

Olanzapine-induced restless leg syndrome (Willis–Ekbom disease): A case report

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Abstract

Restless leg syndrome, also known as Willis–Ekbom disease, is a neurological sensorimotor disorder accompanied by an irresistible urge to move the legs with a fluctuating course of symptoms. It is a common disorder affecting all ages, with existing comorbidities and positive family history being associated with increased prevalence. Herein, we present a case of a 51-year-old female diagnosed with the bipolar affective disorder who developed restless leg syndrome following the use of olanzapine. Olanzapine is a second-generation antipsychotic which can cause restless leg syndrome due to its anti-dopaminergic action on the nervous system, particularly the spinal cord. Existing literature on olanzapine-induced restless leg syndrome has suggested managing this disorder by reducing the dose or replacing olanzapine with other drugs such as clonazepam, quetiapine, and aripiprazole. In our case, olanzapine was not replaced with other medications as the patient showed a significant improvement in bipolar affective disorder symptoms using olanzapine. Instead, clonazepam was added to the treatment regimen which was scheduled to be taken before olanzapine.

Keywords

Case report, olanzapine, antipsychotic, restless leg syndrome, second-generation antipsychotic, Willis–Ekbom disease

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Introduction

Restless leg syndrome (RLS), also known as Willis–Ekbom disease, is a neurological sensorimotor disorder accompanied by an irresistible urge to move legs with a fluctuating course of symptoms.^{1–3} It is a common disorder affecting all ages, with prevalence ranging from 4% to 29% across the globe.^{4–7} Existing comorbidities and positive family history are associated with increased prevalence of RLS.^{5,7} Oftentimes, RLS with increased severity is reported in iron deficiency anemia (IDA) patients.^{8,9} So far, literature mentions that RLS can be managed using $\alpha 2\delta$ ligands or low doses of dopaminergic drugs, with the treatment of existing comorbidities to prevent augmentation of the condition.¹⁰ Olanzapine is a second-generation antipsychotic which can cause RLS due to its anti-dopaminergic action on the nervous system particularly the spinal cord, and existing literature on olanzapine-induced RLS has suggested managing this disorder by reducing the dose or replacing olanzapine with other drugs such as clonazepam, quetiapine, and aripiprazole. In our case report, we present a case of a 51-year-old female diagnosed with the bipolar affective disorder (BD) who developed RLS following the use of olanzapine.

Olanzapine was not replaced with other medications as the patient showed a significant improvement in BD symptoms using olanzapine. Instead, clonazepam was added to the treatment regimen which was scheduled to be taken before olanzapine.

Case report

A 51-year-old female, with 24 years history of BD, presented to the psychiatric unit with her family. She was alert, had fair hygiene, and had good eye contact. Informants described her

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Table 1. Investigation and results.

Investigations	Result	Normal reference range
Albumin/globulin ratio	1.2	0.8–2.0
Alkaline phosphatase	105	44–147 IU/L
Total serum bilirubin	0.31	0.1–0.2 mg/dl
Serum globulin	3.7	2.0–3.5 g/dl
Total serum protein	7.88	6–8.3 g/dL
Basophils	0.8	0.5%–1%
Eosinophils	9.2	1%–4%
Packed cell volume	33.2	35.5%–44.9%
Hemoglobin	10.5	11.6–15 g/dL
Lymphocytes	20.2	20%–40%
Mean corpuscular hemoglobin concentration	31.7	32–36 g/dL
Mean corpuscular hemoglobin	24.1	27–31 pg/cell
Mean corpuscular volume	76.1	80–92 fl
Monocytes	8.3	2%–8%
Neutrophils	61.5	54%–62%
Platelet count	503	150–450 × 10 ³ /mCL
Erythrocyte count	4.36	4.2–5.4 million cells/ mCL
Total leukocyte count	9.1	4.5–11 × 10 ⁹ /L
Ammonia plasma	56	15–45
Serum valproate	87	50–125 mcg/mL
Serum lithium	0.79 mEq/L	0.6–1.2 mEq/L

with increased psychomotor activity, tone, volume, and speech tempo, aggressiveness, irritability, muttering to self, decreased need for sleep, and frequent anger outbursts for 4 months, with worsened symptoms 3 weeks prior to presentation, suggestive of a manic episode of BD. The patient was oriented to person and place. She also had a history of nicotine use in the form of chewing betel leaf. Her mental status examination suggested a delusion of persecution and reference, second person auditory hallucinations, irritable mood, dysphoric affect, crying spells, impaired judgment, and absence of insight and impulse control.

On investigation, her complete hemogram showed an Hb concentration of 10.5 g/dL, and MCV 76.1 as shown in Table 1. Henceforth, she was also diagnosed to have IDA. Initial lithium concentration in the serum was undetectable. Other hematological and biochemical parameters, including blood sugar, MCHC, MCH, HCT/PCV, RBC count, platelet count, renal, liver, and thyroid function were within normal limits as shown in Table 1.

