CASE REPORT

Pramipexole induced psychosis in a patient with restless legs syndrome

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SUMMARY

In the last few years, dopamine agonists (DA) have been used as first-line treatment for restless legs syndrome (RLS), a disabling sensorimotor disorder. Only recently have they reported some possible iatrogenic side effects, as shown below. The following case presents a RLS patient who developed hallucinatory and delusional symptoms with paranoid ideation after pramipexole assumption; these symptoms gradually decreased after pramipexole suspension and treatment by an oral antipsychotic therapy (quetiapine XR). Correlation between DAs assumption and psychotic symptoms is still not clear. The development of these side effects might be related to many risk factors such as genetic susceptibility, premorbid personality and psychosocial stressor; in order to minimise the risk of iatrogenic psychosis it could be useful to assess patients' vulnerability factors selecting an alternative medication regime.

BACKGROUND

Restless legs syndrome (RLS) is defined as an intense sensation in the lower extremities, with an irresistible urge to move legs to relieve pain, that begin or worsen during periods of inactivity, particularly at night.¹ Its prevalence ranges between 3.9% and 14.3%,¹ twice as common in women compared to men² and increasing up to 80 years old.³ RLS has a significant impact on physical and mental health² with a poor quality of life.⁴⁻⁵ Dopamine agonists (DA) ropinirole⁶ and pramipexole⁷ have been considered the first choice for treating moderate-to-severe RLS. Pramipexole is an effective and well-tolerated drug⁸; however, its use could be associated with rare but serious side effects: sleep attacks, compulsive behaviours, pathological gambling and psychosis.⁹ Although not very common, we observed this last side effect in a patient affected by RLS treated with pramipexole; he had developed hallucinatory and delusional symptoms that disappeared after pramipexole suspension and treatment with quetiapine XR.

CASE PRESENTATION

The patient is a 63-year-old unemployed man who was referred to our psychiatry unit. He appeared restless and upset and with a poor compliance. He showed a careful and mistrustful nature. He described himself as a rummy kind of man, who loved jokes and pranks. He also told us that he had to change jobs many times because he often had quarrels with colleagues or bosses for petty reasons, believing he was always right. He also

mentioned that at his work place his colleagues often talked behind his back and his chief made a plot to fire him. One year ago, after he was fired, he started to feel discomfort in his legs, with pain and a burning sensation at night that often forced him to wake and stand up and walk for a while to have relief. He was hospitalised in the neurology unit and it was observed that he had nighttime leg twitching, periodical limbs movement and repetitive cramping or legs jerking during sleep. He was diagnosed with RLS and he was prescribed with pramipexole 0.25 mg/die. Despite the symptomatology improvement, after a couple of weeks he began showing several hallucinatory symptoms, either auditory or visual (he heard his wife's voice calling him; when he was lying on his bed he heard like a buzzing of a bee swarm all around his head; he saw his dead mother near his bed talking with him or the gliding ceiling or a panoramic view of the sea becoming closer from the sky to the roof). Severity of hallucinatory symptoms increased quickly over the following weeks and he became testy with his family and mistrustful with his neighbours and shopkeeper. Many times he was shouting at people speaking on TV news and talk shows, suspecting that they were speaking about him and his situation, never suspecting he could be wrong. Therefore, in August he visited our psychiatric unit. At the psychiatric examination, he showed psychomotor excitement and irritability. He was restless, hot-tempered and easy to irritate, then we had to be patient and we talked to him for a long time, choosing the right words to calm him down. His speech was fast and plentiful; his answers were pertaining to his problems but often full of useless details and characterised by tangentiality and circumstantiality. He talked about his hallucinatory symptoms as a 'brightness mind experience' referring us that before pramipexole assumption "I was walking into the darkness and now I feel like a goodness into the sky."

INVESTIGATIONS

Clinical rating was made by the Positive and Negative Syndrome Scale (PANSS) and the Schedule for the Assessment of Insight (SAI). At baseline total PANSS score was 115, with a positive PANSS score of 45 and a negative PANSS score of 16; the SAI score at baseline was 6. At 1 and 2 months follow-up psychological assessment was repeated; PANSS total score was 95 and 66, respectively. After 6 months of follow-up PANSS total score was 27 and SAI score was 12.

