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Delirium and Pseudoparkinsonism in a Bipolar Patient: Case Report

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Abstract

Background

Bipolar patients are at higher risk of delirium, in comparison to other psychiatric patients, regardless of being under lithium treatment. Indeed, lithium and antipsychotics are the mainstay drugs in the management of bipolar disorder. In clinical practice, the combinations of these drugs are commonly used in the management of acute phase of mania. Despite rare previous cases of olanzapine-associated delirium and cases of delirium with extrapyramidal signs due to a lithium-olanzapine combination therapy, these are mainly reported in elderly or severely ill patients.

Case Presentation

This case report illustrates a complex neuropsychiatric syndrome characterized by olanzapine-associated delirium alongside parkinsonism induced by aripiprazole, during a severe manic episode, in an antipsychotic-naïve young adult bipolar patient, under lithium maintenance treatment.

Conclusions

This case highlights the need for caution regarding delirium and extrapyramidal symptoms when treating antipsychotic-naïve bipolar patients under lithium maintenance therapy. The risk factors and the underlying physiopathology of this iatrogenic neuropsychiatric syndrome are discussed. We hypothesise a central cholinergic antagonism in the pathophysiology for delirium, and both pharmacokinetic and pharmacodynamic mechanisms for Parkinsonism, namely a putative flaw functioning of CYP2D6 or CYP3A4 cytochromes, bringing about a failure in metabolising aripiprazole at a normal rate, and a synergistic effect of lithium and antipsychotics on dopaminergic blockade.

Keywords : Delirium; Pseudoparkinsonism; Iatrogenic Parkinsonism; Bipolar Disorder

Background

Some evidence suggest that bipolar patients are at higher risk of delirium, in comparison to schizophrenic patients, independently of being under lithium treatment (1). However, it remains unclear whether it is due to an inherent predisposition of bipolar patients or to the combination of different class drugs. Lithium and antipsychotics are the mainstay drugs in the management of bipolar disorder. In clinical practice, the combinations of these drugs are commonly used in the management of acute phase of mania.

Herein, we present an olanzapine-associated delirium and aripiprazole-induced parkinsonism case, in a healthy and antipsychotic-naïve young adult bipolar patient, under lithium maintenance treatment, in the interest of its rarity.

Case Presentation

A 46-year-old male with bipolar disorder on maintenance treatment with lithium (800 mg/day), with no other previous psychotropic medications and irrelevant past medical history, was hospitalized for dysphoric mood, grandiosity, and persecutory delusions, being initially medicated with lithium (800 mg/day), aripiprazole (20 mg/day) and diazepam (30 mg/day). Laboratory testing was unremarkable. Drugs screening was positive for cannabis. The patient denied having consumed other psychoactive drugs before admission. A shuffling gait was noticed during the first week. On day 9, aripiprazole was reduced (15 mg/day) and valproic acid (400 mg/day) was started. Owing to psychopathologic worsening, olanzapine (20 mg/day) was introduced, and mood stabilizers were gradually augmented. On day 21, shortly after the olanzapine dose increase (25 mg/day), the patient manifested a clinical

picture characterized by psychomotor agitation alternating with somnolence, festination, loss of arm swing movements, rigidity (scoring 3 on the subscale III of Unified Parkinson's Disease Rating Scale – UPDRS), bradykinesia (scoring 3 on the subscale III of UPDRS), hypomimia (scoring 3 on the subscale III of UPDRS), bradyphrenia, hypophonia and slurred speech (scoring 3 on the subscale III of UPDRS). At that time, his therapeutic regimen was lithium (1000 mg/day), aripiprazole (15 mg/day), olanzapine (25 mg/day), valproic acid (1000 mg/day) and diazepam (30 mg/day). Meanwhile biperiden was added. From day 24 onwards, shortly after biperiden dose increase (4 mg/day), he developed an acute delirious state, characterized by elementary visual hallucinations (in the form of photopsias, lines and myodesopsia), delusional beliefs, carphologia (picking at non-existent "luminous rays of laser" with stereotyped hand movements), incoherent speech, dysgraphia, dyspraxia, hypoprosexia, disorientation, short-term memory impairment, superficial sleep with hypnopompic hallucinations, suggesting a diagnosis of delirium superimposed on mania. No signs of autonomic activation were observed. Delirium Rating Scale-Revised-98 (DRS-R-98) severity score was 26 and total score was 31, Mini Mental State Examination (MMSE) scored 17 and Clock Drawing Test (CDT) scored III/X. Serum levels of lithium and valproate were within normal range. Laboratorial evaluations did not reveal specific findings on complete blood count, ammonia, thyroid hormones, electrolytes, glucose, creatinine kinase, renal or liver function tests. Computed tomography brain scan was unremarkable.

