America and England<sup>2)</sup>. We thought that it was important for pediatricians to remind the RLS in children and reported this case which was confirmed by polysomnograph (PSG), even though there was one reported case of childhood-onset RLS in Korea<sup>3)</sup> using the electromyogram for diagnosis.

### Case Report

A 5-year-old boy was brought to the clinic with dyspnea on exertion, and leg pain while sleeping. Dyspnea and lip cyanosis after exercise appeared for a few months and snoring and leg pain during sleep had been present since the age of three. He had suffered from frequent sneezing and persistent cough for 1 year. Leg pains often occurred on his thigh, calf and knee areas with frequent leg movements before sleep and he complained about the difficulties to sleep due to leg pain. These were so disruptive to sleep that he

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Address for correspondence : Young Min Ahn, MD.

Department of Pediatrics, School of Medicine, Eulji University  
280-1, Hage-1 dong, Nowon-gu, Seoul 139-711, Korea

Tel : +82.2-970-8221, Fax : +82.2-976-5441

Email : aym3216@ulji.ac.kr

woke up frequently and moved restlessly during the sleep. Her mother worried about tiredness, irritability and progressive worsening of his attention problem during the daytime.

The patient had the history of atopic dermatitis, asthma, allergic rhinitis, sinusitis and severe facial swelling after ingestion of melon, watermelon, and walnut. He was also sensitive to dog with immediate swelling when a dog licked on him.

The patient's mother had a history of allergic rhinitis and food allergy to fruits.

She had experienced pain in her lower extremities and had IDA since childhood. She could remember that her father (patient's grandfather), who was died several years ago, had complained of leg pains frequently. She was also operated for thyroid cancer one year before.

On physical examination, his height (>97 percentile) and weight (75-90 percentile) was adequate. Nasal turbinates were edematous and pale, but postnasal drip or palatine tonsillar hypertrophy was not observed. Breathing sounds were clear without wheezing or rales. Tenderness, limitation of movement, heating sensation, and edema in legs and joints were not present.

Mild adenoid enlargement was evident on PNS X-ray.

On laboratory tests, levels of hemoglobin, hematocrit, serum iron, and total iron binding capacity (TIBC) were nor-

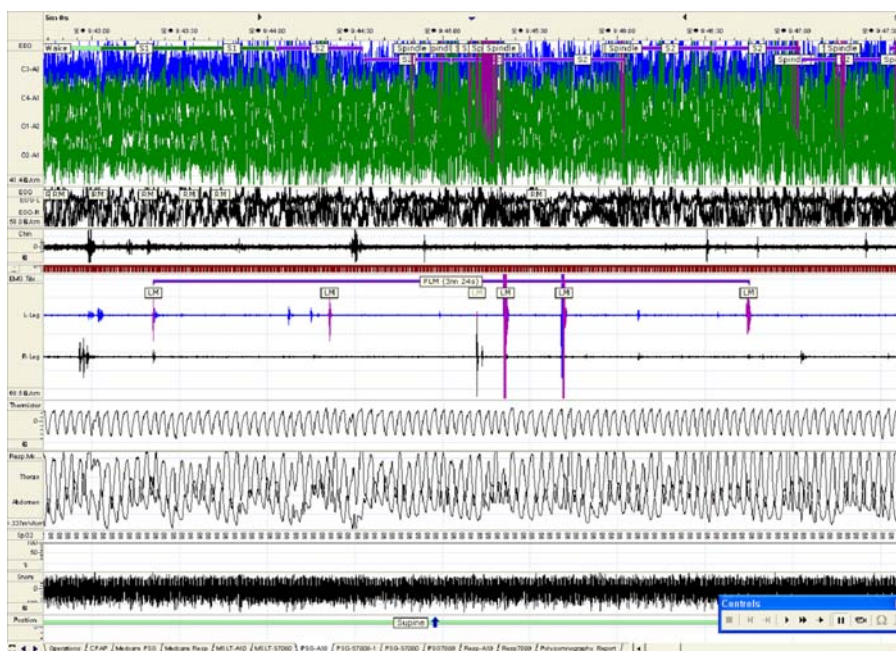
mal. But ferritin level was 34.9 ng/dL, low normal. Total eosinophil count ( $619/\text{mm}^3$ ) and total IgE (1439.8 IU/mL) were elevated. On skin prick test, positive results of house dust mite (5+), walnut, dog hair (3+), several tree pollens (3+), and mugwort (3+) were observed.