The patient was admitted to the inpatient psychiatric hospital for her manic symptoms, and risperidone was initiated at a dose of 2 mg, which was consequently titrated to 6 mg. The patient however developed postural hypotension, for which it was tapered and stopped. Lithium in the dose of 900 mg was given. However, the patient showed no improvements. Hence, lithium was cross-tapered with valproate, and valproate was titrated up to 1500 mg. As lithium and valproate both showed partial improvements, a combination of lithium and valproate was maintained. Olanzapine was started at a dose of 10 mg, which was increased to 30 mg

after 3 days owing to partial improvement. The patient complained of irritative sensation in the bilateral calf muscles after 6 days of starting olanzapine 30 mg, which improved during movement, worsened on rest, and was particularly distressing at night. Diagnostic criteria from the International RLS Study Group (IRLSSG) are as follows:

1. An urge to move the legs usually but not always accompanied by or felt to be caused by uncomfortable and unpleasant sensations in the legs.
2. The urge to move the legs and any accompanying unpleasant sensations begin or worsen during periods of rest or inactivity such as lying down or sitting.
3. The urge to move the legs and any accompanying unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues.
4. The urge to move the legs and any accompanying unpleasant sensations during rest or inactivity only occur or are worse in the evening or night than during the day.
5. The occurrence of the above features is not solely accounted for as symptoms primary to another medical or behavioral condition (e.g. myalgia, venous stasis, leg edema, positional discomfort, and habitual foot tapping).

Based on the IRLSSG diagnostic criteria, the patient met all the criteria and was diagnosed with RLS, for which

clonazepam 1 mg/day was started, and instructed to take clonazepam before olanzapine. The patient showed improvement after the addition of clonazepam.

Discussion

In this patient, we considered a differential diagnosis of volitional movements, akathisia, leg cramps, psychogenic cause, and peripheral neuropathy.¹¹ Although there was no significant family history of RLS in the patient, she had IDA, which is associated with increased prevalence and severity of RLS.^{8,9} Also, it is possible that IDA leads to alteration of dopaminergic receptor profile and contributes to RLS.¹¹ Since the symptoms suggesting RLS began only after a few days of administration of olanzapine, and her IDA existed before her admission to the hospital, we suspected olanzapine to be the root cause for her RLS with IDA worsening the severity of the syndrome. She was managed with iron supplementation, and clonazepam to treat RLS along with her drug regimen for BD.

Basu et al.¹¹ and Aggarwal et al.¹² reported symptoms of RLS on 15 mg/day of olanzapine. Other studies reported symptoms of RLS in patients on 20 mg/day of olanzapine.^{13,14} Also, Kraus et al.¹³ found symptoms of RLS on 20 mg/day of olanzapine in a female in her fifties diagnosed with BD. So far, olanzapine-induced akathisia has been reported in both males and females with bipolar disorder or schizophrenia.^{11–15} In our case, the patient was a female in her 50s, diagnosed with BD, and reported symptoms after 6 days of olanzapine at 30 mg/day.

It is hypothesized that olanzapine can lead to RLS due to its anti-dopaminergic action on the nervous system, particularly the spinal cord.¹¹ It is interesting to note that risperidone, an anti-dopaminergic drug, was used in our case. However, the patient did not show RLS following the use of risperidone. This warrants further investigation into the probable mechanism leading to RLS, which may reveal other possible mechanisms leading to this condition.

Earlier cases of olanzapine-induced RLS were managed by reducing the dose or replacing olanzapine with other drugs such as clonazepam, quetiapine, and aripiprazole depending on the response.^{3,11} Kraus et al.¹³ managed the condition by replacing olanzapine with quetiapine. In a case series of five patients, the management was done by either reducing the dose, stopping the drug, or replacing it with alternatives such as ropinirole and clonazepam.¹⁵ In another case series, patients were managed by replacing olanzapine with risperidone, quetiapine, or aripiprazole.¹² In our case, we did not replace olanzapine, as the patient showed improvement in BD. Instead, we added clonazepam before taking olanzapine as it was a safe drug for these patients and effective in treating RLS.^{3,16}

Conclusion

We present the case of a female in her 50s diagnosed with the BD who developed RLS after using olanzapine 30 mg/day for 6 days. The addition of clonazepam before taking olanzapine was given to manage RLS in the context of olanzapine. Olanzapine dose was not decreased as the patient showed improvement in BD symptoms. This case adds to the existing literature on diagnosing and managing olanzapine-induced RLS. Our case showed that RLS could be managed by adding benzodiazepines without switching, stopping, or decreasing the dosage of antipsychotics such as olanzapine if the patient shows improvement in psychiatric symptoms using antipsychotics like olanzapine.

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Ethics approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed consent

Written informed consent was obtained from the patient for their anonymized information to be published in this article. Patient regained fair insight and judgment over the course of her treatment regime to provide written informed consent by herself.

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