On day 30, all medication was discontinued with a remarkable improvement of his mental status 24 hours later (DRS-R-98 severity score: 15, total score: 20; MMSE: 26; CDT: IX/X). Delirium symptoms subsided in less than 48 hours, remaining lacunar amnesia, and parkinsonism resolved in the following week. Since the patient still presented emotional lability, lithium therapy was reintroduced (400 mg/day) on day 36, being discharged four days later with a complete recovery.

Discussion and Conclusions

Normal serum levels of lithium can induce neurotoxicity, bringing about neuropsychiatric side effects, including delirium, either in monotherapy, or in combination with antipsychotics, such as olanzapine (2). There are also some reports of delirium induced by olanzapine either alone (3, 4), mostly in geriatric cases (5, 6, 7), or combined with lithium (2). Valproate can also induce delirium mediated by hyperammonemia (8). However, our patient's ammonia blood levels were normal and temporal relation is not in favour, making this hypothesis unlikely.

The patient was already under lithium treatment. There was an evident chronological relationship between the onset of the first signs of delirium and the olanzapine augmentation, namely the altered level of consciousness with fluctuations alongside pseudoparkinsonism, eventually manifesting a full-blown delirium triggered by the addition of biperiden to the ongoing treatment regimen. A thorough anamnesis and diagnostic workup did not reveal other obvious medical causes that could better account for the development of delirium. Moreover, the patient presented a rapid and noticeable clinical recovery when all the medication was eventually withdrawn, corroborating the iatrogenic aetiology.

Iatrogenic delirium may occur by several mechanisms, involving different neurochemical circuitry, via an increase in the production of dopamine and glutamate and a decrease in cholinergic activity. Anticholinergic medications and their metabolites predominantly induce delirium through competitive antagonism of postsynaptic M1 muscarinic receptors. Both olanzapine and biperiden have high anticholinergic activity, blocking muscarinic receptors. Biperiden is a M1 receptor selective antagonist and olanzapine has a moderate affinity to the muscarinic acetylcholine receptor (9). Therefore, we hypothesize a central cholinergic antagonism in the pathophysiology of our patient's delirium, in which olanzapine was the probable cause, as an initial trigger, scoring 6 on the Naranjo Adverse Drug Reaction Probability Scale, with a further worsening after biperiden addition. The pharmacokinetic profile of olanzapine is consistent with the time course of delirium recovery after its withdrawal. Moreover, biperiden was determinant to the manifestation of a full-blown delirium. The estimated anticholinergic burden on the Modified Anticholinergic Risk Scale (mARS) scored 11 (mARS subscores: biperiden 4, olanzapine 3, lithium 2, valproic acid 1, diazepam 1).

Regarding pseudoparkinsonism, the first extrapyramidal signs (EPS) appeared when aripiprazole was added to lithium maintenance treatment. Amongst atypical antipsychotics, aripiprazole has the least prevalence of parkinsonism on its side effects. According to several studies long-term administration of aripiprazole in combination to lithium is well tolerated and there are no clinically significant effects due to pharmacokinetic interactions at therapeutic doses (10). There are few previous reports of pseudoparkinsonism with aripiprazole, some of which could be explained by an impairment in its metabolism rate or pre-existing neurologic damage (11, 12, 13, 14, 15). Likewise, in our case, pseudoparkinsonism stemmed primarily from aripiprazole, since the patient was already under lithium maintenance treatment with a good tolerance. A deficiency in CYP2D6 or CYP 3A4 cytochromes, which metabolizes aripiprazole, could be a plausible mechanism, explaining the appearance of the first EPS with the introduction of aripiprazole. The further motor impairment might be explained either by the addition of valproic acid or olanzapine. Considering that there is a synergistic effect of the olanzapine-lithium combination on dopaminergic circuitry (2, 16), since lithium inhibits pre-synaptic dopamine release and atypical antipsychotics block dopamine receptors, these mechanisms might have contributed to the parkinsonism worsening. Nevertheless, we acknowledge some limitations related to the polypharmacy of the therapeutic regimen, and the absence of antipsychotic serum level measurements to rule out toxic levels.

This case report emphasizes the occurrence of a complex iatrogenic neuropsychiatric syndrome characterized by delirium and pseudoparkinsonism in a bipolar patient with no

medical comorbidities and younger than most of the previously reported cases, highlighting the need for monitoring EPS when treating antipsychotic-naïve bipolar patients under lithium maintenance, and delirious states in manic and psychotic patients, in which delirium-specific symptoms can be obscured by more striking background psychopathology, especially in those under treatment regiments comprising drugs with muscarinic receptor activity.

Authors Statements

Ethical Statements

The authors certify that this case report was performed in accordance with the ethical standards as laid down in the declaration of Helsinki and its later amendments or comparable ethical standards for research involving human participants and/or animals.