ADHD index was 20 by Conners' rating scales, above normal range (normal <19).

A polysomnograph (PSG) was performed due to the presence of snoring, sleep disturbance for the diagnosis of suspected obstructive sleep apnea and RLS. Total evaluated sleep time was adequate with 8 hours and 31.8 minutes and sleep efficiency was 90.9%. Relative Snoring time was 1% and apnea-hypopnea index (AHI) was 0.2/hr, indicated no obstructive sleep apnea, with lowest  $\text{SaO}_2$  of 91%. Total limb movements were recorded 161 times with 34 movement associated arousals and he had a PLM index of 5.5 which was graded as mild periodic limb movement disorder (PLMD) (Fig. 1-3).

Before the overnight PSG, we did the suggested immobilization test (SIT) which was compatible to periodic limb movement while wake (PLMW) of RLS (Fig. 4).

Given that the patient met the four essential criteria and two supportive criteria (family history and PLMD on PSG), he was diagnosed with definite RLS. Because of a low ferritin level (less than 50 ng/dL), elemental iron was given and



**Fig. 1.** PLMs are scored only if they occur in a series of 4 consecutive movements lasting 0.5-5 s, have an amplitude of one-quarter or more of the toe dorsiflexion during calibration, and are separated by intervals of 4-90 s.

PLM Statistics

All EMG.Tibialis	Number	Index	During PLM		
			Number	Index	
LM	161	19.4	46	5.5	
LM with Arousals	34	4.1	2	0.2	
LM with Apnea/Hypopnea	0	0.0	0	0.0	
LM with no association	127	15.3	44	5.3	
LM during S1	58	59.0	6	6.1	
LM during S2	59	18.0	25	7.6	
LM during S3	6	4.0	3	2.0	
LM during S4	1	2.6	0	0.0	
LM during REM	37	17.4	12	5.6	
	<b>Total Number</b>	<b>Index</b>	<b>Mean Duration [seconds]</b>	<b>Minimum Duration [seconds]</b>	<b>Maximum Duration [seconds]</b>
Limb Movements (LM)	161	19.4	1.9	0.5	4.9
LM in PLM Sequence	46	5.5	1.1	0.5	4.3
PLM Sequence	7	0.8	251.6	104.3	393.7

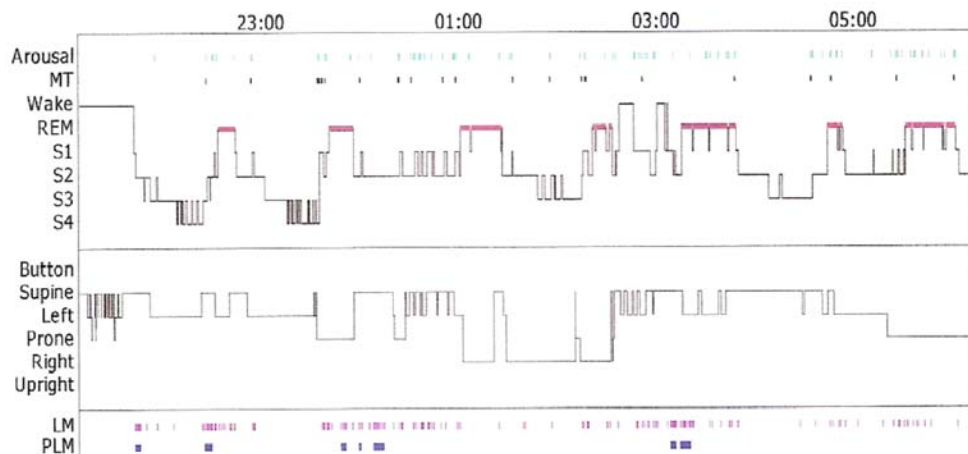
**Fig. 2.** Two of the 3 PLMs appeared at S1 and S2, early stages of NREM. The PLM index of 5.5 on polysomnograph indicated a mild PLM disorder.

after taking it, leg pains were improved slightly.

