Case Report

Restless Legs Syndrome in Opioid Dependent Patients

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ABSTRACT

Although frequently underdiagnosed, several epidemiological studies have estimated the prevalence of restless legs syndrome (RLS) in western countries at 5-15% of the general population. The diagnosis is usually made on a clinical basis, according to the criteria established by the international RLS study group. There are case reports of transient RLS in opiate withdrawal. We describe three opiate (dextropropoxyphene (DPP)) dependent young male patients; two of them had DPP intoxication/withdrawal seizure developing RLS during opiate withdrawal. However, their RLS persisted even after the remission of other withdrawal symptoms. Thyroid function test, hemogram, serum ferritin were normal in all of them. The cases responded well to a treatment with ropinirole. Hence, there might be a causal association, which required further well-designed studies to substantiate. The sleep disturbances and use of benzodiazepines can be minimized by increasing clinician's sensitivity to diagnose RLS.

Key words: *Dopamine, opioid dependence syndrome, restless legs syndrome*

INTRODUCTION

Opioid dependence is currently seen as a biopsychosocial disorder. Opioids can induce long-lasting alterations in the nervous system. On the other hand, restless legs syndrome (RLS) is a sensorimotor disorder affecting sleep. The prevalence of RLS is estimated at 5-15% of adults, with a relatively linear increase with age and a roughly 50% excess in women. RLS is a clinical diagnosis and is based on the following four essential criteria from the patient's history (as per National Institute of Health criteria):[1]

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1. An urge to move the legs, usually accompanied by uncomfortable and unpleasant leg sensations.
2. Symptoms are worse when lying or sitting.
3. Symptoms are at least partially relieved by movement.
4. Symptoms are worse in the evening or at night.

Transient restless leg syndrome as a complication of opiate withdrawal is known from case report and case series.[2,3] However, persistent RLS even when all other symptoms of opioid withdrawal are remitted is not reported until in the literature. This case report would describe three such cases.

CASE REPORTS

Case 1

A 25-year-old male patient presented with a past history of opioid-dextropropoxyphene (DPP) intoxication seizure with no family history of either seizure or any substance abuse, after remaining abstinent for ~1.5

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years restarted DPP, which was followed by another episode of generalized seizure. However, he continued DPP in dependent pattern for last 4 months.

Case 2

A 26-year-old male patient with no significant past and family history was dependent to opioid (DPP) for last 4 years. He had four episodes of generalized seizure once in withdrawal and others during intoxication. In addition, he started abusing steroid (dexamethasone) for last 6 months and developed exogenous Cushing's disease, which was followed by acute Addison's disease due to abrupt stoppage of steroid. For which steroid supplementation was given.

Case 3

A 32-year-old male with no significant family history and past history of trichotillomania was dependent to opioid (DPP and codeine containing cough syrup) for last 12 years. He tried to quit multiple times, also underwent rapid detoxification under anesthesia a year back, but relapsed eventually.

All these three patients were brought to Drug Deaddiction and Treatment Center, Postgraduate Institute of Medical Education and Research, Chandigarh. They had received clonidine (0.6-0.3 mg/day), non-steroidal anti-inflammatory drugs (ibuprofen/ketorolac) and benzodiazepine (BZD) (clonazepam/nitrazepam) as standard detoxification regime to relieve the withdrawal symptoms. With these medications rhinorrhea, lacrimation, loose motion, bodyache, anxiety had been resolved, but sleep problem persisted in the form of sleep induction and maintenance problem The dose of BZD was increased in each case (nitrazepam up to 30 mg and clonazepam up to 4 mg), but sleep disturbances continued even after 2 weeks.

On further enquiry, they complained creeping/crawling/burning sensation in both the lower limbs especially at night when they lie down, relieved partially by stamping feet on the bed or by walking around. Clinically, this was fulfilling the criteria for RLS. So a neurology consultation was taken to substantiate the diagnosis. Serum urea, creatinine, ferritin, thyroid function test were conducted along with electroencephalogram. All these investigations came out to be normal.

The patients were started on ropinirole 0.75 mg/day. Two of them improved with in next 2 days and the third patient required dose escalation to 1.5 mg/day to have clinical improvement. BZDs were tapered off successfully, but ropinirole was continued for next 1 month then was tapered of over 2 weeks uneventfully.

DISCUSSION

All the patients were young adults dependent to synthetic opioids for a variable period. Two of them had a history of opioid induced seizure. Their RLS like symptoms had persisted beyond 2 weeks when all other symptoms of opioid withdrawal had resolved. So RLS can be viewed as an independent disorder in these patients. It's response to dopamine agonist rather than formal treatment of withdrawal further substantiates it as a separate disorder. Let's see if there is any common etiopathogenic mechanism to explain the association between the opioid dependence and RLS. As we know dopamine[4] (as evidenced by improvement with Levo-dihydroxy phenyl alanine (L-DOPA), circadian symptom pattern, increased symptom with dopamine antagonists and decreased level of D2-receptor in the striatum, fluoro-dihydroxyphenylalanine (FDOPA) uptake was found reduced in putamen and caudate nucleus) and opioid[3] (response to opioid agonist and significant negative correlation between opioid receptor availability and severity of RLS symptoms) have being implicated for a long time in the pathogenesis of RLS. How opioid dependence can cause a relative deficient state of dopamine and opioid, is the area to be discussed.

Once in the brain, the opioid binds to opiate receptors in certain areas of the brain, part of the cerebral cortex, the ventral tegmental area (VTA), nucleus accumbens, thalamus, brainstem and spinal cord. Of which VTA, nucleus accumbens and cortex are part of the reward pathway and thalamus, brainstem and spinal cord are related to pain pathway.[5] In short-term opiates binding to opiate receptors in the nucleus accumbens, i.e., reward pathway causes increased dopamine release in the VTA. In the long run, there are more permanent subcellular changes upon chronic opioid exposure, which causes induction of adenylyl cyclase and protein kinase A which in turn causes electrical excitability and increased activity of tyrosine hydroxylase[1] (a rate limiting enzyme for dopamine synthesis) and a decrease in endogenous opiates. So in opioid withdrawal state, there is a sharp decline in the level of aforementioned substrates, causing a dopamine and opioid depleted state in brain especially in the basal ganglia/spinal cord region, implicated in RLS.

CONCLUSION

There might be an association between opioid dependence and RLS, which merits further large scale and well-designed studies. Patients withdrawing from opioids with persistent sleep disturbance should be screened for RLS before prolonging hypnotic prescriptions. The putative etiological link between the two conditions and its management implications are discussed.

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