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DIFFERENTIAL DIAGNOSIS

Substance-induced psychosis diagnosis was confirmed with DSM IV-TR SCID I interview, that excluded other disorders like schizophrenia, schizophreniform and/or schizoaffective disorder and acute psychotic disorder. Mood disorders with psychotic manifestations were excluded too. Brain computed tomography and magnetic resonance imaging reports excluded any organic damages.

TREATMENT

It was decided to stop pramipexole immediately and he was prescribed a therapy with quetiapine XR 600 mg/day.

OUTCOME AND FOLLOW-UP

After 4 weeks of therapy, there was a gradual but steady decreasing of his psychotic symptoms and the patient showed a progressive disappearance of hallucinations (positive PANSS score 31) while delusional symptoms were not changed yet. Since he still appeared suspicious, mistrustful, testy, impulsive and verbally aggressive against neighbours and strangers, it was decided to increase quetiapine 900 mg/day and to introduce sodium valproate 200 mg/day. At 2 months of follow-up delusional symptoms were decreased (positive PANSS score 24) but he still was irritable, then sodium valproate was increased up to 300 mg/day.

The patient obtained a stable improvement of psychopathological feature after 6 months of full therapy (PANSS total score 27) also showing an increased insight of illness (SAI score 12). For this reason quetiapine was reduced to 600 mg/day. Actually, he is keeping on with the same therapy to reach full stabilisation.

DISCUSSION

This report showed a case of psychosis related to assumption of pramipexole, a DA, recently introduced for the treatment of patients affected by RLS.¹

Ropinirole and pramipexole, non-ergoline derivatives stimulating electively D2, D3 and D4 receptors, were respectively approved in 2005 and 2006 for the treatment of moderate-to-severe RLS and are currently used as first-line therapy for primary RLS.

The question whether certain dopaminergic drugs do have a higher potential to induce psychosis is not clear.¹⁰ A controversial association between psychosis and dopaminergic treatment was described.

The incidence of hallucinations after assumption of DAs was 5% for ropinirole and 7–9.3% for pramipexole in RLS patients¹¹; these data were cleared up by many factors such as a combination of genetic susceptibility, psychosocial stress and the possible dopamine supplementation.¹²

Our patient's clinical features were characterised by delusions with paranoid ideation, he preserved alertness and lack of significant cognitive impairment. This clinical setting was described by Stefanis *et al*¹² who presented a 'delusional syndrome' in a case series of four Parkinson's disease patients after treatment with DAs.

Moreover, our patient's paranoid premorbid personality was amplified because of pramipexole assumption, worsening suspiciousness and mistrustfulness. In multivariate models, Bogren *et al*¹³ provided some evidence for a relationship between premorbid cluster-A traits and psychosis vulnerability; in particular they reported paranoid personality as an important predictor of psychosis.¹³ According to literature data, pramipexole assumption could be considered as a trigger for the development of a

psychotic framework¹² in the presence of vulnerability factors such as the paranoid premorbid personality.¹⁴

In our case, we observed that premorbid personality traits may have a 'pathoplastic' effect on symptoms at the onset of psychosis. Infact, psychotic symptoms progressively disappeared simply suspending pramipexole and introducing quetiapine. Delusional syndrome in patients treated with DAs shares similarities either with schizophrenic paranoid psychosis or with substance-induced psychosis (methamphetamine) confirming the dopamine overstimulation hypothesis as a possible aetiological factor.¹⁵

To minimise the risk of psychosis, the appropriate dopaminergic drug should be administered after evaluation of a patient's epidemiological and clinical features, including personality-related factors. Specific interventions such as problem solving and communication skills training can improve social functioning of at-risk patients.¹⁶

Learning points

- The question whether certain dopaminergic drugs do have a higher potential to induce psychosis than others is controversial.
- Pramipexole may play a role in inducing or exacerbating psychosis in restless legs syndrome patients.
- Paranoid premorbid personality characteristics could be amplified after pramipexole assumption and gradually decrease after its suspension, as in our case.
- To minimise the risk of psychosis, the appropriate dopaminergic drug should be administered after evaluation of patient's epidemiological and clinical features.

Contributors DC identified and managed the cases. MSS and EB have got the idea and wrote the manuscript. MCC revised it critically for important intellectual content and gave final approval of the version to be published.

Competing interests None.

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