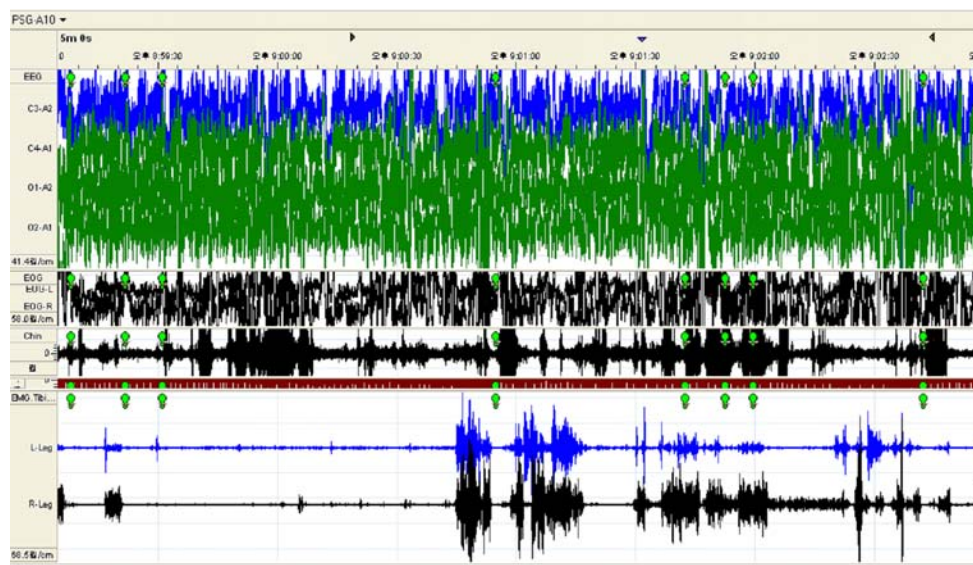
His mother was referred to the psychiatric department and diagnosed to have RLS and treated with ropinirole.

**Discussion**

RLS is characterized by dysesthesias (uncomfortable sensation) and paresthesias (unpleasant sensation) in the legs which worsen during rest and are relieved by movement<sup>1</sup>. It may be difficult to diagnose RLS in some cases. Three clinical features may support the diagnosis in uncertain cases of adult RLS; family history, PLMD, and response to treatment<sup>1</sup>. In idiopathic RLS, more than 50% of patients report



**Fig. 3.** There were several instances of PLM during sleep.



**Fig. 4.** During SIT, the patient pushed the button for pain (green dots); at these instances, EMG showed leg movements.

having a positive family history of RLS. A person with RLS is also 3-6 times more likely to have a family history of RLS than is a person who does not have RLS. Thus, having a positive family history of RLS is supportive of the diagnosis. We could diagnose RLS in his mother who had suffered from unexplained leg pains since her childhood and suspect that his past grandfather also had RLS by careful history taking.

In children, PLMD is characterized by episodes of repetitive and stereotypical jerks of the limbs that occur during sleep and that are associated with clinical sleep disturbance. Patients with RLS in adulthood mostly have PLMD, at least 85%<sup>4)</sup>. The diagnosis of RLS is based primarily on clinical evaluation but objective methods using PSG recordings have been developed to help in the diagnosis of RLS. PSG recordings often reveal the presence of PLM during both sleep (periodic leg movement in sleep, PLMS) and wakefulness (periodic leg movement while awake, PLMW). PLMS are scored only if they occur in series of four consecutive movements lasting 0.5-5 s, have an amplitude of one quarter or more of the toe dorsiflexion during calibration, and are separated by intervals of 4-90 s. Since RLS symptoms are primarily observed during wakefulness, especially when the patient is at rest during the evening and/or during the night, SIT was designed to detect PLMW, in which EMG from right and left anterior tibialis muscles are recorded during 1 hour period of immobilization in a bed at a 45° angle with legs outstretched, taking place in the evening prior to nocturnal PSG recording. The presence of 40 movements or more during SIT was found to discriminate RLS patients from control subjects with a sensitivity and specificity of 81%. During SIT leg discomfort is also estimated by patients every 5 minutes. SIT was suggested the gold standard to assess RLS and SIT-PLMW index significantly correlated with the severity of RLS, but the test to test variability due to the fluctuation of the severity of RLS symptoms according to circadian pattern and daily condition was issued to be discussed<sup>5, 6)</sup>. We did the SIT for this case which was compatible with RLS.

