Restless leg syndrome in the differential diagnosis of entrapment and peripheral neuropathies

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ABSTRACT

Restless leg syndrome (RLS) is an abnormal sensation disorder. Defining the syndrome is difficult. It is transmitted autosomal dominant genetically, is especially prevalent in the lower limbs, and is seen in both genders. In the differential diagnosis of RLS, nocturnal leg cramps, akathisia, peripheral neuropathy, entrapment neuropathy, and vascular disease (for example, deep vein thrombosis) should be considered. A 52-year-old woman was admitted to our clinic with signs of paresthesia, she had abnormal sensation disorder in both legs and the right arm, which she had difficulty defining. She had applied to another center with the same complaints and had been evaluated as entrapment neuropathy, carpal tunnel syndrome, and/or peripheral neuropathy. Her electromyographic examination carried out by us was normal. The history, neurological examination findings, and results of standard laboratory analyses provided a diagnosis of idiopathic RLS. After the diagnosis of RLS in the proband, we questioned other family members. Her large family had 63 members, 35 males, and 28 females. Of 63 members, 17 also had an RLS diagnosis.

Restless leg syndrome (RLS) was first reported in 1940 by Ekbom to describe a disorder characterized by sensorimotor findings of the limbs, present mainly during rest. However, early descriptions date back to the 17th century. Diagnostic criteria were published by the International Restless Leg Syndrome Study Group in 1995 and were revised in 2003. The clinical findings of RLS are characterized by a need to move the legs and a disturbing or unpleasant sense in the legs. Frequently, these complaints are bilateral, however, they can be unilateral, and sometimes can affect the upper limbs as well. Anxiety and the need to move the legs are increased by sedentary activities like resting and sitting and lying down. The symptoms are most prevalent during the evening, especially before going to sleep, the symptoms are decreased by moving the legs.

Restless leg syndrome (RLS) affects approximately 10-15% of the general population. Males and females are affected equally, however, Berger and associates have shown that RLS affects women more frequently than men. Clinical findings may appear at any age, even as early as infancy. The frequency of encountering the disease increases
with age, with the majority of patients being most severely affected at middle age or older.\textsuperscript{2,3} Symptoms seen in RLS may resemble the ones encountered in nocturnal leg cramps, akathisia, peripheral neuropathy, entrapment neuropathy, and vascular disease (for example, deep vein thrombosis). We present a patient admitted with a pre diagnosis of entrapment and/or peripheral neuropathy, which is diagnosed as RLS. By presenting this case, we want to draw attention to RLS diagnosis, which frequently presents with symptoms suggestive of entrapment and/or peripheral neuropathy, and therefore, is often overlooked.

\textbf{Case Report.} A 52-year-old woman presented at our clinic with complaints of paresthesia and abnormal sensations in the legs and right arm that she could not define well. She had been to another center for the same complaints, which had been evaluated at that time as an entrapment syndrome and/or peripheral neuropathy, she was directed to our clinic for further evaluation. A physical history revealed that her complaints had begun as pain and abnormal sensation below the right knee spreading to the end of the fingers 30 years earlier, and similar symptoms had begun to occur in the left leg 10 years earlier, and in the right arm 2 years earlier. While these symptoms occurred predominantly during rest, they decreased with movement. The patient described her pain and abnormal sensations as beginning mildly in the afternoon and increasing in the evening before going to sleep. The abnormal sensations (dysesthesia) caused motor anxiety and the need to move. She explained that she was moving her legs continuously while going to sleep and turning in bed frequently. Therefore, in the morning, she felt drowsy, concentration was difficult, she had headaches and was nervous, and felt as though she had not slept during the previous night. In her family, her siblings, grandchild, uncle and cousins were found to have similar complaints and to be diagnosed as RLS in another center (\textit{Figure 1}). Results of laboratory analyses including total blood count, fasting blood glucose, urea, iron, iron binding capacity, ferritin, vitamin B-12, folate, free T3-T4 and thyroid stimulating hormone levels, sedimentation, and blood electrolyte levels were normal. The results of an electroneurography study were normal. A psychological examination showed a depressive affect, decreased ability to concentrate, difficulty falling asleep, and frequent nocturnal awakenings. Antidepressant therapy (selective serotonin reuptake inhibitors [SSRI]) as given, and pergolide (0.25 mg/day), a dopamine agonist, was given for treatment of RLS. The patient was followed-up as an outpatient, and the dosage of pergolide was adjusted according to her improvements. Three weeks after her initial admission, during a control examination, the anxiety in her legs had decreased, and improvements as the result of the pergolide treatment were recorded. After the proband had been diagnosed with RLS, by the data obtained we constructed the pedigree (\textit{Figure 1}). Her large family had 63 members, 35 males and 28 females. Of those 63 members, 17 were diagnosed as having RLS clinically. Thirteen of affected members were males, and 4 were females. The youngest member with RLS was 14 years old, and the oldest was 73 years old.

