Psychiatria Danubina, 2022; Vol. 34, No. 4, pp 738-740 https://doi.org/10.24869/psyd.2022.738 *Case report*

RESTLESS LEGS SYNDROME AFTER ARIPIPRAZOLE DISCONTINUATION: A CASE REPORT AND REVIEW OF LITERATURE

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received: 27.4.2022; revised: 30.6.2022; accepted: 18.7.2022

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INTRODUCTION

Restless Legs Syndrome (RLS) is a neurological disorder characterized by an urge to move the legs, usually in response to unpleasant sensations that begin or worsen during periods of rest. RLS may occur primarily with no apparent cause other than genetic predisposition or secondarily, with accompanying conditions such as iron deficiency, pregnancy, and kidney failure. Dopaminergic dysfunction is thought to be associated with the disorder, and dopamine agonists are used in its treatment (Allen 2007, 2014). Obsessive-compulsive disorder (OCD) has been associated with serotonergic and dopaminergic neurotransmitter dysfunction. Antipsychotic augmentation is recommended when serotonin reuptake inhibitors (SRI) as first-line pharmacotherapy in OCD are ineffective or only partially beneficial (Del Casale et al. 2019). Here, we present a case of RLS emerging after discontinuation of aripiprazole, which had been initiated as augmentation treatment in an OCD patient.

CASE

A 32-year-old woman diagnosed with OCD had been followed-up since August 2013 in our psychiatric outpatient clinic with obsessive thoughts that she might have harmed children, compulsions to check for signs of possible harm, seeking reassurance, and avoiding children. There was no history of any other medical illness. Her family history was unremarkable. She had previously used clomipramine, sertraline, fluoxetine, fluvoxamine, and amisulpride with no significant improvement. Lastly, she was receiving venlafaxine 300 mg and aripiprazole 10 mg in addition to cognitive behavioral therapy. After a two-year remission, aripiprazole was gradually decreased over 20 months and stopped completely. She reported that she had been having trouble sleeping because of unpleasant sensations that arose in her legs during the nighttime just after the discontinuation of aripiprazole. She described these sensations as "pulling," accompanied by a persistent need to move her legs for relief. The patient emphasized that there had been no such symptoms prior to the cessation of aripiprazole. Subsequent laboratory tests showed that her blood ferritin level was 11 ng/mL (normal limits: 12-263 ng/mL) and her iron level was 51.9 mcg/dL (normal limits: 37-145 mcg/dL). It was found that iron and ferritin levels had also been low in previous laboratory tests, but she had not been adequately treated due to side effects of iron replacement treatment. Nevertheless, she had never experienced RLS symptoms before. The patient was referred to the neurology department and pramipexole 0.25 mg/day was started with the diagnosis of RLS. Her symptoms disappeared completely after pramipexole treatment.

DISCUSSION

This patient met the diagnostic criteria for RLS. Akathisia and withdrawal dyskinesia were excluded since the symptoms appeared only at night and dramatically improved after being started on pramipexole, known to be effective in RLS (Allen et al. 2014, Liu et al. 2016). Besides, she described her symptoms as a disturbing feeling in her legs rather than an involuntary, repetitive movement observed in dyskinesia.

Dopamine deficiency is the most commonly hypothesized cause in the pathophysiology of the RLS. On the other hand, findings showing normal or increased dopamine activation in the central nervous system have also been reported (Allen 2007, Trenkwalder & Paulus 2010, Koo et al. 2016). Furthermore, iron deficiency has been consistently shown to be associated with RLS in case reports, animal models, autopsy, cerebrospinal fluid, and neuroimaging studies (Allen 2007, Trenkwalder & Paulus 2010). This is related to the fact that iron is a cofactor of tyrosine hydroxylase, the rate-limiting enzyme of catecholamine synthesis, and thus impaired iron metabolism causes dopaminergic system alterations (Allen 2007, Koo et al. 2016). Pharmacological treatments, particularly antidepressants,

Table 1. A review of cases of restless legs syndrome associated with aripiprazole