Elevated PLMS indices are also found in several sleep disorders, including narcolepsy, sleep apnea syndrome, REM sleep behavior disorder and advancing age. This patient had no history of hypersomnolence and OSAS was excluded by PSG. PLMD appears to be common in children with RLS, ADHD, and oppositional disorders<sup>1)</sup>. A study showed that up to 44% of subjects with ADHD have been found to have RLS, and up to 26% of subjects with RLS have been found

to have ADHD or ADHD symptoms. One explanation of this association is that sleep disruption associated with RLS might lead to inattentiveness, moodiness, and paradoxical overactivity<sup>7)</sup>. In our case, his mother complained of his inattentiveness and his Conners' rating scale was above normal, which could be caused by sleep disruption because of RLS.

Although the mechanism of RLS development is unknown, there is circumstantial evidence for a role of the dopaminergic system and iron status in the pathophysiology of RLS<sup>8)</sup>. Tyrosine hydroxylase is the rate-limiting enzyme in the production of dopamine and requires iron as a cofactor for hydroxylation of tyrosine<sup>9)</sup>. Therefore, iron deficiency may affect dopamine production indirectly, while dopaminergic agents are effective in therapy for idiopathic RLS<sup>10)</sup>. According to O'Keeffe et al<sup>11)</sup>, serum ferritin levels were reduced in the RLS patients compared with control subject and low serum ferritin status is an important contributor to the development of RLS<sup>11)</sup>. Most people with RLS have a positive therapeutic response to dopaminergic drugs which improve both the sensory and motor symptoms of RLS. More than 90% of patients report relief of their symptoms when treated with these agents. The specificity and completeness of this response for treating all RLS symptoms at a very low dose of medication indicates that the response to the dopaminergic agents strongly supports the diagnosis of RLS<sup>9)</sup>.

There is a significant genomewide association with a common variant in an intron of BTB (Broad-Complex, Tramtrack, and Bric-a-bracPOZ) domain-containing 9 (BTBD9) on chromosome 6p21.2. The association between the A allele of rs3923809 and RLS and PLM in sleep was highly significant. But among people who have just RLS symptoms without PLM, there was no association with the A allele of rs3923809. On the other hand, serum ferritin levels were decreased by 13% per A allele<sup>12)</sup>.

Especially in children, RLS is often misdiagnosed as growing pains. Growing pains are ill-defined limb discomforts in children that do not meet criteria for other diagnoses. The cause of growing pains remains unknown<sup>13)</sup>. Another differential diagnosis included other childhood causes of lower-extremity discomfort, for example, arthritis, leg cramps, sore muscles from overuse, Osgood-Schlatter disease, chondromalacia patella, and familial neuropathy<sup>1)</sup>. Compression of nerves or vascular structures by prolonged or awkward sitting positions should be distinguished from RLS discomfort<sup>1)</sup>. Growing pains differ from RLS in that the

unpleasant sensations are not partially or totally relieved by movements of the lower extremities<sup>13</sup>. Typically, children with growing pains may awaken in the middle of the night complaining of a "throbbing" pain in the legs<sup>14</sup>. Onset of growing pains usually occurs during early to late childhood, and the location of the pain is prominent in the front of the thighs, calves, or behind the knees<sup>14</sup>. RLS-related pain in children typically occurs from both knees down and especially involves the calves, although thigh pain may also appear<sup>14</sup>. Symptoms of growing pains may be alleviated with massage, ice packs, warm compresses, and acetaminophen or ibuprofen<sup>14</sup>.

