Reumatismo, 2023; 75 (4): 190-195

Can restless legs be a sign of something else? A case report of spondyloarthritis presenting with restless legs syndrome and a review of the literature

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SUMMARY

Restless legs syndrome (RLS) is a chronic movement disorder characterized by an urge or need to move the limbs, usually associated with uncomfortable sensations in the legs and sleep disorders. In general, two clinical forms of RLS are described: primary and secondary. Although primary RLS has a familial component, the underlying mechanism is still not fully understood but seems to be related to abnormalities in the dopaminergic and glutamatergic pathways of the central nervous system. The secondary forms of the syndrome are associated with iron deficiency, renal failure, pregnancy, diabetes mellitus, peripheral neuropathy, and several rheumatologic disorders such as rheumatoid arthritis and Sjögren's syndrome. In a few clinical trials, an increased frequency of RLS has been reported in patients with spondyloarthritis. In this report, a case of coexistence of spondyloarthritis and RLS is presented, showing satisfactory improvement with conservative treatment and additionally adding naproxen. Anemia of chronic disease occurring in rheumatic diseases, and associated iron deficiency may contribute to the development of RLS.

Key words: *Restless legs syndrome, spondyloarthritis, awareness.*

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INTRODUCTION

Restless legs syndrome (RLS) is a chronic movement disorder characterized by an urge or need to move the limbs, usually associated with uncomfortable sensations in the legs and sleep disorders. These symptoms mainly occur at night, are worse at rest, and are relieved by movement. Epidemiological studies indicate that the symptoms of RLS are present in about 5-15% of the general population. In general, two clinical forms of RLS are described: primary and secondary. Although primary RLS has a familial component, the underlying mechanism is still not fully understood but seems to be related to abnormalities in the dopaminergic and glutamatergic pathways of the central nervous system. The secondary forms of the syndrome are associated with iron deficiency, renal failure, pregnancy, diabetes mellitus, peripheral neuropathy, and several rheumatologic disorders such as rheumatoid arthritis (RA), Sjögren's syndrome, scleroderma, and systemic lupus erythematosus (SLE) (1).

Spondyloarthropathies (SpA) are a group of diseases with similar clinical, laboratory, and radiological features. They are characterized by inflammation of vertebrae, peripheral joints, and periarticular tissues. According to clinical characteristics, the SpA group is divided into two subgroups: axial (involvement in the sacroiliac joints, spine, or both) and peripheral (peripheral arthritis, enthesitis, and dactylitis). Clinical findings include inflammatory low back pain, oligoarthritis, especially involving the large joints of the lower extremities, enthesitis, dactylitis, and various extra-articular findings such as psoriasis, anterior uveitis, and inflammatory bowel disease (2, 3). In a few clinical trials, an increased frequency of RLS has been reported in patients with SpA (4-7). Here, a case of coexistence of spondyloarthritis and RLS showing satisfactory

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improvement with conservative treatment, additionally adding non-steroidal anti-inflammatory drug (NSAID), is detailed.

