OLGU SUNUMU CASE REPORT

DOI: 10.31609/jpmrs.2020-79096

Duloxetine-induced Restless Legs Syndrome in a Patient with Fibromyalgia Syndrome

Fibromiyalji Sendromlu Bir Hastada Duloksetine Bağlı Huzursuz Bacak Sendromu

Cevriye MÜLKOĞLU[a], Hakan GENÇ[a]

[a]Department of Physical Medicine and Rehabilitation, University of Health Sciences Ankara Training and Research Hospital, Ankara, TURKEY

ABSTRACT Restless legs syndrome (RLS) is a neurological sleep disorder characterized by unpleasant sensations that worsen with resting and sleep, and relieving with moving the limbs. Herein we report a 47 year-old woman diagnosed with fibromyalgia syndrome and the dose of 30 mg duloxetine was administered to her. Four weeks later from starting duloxetine, uncomfortable sensations appeared in her lower limbs. After the dose of duloxetine had been decreased, her symptoms were alleviated gradually within one week. RLS due to new generation antidepressants is rare and limited with a few case reports in the literature. To the best of our knowledge, this case report is the first report of RLS symptoms induced by duloxetine during treatment of fibromyalgia syndrome.

Keywords: Restless legs syndrome; duloxetine; antidepressants; fibromyalgia syndrome

ÖZET Huzursuz bacak sendromu (HBS), dinlenme ve uyku ile kötüleşen ve ekstremiteleri hareket ettirmekle rahatlayan nahoş hislerle karakterize nörolojik bir uyku bozukluğudur. Burada fibromiyalji sendromu tanısı alan 47 yaşında bir kadın hastaya, 30 mg duloksetin verildi. Duloksetine başladıktan 4 hafta sonra, alt ekstremitelerinde rahatsızlık hissi ortaya çıktı. Duloksetin dozu düşürüldükten sonra semptomları 1 hafta içinde kademeli olarak hafifledi. Yeni nesil antidepresanlara bağlı HBS nadirdir ve literatürde, birkaç olgu sunumu ile sınırlıdır. Bildiğimiz kadarıyla bu olgu sunumu, fibromiyalji sendromunun tedavisi sırasında duloksetinin neden olduğu HBS semptomlarının ilk raporudur.

Anahtar Kelimeler: Huzursuz bacak sendromu; duloksetin; antidepresanlar; fibromiyalji sendromu

Restless legs syndrome (RLS) also known as Willis-Ekbom disease is a sensorimotor disorder described with uncomfortable sensations and irresistible desire to move the limbs that lead to sleep disturbances.[1] Patients have various symptoms that worsen with inactivity and sleep especially in the evening or night and relieving by movements of the legs such as walking or activity.[2] RLS occurs mostly in females and the prevalence increases with age. RLS affects 2.1%-5% of general population.[3] Fibromyalgia syndrome is a non-rheumatological disease characterized by chronic generalized pain, stiffness, fatigue, mood and cognitive failure in patients. Duloxetine and pregabalin are frequently used for treatment of neuropathic pain in patients with fibromyalgia. Duloxetine is a serotonin-norepinephrine reuptake inhibitor (SNRI), a novel second generation antidepressant. SNRIs are antidepressants with a dual mechanism of action, inhibiting the reuptake of both serotonin and norepinephrine. Herein, we reported a patient with fibromyalgia who has developed duloxetine-induced RLS. To the best of our knowledge, this is the first case to develop RLS symptoms during duloxetine treatment for fibromyalgia syndrome.

Correspondence: Cevriye MÜLKOĞLU
Department of Physical Medicine and Rehabilitation, University of Health Sciences Ankara Training and Research Hospital, Ankara, TURKEY/TÜRKİYE
E-mail: drckaraca@hotmail.com

Peer review under responsibility of Journal of Physical Medicine and Rehabilitation Science.