The neurologic examination is normal in patients with RLS, but patients with late-onset RLS symptoms may show evidence of a peripheral neuropathy or radiculopathy<sup>11</sup>. Evaluations of serum ferritin levels and percent iron saturation are strongly recommended as part of the medical evaluation for RLS<sup>11</sup>.

There are various treatment modalities. In cases of mild symptoms, non-medical therapy may be efficient; for example, standardization of bed and wake time, hot baths, delayed sleep time until more tired, avoidance of excessive exercise, leg vibration, massage, etc<sup>14, 19</sup>.

A study reported that most patients with severe RLS had ferritin levels  $\leq 50$  ug/L<sup>15</sup>. Therefore, clinicians tend to prescribe the elemental iron at first in addition to recommending good sleep hygiene to patients with less than 50 ug/L in serum ferritin. In our case, the level of ferritin was 34.9 ng/dL. Symptoms improved after taking elemental iron. At present, legs trembling continues but leg pain has disappeared.

Through the evaluation of this case, we could diagnosis the patient's mother to have RLS, who had suffered from RLS symptoms since early childhood but did not be diagnosed RLS. This finding helped to confirm the diagnosis of her son symptoms while at the same time, facilitated proper treatment of the mother's chronic legs pain.

Currently, the US Food and Drug Administration has approved no medications for RLS in children, although ropinirole has been approved for the treatment of moderate-to-severe primary RLS in adults<sup>14</sup>. Certain medications have been tried in children with RLS, including levodopa/carbidopa, dopamine agonists (e.g. ropinirole, pramipexole), benzodiazepines (e.g. clonazepam), and alpha-adrenergics (e.g. clonidine)<sup>14</sup>. But the long-term risks of treating children for RLS or PLMD with existing medications are unknown and usually not recommended<sup>14</sup>. Moreover, clonazepam should be used

with caution in children suspected of sleep-disordered breathing as it can relax the upper airway muscles, thereby increase the likelihood of upper airway collapse<sup>14</sup>. Dopaminergic medications may be considered for children with severe cases of RLS, although the long-term effects are unknown<sup>14</sup>. They are generally well tolerated in children; however, up to 20% of children taking carbidopa/levodopa may develop nausea<sup>14</sup>. Several case studies demonstrate good efficacy and tolerance of carbidopa/levodopa and ropinirole in children with ADHD and RLS<sup>14</sup>.

As stated above, recent questionnaire surveillance reported that the prevalence of RLS in children and adolescents was about 2% in America and England<sup>2</sup>, and that was more frequent than non-febrile seizure, diabetes mellitus in children<sup>2</sup>. However, physicians have low interest in RLS yet and so, often misdiagnose it.

In our case, we diagnosed RLS using the history, family history and polysomnograph and improved the symptoms of the patient with iron. Authors report this RLS case confirmed by supportive PSG findings to inform the pediatricians.

## 한글 요약

### 성장통으로 발견된 하지 불안 증후군 1예

울지대학교 의과대학 소아과학교실, 코모키 수면센터\*

김동순 · 신홍범\* · 안영민

하지 불안증후군은 다리의 감각 둔화와 감각이상을 호소하며, 쉬고 있을 때 악화되고 움직이면 완화되는 특징을 보이는 증후군이다. 정확한 원인은 아직 알려진 바 없으며 아동기 시작되는 하지 불안증후군은 철분 결핍 및 가족력과 연관된 것으로 되어 있다. 또한 하지 불안증후군은 주의력 결핍 과잉행동 장애를 흔히 동반하며, 수면 다원 검사로 확진되는 주기성 사지 운동증과 같은 선상의 질병으로 여겨진다. 저자들은 하지 통증을 호소하는 5세 남아에서 어머니의 가족력을 발견하고 주의력 결핍 장애의 증상을 동반하며 수면 다원 검사로 진단된 경도의 주기성 사지 운동증으로 확진한 하지 불안 증후군을 진단하고 철분제 복용 후 증상 호전을 보인 사례를 경험하였기에 이를 보고하며, 성장통으로 내원하는 아이들에서 하지 불안 증후군을 감별할 것을 제안하는 바이다.

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