CASE REPORT

A 44-year-old male was submitted to the Physical Medicine and Rehabilitation Department with pain in his legs for 10 years. His pain was aggravated by rest at night and relieved by movement. He described an uncomfortable itching and creepy-crawling sensation on his legs, aching and tension in calf muscles, and a desire to move the legs in the evenings, and this has negatively impacted his sleep and quality of life. He also had low back pain when he got up in the morning and heel pain when he put his feet on the ground. He also had morning stiffness for about 30 minutes. He had hypertension and RLS in his history. The diagnosis of RLS was made according to the International Restless Legs Syndrome Study Group (Table I) (8). He had been using pramipexole and quetiapine for RLS and sleep disorders for 5 years. He noted that his complaints did not improve despite the medication. On physical examination, the range of motion values of all joints were within normal limits, as were muscle strength and neurological examination. He had no painful, tender, red, or swollen joints. The flexion-abduction-external rotation of the hip and the flexion-adduction-internal rotation of the hip tests were slightly positive. His measures of the modified Schober test, chest expansion, tragus-wall distance, occiput-wall distance, and hand-ground distance were normal. His significant laboratory findings showed elevated C reactive protein (CRP) of 19.1 mg/L (range 0-5 mg/L), elevated erythrocyte sedimentation rate (ESR) of 27 mm/hour (range 0-20 mm/hour), decreased hemoglobin of 12.8 g/dL (range 14-16 g/dL), decreased iron of 31 ug/dL (range 70-180 ug/dL) and decreased 25(OH)D^3 of 14.2 mg/dL. Serum glucose, thyroid, kidney, and liver function tests, vitamin B12, and folate were within normal limits. The infective panel, including tests for Epstein-Barr virus, toxoplasma, rubella, cytomegalovirus, herpes simplex virus, *Brucella* and *Salmonella* tube agglutination, hepatitis, HIV/AIDS, and venereal disease research laboratory tests, were all negative. Tumor markers were also negative. Anti-nuclear antibodies, rheumatoid factor, anti-cyclic citrullinated peptide, anti-Sjögren's syndrome-related antigen A autoantibodies, anti-Sjögren's syndrome type B antibodies, autoantibodies against topoisomerase I, anti-double-stranded DNA, and anti-neutrophilic cytoplasmic antibodies were negative, and complement dosage was normal. HLA-B27 was negative. Nerve conduction tests performed by standard electromyography (EMG) were normal, but a prolonged latency and a shorter duration in the cutaneous silent period, which is a non-invasive technique providing insight into the function of the small-diameter nerve fibers, were observed in his lower extremities. The lumbosacral radiograph showed enthesopathic changes on the bilateral superior posterior iliac spine and bilateral sacroiliitis, sclerosis, and widening of joint spaces (Figure 1). Also, in the lateral radiograph of the foot and ankles (Figure 2), there were enthesopathic changes at the insertion of the Achilles tendon in the calcaneus posterior. Magnetic resonance imaging of the sacroiliac joints showed edema and narrowing of the bilateral sacroiliac joints. The patient was diagnosed with axial SpA (axSpA) according to the assessment in ankylosing spondylitis (AS) criteria (9). The clinical disease scores of the patient were as follows: Bath ankylosing spondylitis disease activity index (BASDAI): 2.6; Bath ankylosing spondylitis functional index (BASFI): 1.2; and ankylosing spondylitis disease activity score

Table I - The diagnostic criteria suggested by the International Restless Legs Syndrome Study Group.

The four essential criteria are as follows:
1) the urge to move the legs is usually accompanied by or caused by uncomfortable sensations deep in the legs;
2) the above symptoms begin or worsen when resting or inactivity such as lying or sitting;
3) the symptoms can be partially or totally relieved by movement such as walking or stretching;
4) the symptoms are worse in the evening or at night rather than during the day or they only occur in the evenings or at night.

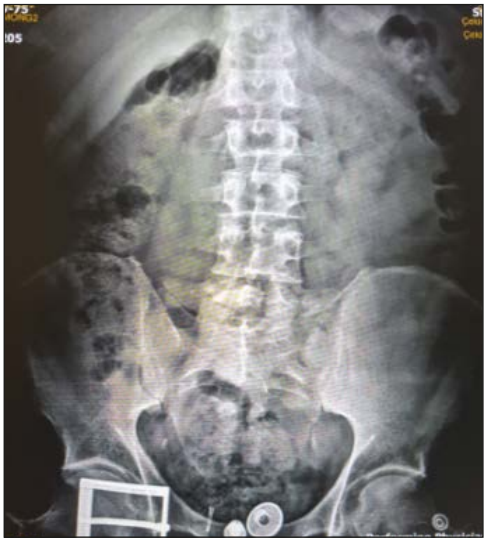

Figure 1 - Bilateral enthesopathic changes of the superior posterior iliac spine and sacroiliitis, with sclerosis and widening of joint spaces on lumbosacral X-ray imaging.

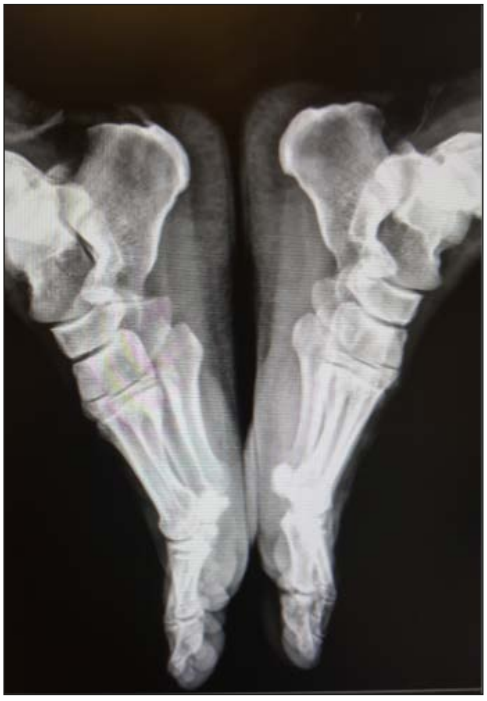

Figure 2 - Bilaterally enthesopathic changes at the insertion of Achilles tendon in calcaneus posterior.