Consent for Publication

Not applicable.

Competing Interests

The authors declare that they have no potential conflict of interest to disclose.

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Author's Contributions

Joana Regala (first author): Psychiatric assessment of the patient. Preparation of the manuscript.

Camila Nóbrega (second author): Neurological assessment of the patient. Scientific review.

João Gama-Marques (third author): Preparation of the manuscript. Scientific review.

Francisco Moniz-Pereira (fourth author): Psychiatric assessment of the patient. Scientific review and approval of the final version of the manuscript.

References

1. Ritchie J, Steiner W, Abrahamowicz M. Incidence of and risk factors for delirium among psychiatric inpatients. *Psychiatr Serv* 1996; 47:727-30. https://doi.org/10.1176/ps.47.7.727
2. Tuglu C, Erdogan E, Abay E. Delirium and Extrapyramidal Symptoms Due to a Lithium-Olanzapine Combination Therapy: A Case Report. *Journal of Korean Medical Science*. 2005; 20:691-4. https://doi.org/10.3346%2Fjkms.2005.20.4.691
3. Robinson RL, Burk MS, Raman S. Fever, delirium, autonomic instability, and monocytosis associated with olanzapine. *J Posgrad Med*. 2003; 49:95. https://doi.org/10.4103/0022-3859.916
4. Morita T, Tei Y, Shishido H, Inoue S. Olanzapine-induced delirium in a terminally ill cancer patient (letter). *J Pain Symptom Manage*. 2004; 28: 102-3. https://doi.org/10.1016/j.jpainsymman.2004.04.008
5. Lim CJ, Trevino C, Tampi RR. Can olanzapine cause delirium in the elderly? *Ann Pharmacother. 2006; 40*(1):135-8. https://doi.org/10.1345/aph.1g318
6. Sharma RC, Aggarwal A. Delirium associated with olanzapine therapy in an elderly male with bipolar affective disorder. *Psychiatry Investig. 2010;7*(2):153-154. https://doi.org/10.4306%2Fpi.2010.7.2.153
7. MacKintosh D. Olanzapine induced delirium - a "probable" adverse drug reaction. *Annals of Palliative Medicine*. 2017; 6:257-259. https://doi.org/10.21037/apm.2017.06.04
8. Dixit S, Namdeo M, Azad S. Valproate Induced Delirium due to Hyperammonemia in a Case of Acute Mania: A Diagnostic Dilemma. *Journal of Clinical and Diagnostic Research*. 2015; 9: VD01-VD02. https://doi.org/10.7860/JCDR/2015/.5758
9. Lavalaye J, Booij J, Linszen DH, Reneman L, Van Royen EA. Higher occupancy of muscarinic receptors by olanzapine than risperidone in patients with schizophrenia. A[123I]-IDEX SPECT study. Psychopharmacology (Berl). 2001; 156:53-7. https://doi.org/10.1007/s002130000679
10. Boulton DW, Kollia GD, Mallikaarjun S, Kornhauser DM. Lack of a pharmacokinetic drug-drug interaction between lithium and valproate when co-administered with aripiprazole. *J Clin Pharm Ther*. 2012; 37:565-70. https://doi.org/10.1111/j.1365-2710.2012.01331.x
11. Chen M-H, Liou Y-J. Aripiprazole-Associated Acute Dystonia, Akathisia, and Parkinsonism in a Patient with Bipolar I Disorder. *J Clin Psychopharmacol*. 2013; 33:269-70. https://doi.org/10.1097/jcp.0b013e3182856826
12. Hedayati A. Caution in co-administration of aripiprazole and lithium in patients with learning disability. *MedCrave Online Journal of Women's Health*. 2017; 5:324-325. https://doi.org/10.15406/mojwh.2017.05.00144
13. Pasquier de Franclieu S, Germain C, Petitjean F. Aripiprazole induced Parkinsonism: *A case report. Encephale.* 2009; 35: 496-8. https://doi.org/10.1016/j.encep.2008.06.019
14. Sharma A, Sorrell JH. Aripiprazole-induced parkinsonism. *Int Clin Psychopharmacol*. 2006; 21:127–129. https://doi.org/10.1097/01.yic.0000185025.40656.30
15. Zacher JL, Hatchet AD. Aripiprazole-Induced Movement Disorder. *Am J Psychiatry. 2006; 163*(1):160-1. https://doi.org/10.1176/appi.ajp.163.1.160-a
16. Kar KK, Rathi A, Sitholey P. Cog-Wheel Rigidity in a Young Adolescent due to Short Term Lithium – Olanzapine Combination Therapy. *Delhi Psychiatry Journal*. 2012; 15:1. https://api.semanticscholar.org/CorpusID:147552584