\begin{figure}
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\includegraphics[width=\textwidth]{Figure1.png}
\caption{The pedigree of the patient.}
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Discussion. Restless leg syndrome is a drawing, burning, creeping, or undefined sensation disorder that develops in the lower limbs that can delay the onset of sleep. The circadian feature of symptoms, being prominent in the evening and night, and occurring and increasing with rest are characteristic. The patient must move the legs or walk to relieve these symptoms. The pathogenesis of RLS is unclear. Ekborn suggests accumulation of metabolites in the legs owing to venous congestion as a reason. Although peripheral nerve abnormalities have been proposed, no associated structural change in nerve endings has been demonstrated. Dopaminergic or opiate abnormalities are also associated with RLS. Single-photon emission CT imaging results have demonstrated a deficiency of dopamine D2 receptors in patients with RLS. Also, in patients with RLS, centrally acting dopamine receptor antagonists can activate symptoms of the disease. However, sympathtic nerve blockade relieves periodic limb movements of sleep, and alpha-adrenergic blockers can reduce the severity of symptoms of RLS. Studies also suggest a possible under activity of the serotonin and gamma-aminobutyric acid neurotransmitter systems.

The diagnosis of RLS is based primarily on clinical history. Our patient presented with all the criteria of the International Restless Leg Syndrome Study Group. She was evaluated as grade 3 according to John Hopkins RLS severity score (grade 0, no symptoms; grade 1 symptoms only at night; grade 2, symptoms only in the evening after 18:00; and grade 3, grade-2 symptoms as well as symptoms before 18:00). The disease may occur as idiopathic (primary) or non idiopathic (secondary). The majority of RLS cases are idiopathic. Idiopathic disease is familial in 25-75% of all cases. In familial cases, the disease appears to follow a pattern of autosomal dominant inheritance. The possibility of inheritance of the disease was reported firstly by Oppenheim in 1923. In some families, a progressive decrease in the age of onset through subsequent generations (namely, genetic anticipation) has been described. Patients with familial RLS tend to have an earlier age of onset (<45) and slower progression. In these patients, a neurologic examination reveals normal findings. The non idiopathic form develops at older ages. This form has been suggested as being inherited by free transmission. It is seen due to certain conditions or factors, particularly from iron deficiency and peripheral neuropathy. These 2 conditions should be excluded before RLS is labeled as the primary form. Moreover, the disorder may be associated with conditions like chronic renal failure, uremia, pregnancy, folate or magnesium deficiency, polynuropathy (either idiopathic or caused by alcohol abuse), amyloidosis, diabetes mellitus, lumbosacral radiculopathy or myelopathies, multiple sclerosis associated with spinal cord involvement, cord compression, Parkinson’s disease, dystonia responsive to L-dopa, akathisia due to neuroleptic intake, stiff person syndrome, Tourette syndrome, Lyme disease, monoclonal gamopathy of undetermined significance, rheumatoid arthritis, Sjögren’s syndrome, coxarthrosis, carcinoma, Celiac disease, or vitamin B-12 deficiency. Spinal injury and injury of the sensorial spinal pathways also have been reported as facilitating development of RLS. Moreover, in the differential diagnosis of RLS, nocturnal leg cramps, akathisia, peripheral neuropathy and vascular disease (for example, deep vein thrombosis) should be also considered. Nocturnal leg cramps are typically unilateral, painful, involuntary muscle contractions and occur often local, with a sudden onset. They have physical changes including a muscle hardening not seen in RLS. Akathisia is characterized by excessive urge to move the entire body. It does not correlate with rest or show circadian variation, and it is usually associated with medications such as neuroleptics or other dopamine-blocking agents. Leg symptoms then can be defined in peripheral neuropathy, usually are neither associated with motor restlessness nor helped by movement and do not worsen in the evening or nighttime. Our patient’s electromyography and neurological examination were not compatible with neuropathy, and other probable diagnosis were excluded with clinical history. The RLS symptoms also were found in our patient’s uncle, cousins, siblings, and grandchild, which supports autosomal inheritance. An absence of drug intake and the metabolic or other disorders described above made us exclude the diagnosis of secondary RLS.

Restless leg syndrome is thought to be caused by a deficiency in central spinal dopaminergic transition. In patients with idiopathic RLS, treatment is accomplished with dopamine agonists, L-dopa, antiepileptic drugs (especially gabapentin), benzodiazepines (especially clonazepam). In the symptomatic group, etiologic factors should be treated. Our patient was given a dopamine agonist (pergolide, 0.05 mg, and then 0.1 mg one week later) due to the diagnosis of idiopathic RLS. At the end of the third week, pain and abnormal sensation had resolved, and she began to sleep comfortably, and her sleep was of good quality. Her concentration also returned to normal.

In conclusion, a patient was referred to our clinic with a prior diagnosis of entrapment syndrome and/or peripheral neuropathy and delayed diagnosis of RLS was established. The fact that our patient’s arm was also affected is rare. Physicians should be alert to this syndrome.

References


**REFERENCES**

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