JRD Journal of Rheumatic Diseases Vol. 23, No. 5, October, 2016
https://doi.org/10.4078/jrd.2016.23.5.332

Case Report

Serotonin Syndrome following Duloxetine Administration in a Fibromyalgia Patient: Case Report and Literature Review

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Serotonin syndrome, an adverse drug reaction, is a consequence of excess serotonergic agonism of central nervous system receptors and peripheral serotonergic receptors. Serotonin syndrome has been associated with large numbers of drugs and drug combinations, and serotonin-norepinephrine reuptake inhibitor-induced serotonin syndrome is rare. It is often described as a sign of excess serotonin ranging from tremor in mild cases to delirium, neuromuscular rigidity, and hyperthermia in life-threatening cases. Diagnosis is based on the symptoms and patient's history, and several diagnostic criteria have been developed. We experienced a rare case of fibromyalgia accompanied by tremor, hyperreflexia, spontaneous clonus, muscle rigidity, and diaphoresis after 10 days of single use of duloxetine 30 mg. Only one case of serotonin syndrome resulting from administration of duloxetine has been reported in Korea, however that case resulted from co-administration of fluoxetine. We report here on this case along with a review of the relevant literature. **(J Rheum Dis 2016;23:332-335)**

Key Words. Serotonin syndrome, Fibromyalgia, Duloxetine

INTRODUCTION

Serotonin syndrome is a rare drug reaction resulting from the use of serotonergic medications. The list of drugs and drug combinations associated with serotonin syndrome is extensive, generally occurring in patients who have ingested drugs that cause a synergistic increase in synaptic serotonin. These include monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), opioid analgesics, antibiotics, antiemetics, and herbal products [1]. Serotonin-norepinephrine reuptake inhibitors (SNRIs)-induced serotonin syndrome is rare, and occurs mainly with co-administration of SSRIs or opioids [2-4]. Symptoms range from mild to life-threatening, with signs of excess serotonin ranging from tremor and diarrhea in mild cases to delirium, neuromuscular rigidity, and hyperthermia in life-threatening cases. Diagnosis is based on the symptoms and patient's history, and several diagnostic criteria have been developed. Management involves removal of the precipitating drugs, provision of supportive care, control of agitation, administration of 5-hydroxytryptamin (5-HT)$_{2A}$ antagonists, control of autonomic instability, and control of hyperthermia [1].

We experienced a rare case of fibromyalgia accompanied by tremor, deep tendon hyperreflexia, spontaneous clonus, muscle rigidity, agitation, akathisia and diaphoresis after 10 days of single use of duloxetine 30 mg. Only one case of serotonin syndrome resulting from administration of duloxetine has been reported in Korea [5], however that case was reported to occur with the co-administration of fluoxetine. No case involving single use of duloxetine-induced serotonin syndrome has been reported. We report here on this case along with a review of the relevant literature.

Received : April 21, 2016, **Revised :** June 10, 2016, **Accepted :** June 29, 2016

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pISSN: 2093-940X, eISSN: 2233-4718

CASE REPORT

Patient information

A 24-year-old female.

Chief complaint

Sudden onset of involuntary movement of head and coarse tremor of both extremities, deep tendon hyperreflexia, inducible clonus, muscle rigidity, agitation, akathisia, accompanied by diaphoresis, mild fever, tachycardia, tachypnea, and mydriasis.

Past history

The patient was diagnosed with fibromyalgia in December 2008 and had been taking pregabalin 75 mg daily. She had experienced exacerbated whole body pain, particularly lower back pain with right leg pain since April 2015. Radiologic findings of lumbar spine demonstrated straightening of lumbar curvature. Despite prescription of a higher dose of pregabalin (75～150 mg) and cyclobenzaprine, the symptoms persisted. In March 2016, she started single use of duloxetine 30 mg and reported mild improvement in both back pain and right leg pain.

Familial history

Unremarkable.

Present illness

After 10 days of single use of duloxetine 30 mg, she developed sudden onset of involuntary movement and tremor. The episode started once her physiotherapy for back pain and right leg pain was completed. She experienced dizziness and nausea, accompanied by repetitive rotation of head and involuntary twitching movement of both hands, which discontinued after 20 minutes but restarted and she was brought to the emergency department of our hospital.

On examination, her mentality was clear and she exhibited mild fever (37.2°C), tachypnea (22 breaths/minute), tachycardia (133 beats/minute), generalized tremor, myoclonus, inducible clonus, deep tendon hyperreflexia, agitation, akathisia and marked diaphoresis. Bowel sounds increased slightly, but there was no history of diarrhea.