Received: 22 Sep 2020 ***Received in revised form:*** 24 Nov 2020 ***Accepted:*** 09 Dec 2020 ***Available online:*** 05 May 2021

CASE REPORT

A 47 year-old-female patient applied to our outpatient clinic with complaints of generalized pain, morning stiffness and fatigue. She was diagnosed with fibromyalgia syndrome according to the 2016 revised diagnosis criteria. At the dose of 30 mg duloxetine per day was started to her for treatment of fibromyalgia syndrome. After 4 weeks-follow up, her symptoms associated with fibromyalgia syndrome have alleviated, on the other hand, deep pain, restlessness and paresthesia started especially at nights in her legs. The patient declared that she had no this kind of complaints before initiating duloxetine. Her symptoms had appeared within 2 weeks after duloxetine was prescribed. First of all, a desire to move her legs after resting was started. When she was sitting for a long time or resting, she had a strong desire to move and stretch her legs. Then, unpleasant sensations were spread to her arms and body. There was paresthesia in her limbs. Likewise, she had an increased desire to move her limbs and trunk, especially at nights. She had to wake up and walk inside the house approximately every ten minutes during the night. Unpleasant, restless feelings in her extremities were improving by walking or movement. A detailed anamnesis was obtained and a careful physical examination was performed. Our patient had no history of alcohol, tobacco or any other drug use. She had no chronic liver or kidney disease, diabetes mellitus, vitamin B_{12}/folate deficiency, peripheral neuropathy, rheumatoid arthritis, spinal disorders such as spinal nerve root irritation. Physical and neurological examination of the patient was completely normal. All laboratory tests including blood chemistry, thyroid function tests, liver and kidney tests were normal except for the vitamin D. 25-hydroxy vitamin D level was 7.18 µg/L. serum ferritin was 11.8 µg/L and serum iron level was 64 µg/dL. Blood urea nitrogen was 25 mg/dL and serum creatinine was 0.62 mg/dL. The patient has not been initiated vitamin D and ferritin replacement for distinguishing whether RLS is the side effect of the duloxetine. According to these findings, we diagnosed her as duloxetine-induced RLS and we suggested her to reduce dose of the drug. The patient noticed that RLS-related complaints were decreased when she used duloxetine on alternate days. Therefore, duloxetine dose was reduced daily and the patient was followed up closely. At one month follow-up visit, both fibromyalgia and RLS symptoms have improved almost completely by taking duloxetine on alternate days.

DISCUSSION

RLS also known as Willis-Ekbom disease is a sensorimotor sleep disorder in which patients have unpleasant feelings and an irresistible desire for moving the limbs. Paresthesia, dysesthesia, deep aching and uncomfortable sensations inside the limbs can cause the patient to wake up frequently and lead to sleep disturbances.[1] There was periodic limb movements in about 70% of the patients with RLS. There are symptoms that change from patient to patient worsen with resting, inactivity and sleeping especially in the evening or night and relieving by movements of the limbs. Therefore, patients frequently wake up, walk within the house and move the limbs for relieving.[2] The diagnostic criteria which International Restless Legs Syndrome Study Group developed for RLS: (a) an urge to move the legs; (b) the urge is induced or aggravated during periods of rest or inactivity; (c) the urge is relieved partially or totally by movement; (d) symptoms are worse or only occur in the evening or night; (e) the symptoms are not connected to another medical or behavioral condition.[2,4] Mostly the legs are affected but rarely arms and other limbs may be involved. Patients often have periodic limb movements in sleep. There are abnormal sensations such as paresthesia, dysesthesia, tingling, burning, cramp and deep aching in the limbs. The quality of life in RLS patients decreased because of interrupted sleep, sleep disturbances and somnolence. Symptoms are mostly at nights, but also during the day as the disease progresses. RLS can occur as primary (idiopathic) or secondary. Dopaminergic transmission dysfunction and genetic factors are among the primary causes of RLS. Both increased frequency in subjects with the family members diagnosed as RLS, and relief of symptoms with L-dopa administration support this condition. Brain iron deficiency and dopaminergic neurotransmission impairments play a central role in the pathogenesis of RLS. Using special magnetic resonance imaging techniques to quantify brain iron

concentrations, RLS patients were found to have lower iron concentration in the substantia nigra and in the putamen.[5] Secondary causes which contribute RLS symptoms include iron metabolism disorders, end-stage renal disease, pregnancy, excessive alcohol consumption, vitamin B_{12}/folate deficiency, peripheral neuropathy (associated with diabetes mellitus), rheumatoid arthritis, spinal disorders such as spinal nerve root irritation, Parkinson's disease, spinocerebellar ataxia (particularly SCA 3) and Charcot-Marie-Tooth disease (type 2).[6-8]