with CRP (ASDAS-CRP): 2.2. The patients received oral naproxen (750 mg/day), iron (100 mg/twice a day), and vitamin D3 (800 IU/day). His leg and low back pains completely recovered, as did his RLS symptoms. The patient obtained normal sleep after one month. His laboratory findings and clinical disease scores after the first month of treatment were as follows: CRP 7.71 mg/L, ESR: 10 mm/hour, BASDAI: 0.8, BASFI: 0.6 and ASDAS-CRP: 1.7. There was no complaint from the patient at the 6-month follow-up when his laboratory findings and clinical disease scores were as follows: CRP: 2.18 mg/L, ESR: 8 mm/hour, BASDAI: 0.4, BASFI: 0.2, and ASDAS-CRP: 1.1.

DISCUSSION

In previous studies, it has been shown that the frequency of RLS was increased in patients with SpA (4-7). It has even been suggested that RLS is more frequent in SpA patients than in the general population (7). In this report, a patient with axSpA presenting RLS being relieved *via* conservative treatment, additionally adding NSAID, is described.

RLS is a chronic sensorimotor disorder that causes leg movements to relieve discomfort and unpleasant sensations in the legs. Also, RLS may cause sleep disturbances and impaired quality of life. RLS is common in rheumatologic disorders such as RA, Sjögren's syndrome, scleroderma, SLE, and fibromyalgia (FM) as well as SpA (1, 4-6, 10). In a review conducted by Hening et al. (10), 31% of patients with FM, 25% with RA, 24% with Sjögren syndrome, and 22% with scleroderma had RLS. The pathophysiology of RLS is focused on the dopaminergic system, reduced central nervous system iron levels, and genetic linkages. Therefore, dopaminergic and iron replacement therapy relieves most symptoms of RLS. A possible association between RLS symptoms and iron deficiency has long been recognized. Low serum iron levels were present in 25% of patients with severe RLS. The severity of the symptoms was found to be correlated with serum ferritin levels (1, 11). It has been proposed that dopaminergic dysfunction can be mediated by low brain iron levels since iron is needed as

a cofactor for tyrosine hydroxylase, which is the rate-limiting enzyme in the synthesis of dopamine, and because the D2 dopaminergic receptor is a protein containing iron (3, 12). The serum iron level was decreased in our patient, and his complaints improved after replacement therapy.

According to a review by Weinstock et al. (13), 95% of conditions related to RLS are associated with systemic inflammation and/or immune alterations, 47% with iron deficiency, 37% with peripheral neuropathy, and 32% with bacterial overgrowth in the small intestine. This suggests that RLS is associated with altered immune mechanisms. Also, altered host defenses due to genetic variants may predispose individuals to inflammation or an altered immunological response leading to RLS. Chronic inflammation may lead to iron deficiency because it causes its entrapment in macrophages and reduces the iron supply to the bone marrow. Subsequently, iron deficiency in the central nervous system may result in RLS. Moreover, an immune reaction to gastrointestinal bacteria or other antigens may lead to RLS through a direct immunological attack on the central or peripheral nervous system. Bacterial overgrowth in the small intestine may also cause systemic iron deficiency anemia due to decreased iron absorption from the duodenum and enhanced uptake of iron by the bacterium. Besides, hepcidin, the primary iron-regulating hormone, has been found to be associated with RLS, and the upregulation of hepcidin by inflammation has been shown to be responsible for increased iron stores in the liver. Lipopolysaccharides, which are breakdown products of Gram-negative bacteria, interleukin-6, and hypoxia, can increase hepcidin levels. Hepcidin binds to ferroportin in human choroid plexus cells and decreases the availability of iron for the central nervous system, resulting in RLS (13). Immune system abnormalities have been suggested as one of the reasons why RLS is more common in rheumatic diseases (4). Also Demirci et al. proposed that the increased frequency of RLS in AS patients may be related to an abnormality of the immune system (5).

Another reason for the development of RLS is anemia of chronic diseases. Chronic inflammation may cause anemia, with hepcidin preventing iron absorption from the intestine or the release of iron from the reticuloendothelial system (13). Demirci et al. found that there was a negative correlation between the RLS severity score and hemoglobin (5). In this case, anemia of chronic disease occurring in rheumatic diseases, and associated iron deficiency may have contributed to the development of RLS.