She denied use of any over-the-counter and prescription drugs or supplements prior to development of episodes. The possibility of serotonin syndrome was considered, therefore duloxetine was stopped and she was managed with benzodiazepines. Despite injection of benzodiazepines, her symptoms persisted, thus cyproheptadine was added on next day. The results of routine examinations, including hematological and biochemical screening were normal and neurologic examination, was also normal. A

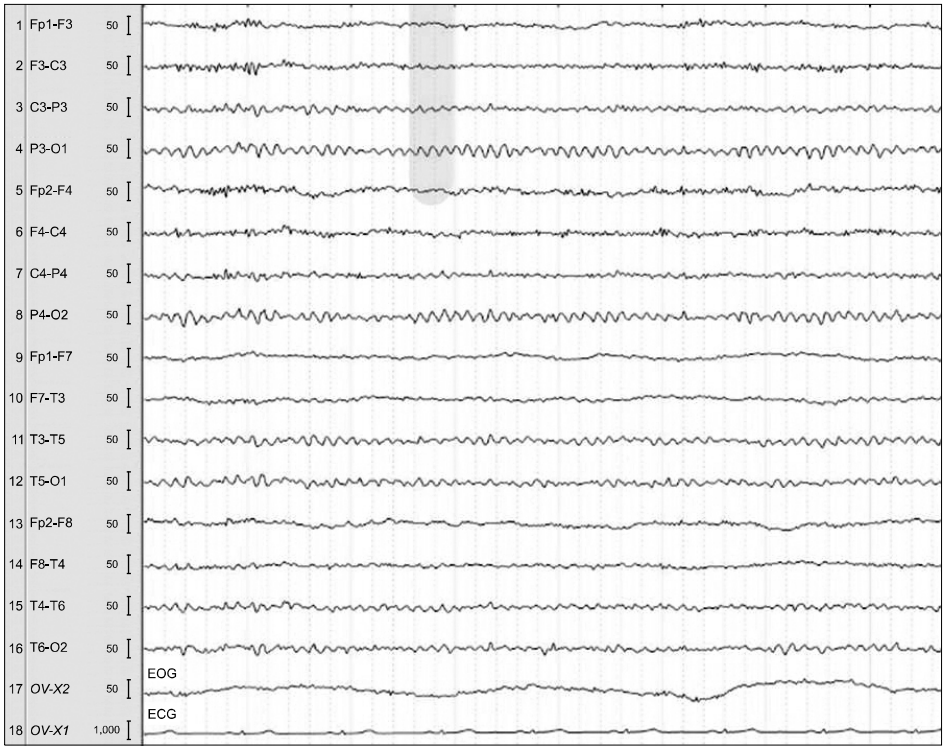

Figure 1. 18-channel electroencephalogram with electrocardiography (ECG) monitoring performed with a patient in awake to drowsy state. EOG: electrooculography.

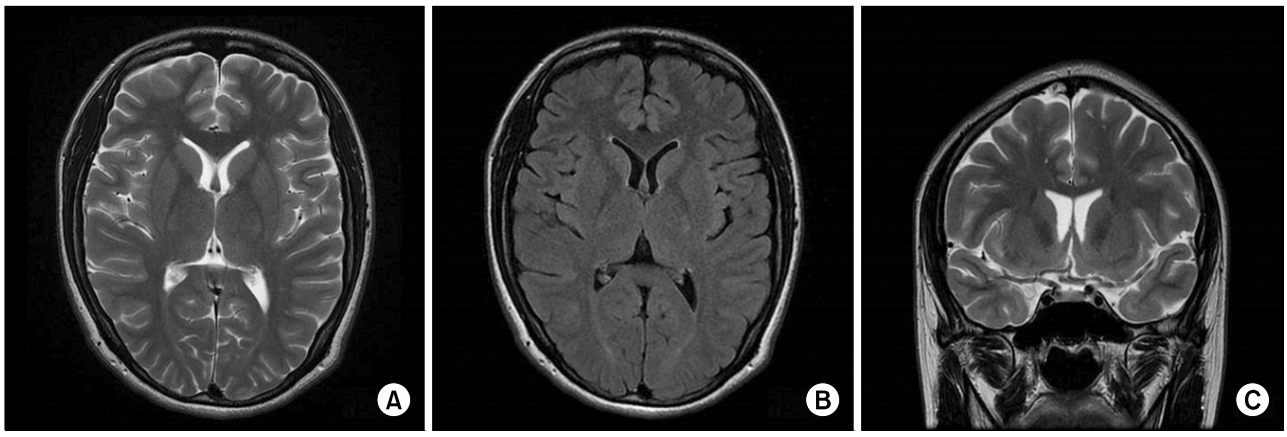

Figure 2. Brain magnetic resonance imaging (MRI). (A) Axial T2-weighted MRI. (B) Axial FLAIR MRI. (C) Coronal T2-weighted MRI.

neurological consult was performed and physical examination confirmed the diagnosis of serotonin syndrome. Electroencephalogram (EEG) (Figure 1) showed no epileptiform discharge or focal slowing. No abnormal findings were detected on brain magnetic resonance imaging (Figure 2). Several days after admission, muscle hypertonicity, predominant lower limbs rigidity, diaphoresis, and foot clonus recurred two or three times per day. The patient was continued on benzodiazepines and cyproheptadine, and she showed complete improvement of autonomic and neurological symptoms after 15 days. She was discharged in a stable condition without neurological signs.