Various medications that block dopamine such as antipsychotics (e.g.promethazine, haloperidol, olanzapine, risperidone), antidepressants (e.g. mirtazapine, escitalopram, venlafaxine, sertraline), beta-blockers, anti-nausea drugs (metoclopramide), antihistamines, anticonvulsants, L-thyroxine, and lithium can induce or worsen RLS symptoms.[7] Among the numerous antidepressants, mirtazapine may be related with higher rates of RLS and periodic limb movements. In addition, venlafaxine may be associated with an increase in RLS findings. Sertraline, fluoxetine, and amitriptyline seem to increase periodic limb movements that do not disrupt sleep and are thus unlikely to be clinically important.[9] RLS also has been reported with the combination of an antidepressant and an antipsychotic. There are a few sporadic case reports related with duloxetine-induced RLS in the literature. Nikolaou et al. presented a patient with RLS associated with combination of duloxetine and paroxetine therapy.[10] Another case was reported with both galactorrhea and RLS symptoms induced with duloxetine.[11] In the open label trial, the frequency of drug-induced RLS symptoms with both venlafaxine and duloxetine was found less than 5%.[12] In a web-based intensive monitoring is an observational prospective cohort study about adverse effects of duloxetine in daily practice, of 398 patients using duloxetine only 6 patients (2%) have developed RLS.[13] Duloxetine-induced RLS is very rare when compared with the old generation antidepressants.

CONCLUSION

To the best of our knowledge, this case report is the first report of RLS symptoms induced by duloxetine during treatment of fibromyalgia syndrome in a female. When duloxetine-induced RLS develops, both the fibromyalgia and RLS symptoms should be controlled by taking duloxetine on alternate days.

Consent for Publication

Written informed consent was obtained from the patient for publication of this case report.

REFERENCES

1. Chahine LM, Chemali ZN. Restless legs syndrome: a review. CNS Spectr. 2006;11:511-20. [Crossref] [Pubmed]
2. Allen RP, Picchietti DL, Garcia-Borreguero D, et al; International Restless Legs Syndrome Study Group. Restless legs syndrome/Willis-Ekbom disease diagnostic criteria: updated International Restless Legs Syndrome Study Group (IRLSSG) consensus criteria--history, rationale, description, and significance. Sleep Med. 2014;15:860-73. [Crossref] [Pubmed]
3. Allen RP, Bharmal M, Calloway M. Prevalence and disease burden of primary restless legs syndrome: results of a general population survey in the United States. Mov Disord. 2011;26:114-20. [Crossref] [Pubmed]
4. Patatanian E, Claborn MK. Drug-induced restless legs syndrome. Ann Pharmacother. 2018;52:662-72. [Crossref] [Pubmed]
5. Allen RP, Barker PB, Wehrl FW, et al. MRI measurement of brain iron in patients with restless legs syndrome. Neurology. 2001;56:263-5. Erratum in: Neurology. 2015;84:105. [Crossref] [Pubmed]
6. Allen RP, Earley CJ. Restless legs syndrome: a review of clinical and pathophysiologic features. J Clin Neurophysiol. 2001;18:128-47. [Crossref] [Pubmed]
7. Klingelhoefer L, Bhattacharya K, Reichmann H. Restless legs syndrome. Clin Med (Lond). 2016;16:379-82. [Crossref] [Pubmed] [PMC]
8. Lin XW, Zhang JF, Qiu MY, et al. Restless legs syndrome in end stage renal disease patients undergoing hemodialysis. BMC Neurol. 2019;19:47. [Crossref] [Pubmed] [PMC]
9. Kolla BP, Mansukhani MP, Bostwick JM. The influence of antidepressants on restless legs syndrome and periodic limb movements: a systematic review. Sleep Med Rev. 2018;38:131-40. [Crossref] [Pubmed]
10. Nikolaou KN, Michopoulos I, Douzenis A, et al. Restless legs syndrome associated with the combined use of duloxetine plus paroxetine. J Clin Psychopharmacol. 2015;35:345-6. [Crossref] [Pubmed]
11. Belli H, Akbudak M, Ural C. Duloxetine-related galactorrhea and restless legs syndrome: a case report. Psychiatr Danub. 2013;25:266-7. [Pubmed]
12. Rottach KG, Schaner BM, Kirch MH, et al. Restless legs syndrome as side effect of second generation antidepressants. J Psychiatr Res. 2008;43:70-5. [Crossref] [Pubmed]
13. Härmark L, van Puijenbroek E, van Grootheest K. Intensive monitoring of duloxetine: results of a web-based intensive monitoring study. Eur J Clin Pharmacol. 2013;69:209-15. [Crossref] [Pubmed] [PMC]