Author	Age	Diagnosis	Treatment	Management/Outcome
Bolaños-Vergaray et al. 2011	45	Major depressive disorder	Olanzapine 5 mg/d and increasing Aripiprazole from 5 mg to 15 mg/d	RLS symptoms emerged after increasing aripiprazole dosage, and after discontinuation, RLS symptoms disappeared.
Kikukawa 2008	42	Attention deficit hyperactivity disorder and restless legs syndrome	Aripiprazole 3 mg/d (administered in the morning)	ADHD symptoms improved after two weeks of treatment, but RLS symptoms continued for six weeks. Symptoms disappeared after changing the time of administration.
Raveendranathan et al. 2013	34	Paranoid schizophrenia	Clozapine 200 mg/d and aripiprazole 10 mg/d	Within the first week of initiating clozapine, RLS symptoms developed. The patient was prescribed aripiprazole 10 mg/d as an augmenting agent to clozapine. Within two days of adding aripiprazole, her RLS symptoms subsided.
Virit et al. 2009	39	Trichotillomania and restless legs syndrome	Aripiprazole 5 mg/d for TTM symptoms	Both TTM and RLS symptoms responded to aripiprazole up to 90% after six weeks.

ADHD: Attention deficit hyperactivity disorder; RLS: Restless legs syndrome, TTM: Trichotillomania

antipsychotics, and antiepileptics, have also been associated with the onset or worsening of RLS. It has been reported that RLS occurs secondary to several antidepressants (Jagota et al. 2012, Patatanian & Claborn 2018), especially mirtazapine (Rottach et al. 2008), and antipsychotics such as quetiapine (Urbano & Ware 2008), olanzapine (Aggarwal et al. 2010, Basu et al. 2014), clozapine (Duggal & Mendhekar 2007, Raveendranathan et al. 2013), and risperidone (Wetter et al. 2002). The mechanism of antipsychotic and antidepressant-induced RLS has been linked to dopaminergic dysfunction as well as changes in serotonin and norepinephrine activity (Patatanian & Claborn 2018). However, aripiprazole has a different mechanism from other antipsychotics in that it acts as a partial agonist at D2 and 5-HT1A receptors and an antagonist at 5-HT2A receptors, thereby acting as a "dopamine stabilizer" by changing dopaminergic activity in diverse regions of the brain (Stahl 2013). To our knowledge, three cases in which RLS was improved and one case in which it was induced have been reported with aripiprazole (Table 1).

The presence of chronic iron deficiency in our case and a history of RLS-like symptoms in her father indicates the predisposition of the patient to develop RLS. Venlafaxine treatment may also have contributed to the manifestation of symptoms, but not having RLS symptoms previously despite the long-term administration makes it difficult to determine a clear association. Although a direct impact can not be claimed in our case, it is still plausible to highlight the role of aripiprazole, given that the patient attributed her complaints directly to the discontinuation of aripiprazole and that she had no RLS symptoms before. The vulnerability of this patient to dopaminergic dysfunction might have manifested with RLS symptoms after the dopaminergic stabilizing effect of aripiprazole had ceased.

Clinicians should be aware of RLS as it can cause sleep disturbance, which is also seen in many psychiatric disorders, and it can be confused with psychotropic-related side effects such as akathisia. A comprehensive assessment, taking into account the patients' history and risk factors, and an accurate diagnosis are crucial in preventing inappropriate treatments and improving their quality of life. In light of the present case and previous reports showing the improving effect of aripiprazole on RLS symptoms, aripiprazole can be considered as a treatment alternative in patients with susceptibility to RLS or with psychotropic-induced RLS history. However, more direct evidence is needed regarding the relieving impact of aripiprazole on RLS symptoms.

Acknowledgements: None.

Conflict of interest: None to declare.

Contribution of individual authors:

Gonca Dokuz: study design, acquisition of case history, writing, interpretation of data, literature search.

Serhat Ergün: writing, literature search

Volkan Topçuoğlu: writing, interpretation of data, first draft.

All authors approval of the final version.

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