Another reason for the pathogenesis of RLS is peripheral neuropathy (13). As in other rheumatic diseases, peripheral nervous system involvement due to immune dysfunction has been reported in SpA (4). RLS is a common manifestation in cases of acquired polyneuropathy involving particularly small sensory fibers. Dopaminergic cells have been found to have a potentially nociceptive functional capacity. The structures underlying RLS associated with polyneuropathy may presumably include spinal generators that are crossroads for signals traveling either in peripheral nerves or in pyramidal and extrapyramidal pathways. The pathomechanisms of RLS may be activated not only by impaired dopaminergic control but also by peripherally disrupted sensory modulation. It has been proposed as a peripheral mechanism that painful stimuli are transmitted to the spinal cord by A-δ fibers and create a strong postsynaptic inhibition on motor neurons *via* spinal interneurons (4, 14). Although the findings of the standard EMG were normal in this case, the prolongation of latency and a shorter duration of the cutaneous silent period in his legs may indicate neuropathy.

Moreover, vitamin D3 deficiency has been reported to be associated with RLS, and vitamin D3 replacement therapy has been effective in reducing the symptoms of RLS patients. One of the important functions of this vitamin is the regulation of nervous system development and function. It has been shown that vitamin D3 can protect the mesencephalic dopaminergic neurons against toxins that cause a decrease in glutathione content and increase the levels of dopamine or its metabolites in the nigrostri-

atal dopaminergic pathway (15). In this case, the serum level of vitamin D3 was low, and his complaints improved after replacement therapy.

Tekatas et al. determined the prevalence of RLS in patients with AS and also examined factors potentially related to RLS (4). They found that the frequency of RLS was significantly higher in AS patients (30.8%) than in healthy subjects (13.2%). They also found that peripheral arthritis, uveitis, anemia, smoking, and polyneuropathy were significantly higher in AS patients with RLS (4). Demirci et al. assessed the frequency of RLS and its connections with the quality of sleep and life in AS patients (5). They found that the frequency of RLS and the mean RLS severity score were significantly higher in AS patients (36.4%) than in controls (14%). They also found that RLS severity was positively correlated with the scores of disease activity, functional status, sleep quality, and quality of life. They proposed that clinicians should be aware of RLS for early diagnosis and treatment in AS patients, as RLS may adversely affect sleep and quality of life in AS patients (5). Yüksel et al. explored the prevalence of RLS and sleep quality and defined the link between RLS and measures of disease activity and physical function in patients with AS (6). They found that the prevalence of RLS was 55% (11 of 20 patients) in AS patients and 5% in healthy controls. They also found that the scores of disease activity (BASDAI) and physical function (BASFI) were significantly worse in the RLS group compared to the non-RLS group. They suggested that it is significant to define the presence of RLS and poor sleep quality in patients with AS (6). Zontul et al. evaluated the link between quality of sleep and disease parameters and other possible reasons (such as depression, anxiety, and RLS) for sleep disorders in patients with AS (7). They found that the frequency of RLS was 36.1% (44 of 122 patients) in AS patients. They observed that patients with poor sleep quality had a higher rate of RLS and proposed that RLS is a common situation in patients with AS. They also suggested that RLS was much higher than in the general population (7). Depending on the characteristic feature of inflammatory low back pain in patients with SpA, sleep disturbances may occur due to axial pain and stiffness in the second half of the night. In addition, patients may have complaints of poor sleep quality even if the disease activity is low (7).

A cross-sectional study, which investigated the prevalence of insomnia and RLS in outpatients with rheumatic disease, demonstrated that half of the patients with RLS developed the syndrome after the diagnosis of rheumatic disease; RLS and the rheumatic disease developed at almost the same time in a few patients, and the RLS developed before the diagnosis of rheumatic disease in a small proportion of them. The authors proposed that it is necessary to determine whether RLS develops secondary to rheumatic disease (16). Therefore, additional investigations of the underlying rheumatic disease should be performed, especially in patients with RLS who are unresponsive to treatment.

CONCLUSIONS

Clinicians should be aware of the relationship between rheumatological disorders and RLS. The secondary causes must be carefully investigated in patients unresponsive to treatment.

Conflict of interest
The author declares no potential conflict of interest.

Ethics approval and consent to participate
No ethical committee approval was required.

Patient consent for publication
Informed consent was obtained from the patient.

Funding
None.

Availability of data and materials
Data are available from the corresponding author upon request.

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