Clinical Case Report

Amantadine-induced psychosis in Wilson disease

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ABSTRACT

Wilson disease is a rare genetic disorder of copper metabolism causing hepatic dysfunction and neuropsychiatric manifestations. While psychosis in Wilson disease is uncommon, it can occur, especially with certain medications. We describe a 40-year-old woman diagnosed with Wilson disease who developed psychotic symptoms following the initiation and dose escalation of amantadine, a drug commonly used to treat parkinsonism associated with the disorder. Her symptoms included delusions of persecution, irritability and anomalous self-experiences such as 'made' phenomena, which are typically seen in schizophrenia. The psychosis resolved after discontinuing amantadine, without worsening her neurological symptoms. This underscores the importance of monitoring for psychiatric side-effects, particularly Schneiderian first-rank symptoms, in patients with Wilson disease being treated with amantadine. The findings suggest a probable adverse drug reaction, highlighting the need for careful evaluation and dose adjustments in such complex clinical cases.

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INTRODUCTION

Wilson disease is a disorder of copper metabolism that results in hepatic dysfunction and neuropsychiatric manifestations. Psychoses secondary to Wilson disease are reported but uncommon compared to depression, personality changes and neuroses. Parkinsonism is commonly seen in Wilson disease and is treated with medications used to treat Parkinson disease, including amantadine. We describe a woman with Wilson disease who developed psychotic symptoms after the initiation of amantadine.

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THE CASE

A 40-year-old lady presented with an insidious onset illness characterised by bilateral tremors of upper limbs, bradykinesia, rigidity, dystonia and pseudobulbar affect over the past year, along with Kayser–Fleischer ring. Magnetic resonance imaging of the brain revealed signal changes in bilateral thalami and brainstem with mineralization of globus pallidus and substantia nigra. Serum ceruloplasmin was 5.4 mg/dl, serum copper was 22.7 μg/dl, 24-hour urinary copper excretion was 75 μg; liver function tests revealed serum protein of 6.1 g/dl and serum globulin of 2.2 g/dl. She was diagnosed with Wilson disease by a neurologist at a tertiary care neuropsychiatry institute. She was initiated on the following treatment sequentially over 6 months (target dose mentioned in brackets)—zinc acetate (300 mg/day), penicillamine (500 mg/day), trihexyphenidyl (6 mg/day) and later on amantadine due to persistent motor symptoms (200 mg/day). The patient had major improvement in the motor symptoms after concurrent administration of a combination of zinc, penicillamine, trihexyphenidyl and amantadine at the doses mentioned above. After starting amantadine, she developed psychotic symptoms in the ensuing 3 weeks that subsequently peaked in 2 months upon dose escalation characterised by delusions of persecution, reference, irritability, made phenomenon with major acting out behaviour.

The neurologist referred the patient to psychiatry services because of the new-onset psychosis symptoms and resulting behavioural disturbances. Psychiatric evaluation revealed delusions of persecution and reference against family members with the presence of anomalous self-experience (made affect with made volition).[1]

Anomalous self-experiences such as made phenomena are described by Kurt Schneider as part of the first-rank symptoms of schizophrenia.[2] First-rank symptoms of schizophrenia include a set of 11 symptoms that form core criteria to diagnose schizophrenia in the International Classification of Diseases version 10.[3] Made phenomena include made impulse, made act and made affect and constitute 3 of these 11 core symptoms described by Schneider. Persons experiencing these phenomena describe that an external force urges them powerfully to perform an action (made impulse) or describe their actions as being completely controlled by an external agency (made volition) or describe experiencing feelings that are imposed on them against their will (made affect). The common theme is that of the patient being a passive recipient of these experiences that are imposed on them.

She was also quite irritable with her family secondary to the psychopathology. Due to the onset of psychiatric symptoms after initiation of amantadine and subsequent worsening of symptoms after dose escalation from 100 to 200 mg/day, the psychosis symptoms were attributed to amantadine, which was tapered and stopped. The rest of the treatment was continued. The patient showed good improvement in psychotic symptoms, which was assessed through serial mental status examinations, the Brief Psychiatric Rating Scale (BPRS)[4] and the Social and Occupational Functioning Assessment Scale (SOFAS).[5] The baseline BPRS score was 72, SOFAS score was 40 and her repeat assessment

TABLE I. Naranjo adverse drug reaction probability scale

Question	Yes	No	Don't know	Score
Are there previous conclusive reports on this reaction?	+1	0	0	1
Did the adverse event appear after the suspected drug was administered?	+2	−1	0	2
Did the adverse reaction improve when the drug was discontinued, or a specific antagonist was administered?	+1	0	0	1
Did the adverse reaction reappear when the drug was re-administered?	+2	−1	0	0
Are there alternative causes (other than the drug) that could on their own have caused the reaction?	−1	+2	0	0
Did the reaction reappear when a placebo was given?	−1	+1	0	0
Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	0
Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0	1
Did the patient have a similar reaction to the same or similar drug in any previous exposure?	+1	0	0	0
Was the adverse event confirmed by any objective evidence?	+1	0	0	1

Total score: 6 (probable adverse drug reaction)

after 10 days of stopping amantadine revealed a BPRS score of 48. She was discharged as she was much better. At follow-up after 3 months (BPRS score of 30 with SOFAS score of 70), she no longer experienced anomalous self-experiences; in addition, there was no worsening of neurological symptoms after the cessation of amantadine. Naranjo adverse drug reaction probability scale[6] score of six suggests a probable adverse drug reaction to amantadine (Table I). We obtained written, informed consent from the patient for the case report.

DISCUSSION

Amantadine has a dual mode of action—dopaminergic and glutamatergic. It inhibits the N-methyl-D-aspartate receptor and increases the availability of dopamine in the nerve terminals. Adverse effects reported with amantadine include livedo reticularis, weight loss, insomnia, anorexia, constipation, blurred vision, malaise and dizziness.[7] Psychosis symptoms have been attributed to amantadine use and include visual hallucinations, paranoid ideation and delusions.[8–11] There is also evidence that amantadine worsens psychosis in schizophrenia.[10–12] The new onset of psychosis symptoms seen after initiation of amantadine poses challenges in management. However, this is the first case report highlighting the presence of Schneiderian first-rank symptoms (made volition and made affect) following amantadine therapy. Schneiderian first-rank symptoms continue to remain as diagnostic criteria for schizophrenia.

This report highlights new-onset psychosis in a person with Wilson disease after treatment with amantadine that resolved after discontinuation. Pre-existing pseudobulbar affect and Wilson disease led to disruption in the 'sense of agency' following amantadine administration and could have led to the emergence of psychosis. We suggest monitoring for new-onset psychosis with the use of amantadine.

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Conflicts of interest. None declared

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