DISCUSSION

Serotonin syndrome is a rare drug interaction involving clinical manifestation of excess serotonin at postsynaptic serotonin receptors [6]. Serotonin receptors are divided into seven 5-HT families and no single receptor appears to be responsible for the development of serotonin syndrome, although evidence suggests that agonism of 5-HT_{2A} receptors contributes substantially to the condition [1]. Noradrenergic central nervous system (CNS) hyperactivity may play a critical role. The degree to which CNS norepinephrine concentrations are increased in serotonin syndrome may correlate with the clinical outcome. Other neurotransmitters, such as N-methyl-D-aspartate (NMDA) receptor antagonists and γ-aminobutyric acid (GABA), may affect development of the syndrome [7].

The three main mechanisms, in relation to serotonin syndrome, are inhibition of reuptake, presynaptic release, and MAO inhibition. Medications so far implicated in serotonin syndrome are mainly the combination of MAO inhibitors, with SSRIs, TCAs, or opioid analgesics. It has been suggested that the risk of inducing serotonin syndrome might be higher with administration of SNRIs than with SSRIs, particularly when combined with a 5-HT_{1A} antagonist [8]. However, single use of SNRI-induced serotonin syndrome is rare, and mainly occurs with co-administration of SSRI or opioids. Data on the relative risk with milnacipran and duloxetine will be interesting, however in view of the lack of systemic research, sufficient data are unlikely to be available for some time.

Serotonin syndrome encompasses a range of clinical findings. Representative clinical features include 1) neuromuscular hyperactivity—tremor, clonus, myoclonus, hyperreflexia, and pyramidal rigidity, 2) autonomic hyperactivity—diaphoresis, fever, tachycardia, tachypnea, and mydriasis, 3) altered mental status – agitation, and in the advanced stage, confusion [8]. The onset of symptoms is usually rapid, and approximately 60% of patients present within 6 hours after initial dose of medication, an overdose, or a change in dosing. However, 25% of patients present after 24 hours [1]. In this case, the symptoms developed after 10 days of single use of duloxetine 30 mg, which might be due to single use of SNRIs, rather than the use of polypharmacy which may arise from pharmacodynamic interaction in development of serotonin syndrome. Patients with mild manifestations may present with subacute or chronic symptoms, whereas severe cases may show rapid progression to death.

Serotonin syndrome is a clinical diagnosis and no laboratory test is confirmatory. Differential diagnosis includes anticholinergic toxicity, neuroleptic malignant syndrome, and malignant hyperthermia. Clonus is the most important finding in confirming the diagnosis of serotonin syndrome [9]. The Hunter toxicology criteria de-

cision rules are the most widely used diagnostic criteria [10]. Patients meeting the criteria must be on a serotonergic agent and have one of the following: spontaneous clonus, inducible clonus plus agitation or diaphoresis, ocular clonus plus agitation or diaphoresis, tremor plus hyperreflexia, hypertonia plus temperature $>38^{\circ}C$ plus ocular clonus or inducible clonus. Our patient had spontaneous clonus and tremor plus hyperreflexia on presentation, and physical examination and detailed review of her medication confirmed the diagnosis, meeting Hunter criteria.

Removal of the precipitating drugs and supportive care, including administration of intravenous fluids and correction of vital signs, remain a mainstay of therapy. The intensity of therapy depends on the severity of illness. Severely ill patients should receive immediate sedation, control of agitation, and orotracheal intubation. Pharmacologically directed therapy involves the administration of 5-HT_{2A} antagonists. Cyproheptadine is the recommended therapy. Atypical antipsychotic agents with 5-HT_{2A} antagonist activity, such as olanzapine, may be beneficial. Control of autonomic instability involves stabilization of fluctuating pulse and blood pressure. Control of hyperthermia involves elimination of excessive muscle activity. There is no role for antipyretic agents, because the increase of body temperature is due to muscular activity, not an alteration in the hypothalamic temperature set point.

Many cases typically resolve within 24 hours after the discontinuation of serotonergic drugs, but symptoms may persist in patients taking drugs with long elimination half-lives, active metabolites, or protracted duration of action [1]. In this case, symptoms persisted for 14 days, which may be due to the protracted use of duloxetine.

Serotonin syndrome can be avoided by a combination of pharmacologic research, education of physicians, and modifications in prescribing practices. The avoidance of multidrug regimens is critical to prevent of serotonin syndrome. Application of pharmacogenomic principles can potentially protect patients at risk for the syndrome before administration of serotonergic agents.

Although few cases of serotonin syndrome in fibromyalgia patients have been reported, it is a severe, life-threatening condition requiring early detection and management. A timely, multidisciplinary approach to treatment could provide a reduction of symptoms, and clinicians should look for subtle symptoms of serotonin syndrome including agitation, tremor, anxiety, tachycardia, diarrhea, and diaphoresis. Awareness of serotonin syndrome remains most important in its earlier detection.

SUMMARY

We herein reported on a rare case of fibromyalgia accompanied by tremor, hyperreflexia, spontaneous clonus, muscle rigidity, and diaphoresis after 10 days of single use of duloxetine 30 mg. Serotonin syndrome should be considered in patients using serotonergic medications, and requires early detection and management.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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