A Case Series of Memantine-responsive Catatonia Secondary to Stroke and Hyponatremia

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Catatonia is a psychomotor syndrome characterized by a constellation of symptoms usually involving lack of movement and lack of communication; it is associated with several psychiatric disorders like schizophrenia, bipolar affective disorder, depression, autism, and so on as well as many medical disorders or conditions like stroke, liver transplantation, cerebral venous sinus thrombosis, hyponatremia, neurodegenerative disease, and infection.[1] Catatonia has a prevalence of around 10% in the psychiatry ward, and it may be life-threatening in its malignant form.[2] That necessitates proper and adequate management. Guidelines advocate the use of the Lorazepam trial; if it is unsuccessful, Electroconvulsive therapy (ECT) should be administered.[2,3] There are also several case reports of successful treatment of catatonia in mental disorders and cognitive disorders with glutamate antagonists, including memantine, in the past.[2,4] Here we describe three cases of memantine-responsive catatonia due to medical conditions like stroke and hyponatremia, which, to our best knowledge, have never been reported before.

Case Series

All the cases were diagnosed as catatonia by two psychiatrists using the Diagnostic and Statistical Manual, Fifth Edition (DSM-5), and rated using the Bush Francis Catatonia Rating Scale (BFCRS),[5] both pre- and post-treatment. Written informed consent was obtained from patients for using their clinical and demographic data for academic research and publication. Patient demographic details, phenomenology, co-morbidity, and course of treatment with lorazepam and memantine have been described in **Table 1**. There was no past or family history of mental illness, any history of substance use, or any history suggestive of cognitive impairment. We worked up every patient with Magnetic Resonance Imaging (MRI) of the brain except in Case A, due to the presence of a metallic implant in her hip joint, limiting suitability for MRI, where we did a Computed Tomography (CT) scan of the brain.

Case A presented with an acute onset of decreased interaction with family members and reduced food intake for two days. She had a history of receiving diclofenac for around two weeks for osteoarthritis before the onset of these symptoms. On physical examination, she was conscious, her blood pressure was 110/70 mmHg, and there was no sign of hypervolemia or dehydration. On investigation, her blood sodium level was 124 meq/L, and she had a medical diagnosis of hyponatremia secondary to diclofenac. The patient was treated with the discontinuation of diclofenac, fluid restriction, and adding extra salt to the diet with naso-gastric tube feeding. The patient's serum sodium level returned to normal after three days of treatment.

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TABLE 1.

Description of Demographic, Phenomenological, and Treatment Profiles of the Cases.

Cases	Demography and Co-morbidity	Phenomenology and Baseline BFCRS Score	Trial with Lorazepam	Course of Treatment with Memantine
A	62 years, female Old fracture of right femoral neck (metallic implant in situ), osteoarthritis of right hip joint	Immobility, mutism, staring, posturing, negativism, withdrawal, and rigidity, BFCRS Score: 15	Day 11: Lorazepam challenge test Day 2: Lorazepam 6 mg I.M. Day 3: Lorazepam 10 mg I.M.	BFCRS score-9 after one week with Memantine 10 mg; BFCRS score-0 after three weeks with Memantine 20 mg. Catatonia reappeared within one week of stopping memantine; BFCRS score was 0 after two weeks of Memantine 20 mg and was continued for one month till last follow-up. MMSE score at last visit: 30
B	88 years, female	Immobility, mutism, negativism, posturing, and withdrawal, BFCRS score: 14	Day 1: Lorazepam challenge test Day 2: Lorazepam 8 mg I.M. Day 3: Lorazepam 16 mg I.M.	BFCRS score-3 after one week with Memantine 10 mg; BFCRS score-0 after two weeks with Memantine 20 mg. Catatonia reappeared within one month of stopping memantine; BFCRS score was 0 after one week of Memantine 20 mg and was continued for a duration of three months till last follow-up. MMSE score at last visit: 28
C	50 years, male	Immobility, mutism, staring, posturing, rigidity, stereotypy, and withdrawal, BFCRS score: 18	Day 1: Lorazepam challenge test Day 2: Lorazepam 8 mg I.M. Day 3: Lorazepam 16 mg I.M.	BFCRS score-10 after two weeks with Memantine 10 mg; BFCRS score-0 after three weeks with Memantine 25 mg and was continued for a duration of two months till last follow-up. MMSE Score at last visit: 30

BFCRS, Bush Francis Catatonia Rating Scale; IM, Intramuscular; MMSE, Mini-Mental State Examination.

Case B presented with the sudden onset of transient dysarthria and syncope. On physical examination, she was conscious and oriented to time, place, and person; her blood pressure was 170/100 mmHg. Her catatonic symptoms developed one day following hospitalization. On MRI brain, she was found to have white matter ischemic changes and encephalomalacic changes at the right frontal lobe, sequelae to an old infarct. She received a diagnosis of Transient Ischemic Attack from the medical side. She was treated with aspirin (75 mg), clopidogrel (75 mg), amlodipine (10 mg), and atorvastatin (20 mg) through naso-gastric tube feeding.

Case C presented with a sudden onset of inability to move the right side of the body and transient difficulty finding ways in the house. When he was brought to the hospital after about two days of the onset of symptoms, he had already developed catatonic symptoms. On physical examination, he was conscious, his blood pressure was 150/100 mmHg, and on testing superficial reflexes, the Babinski sign was positive on the right. On MRI brain, he had white matter ischemic changes and micro-bleeds at the left posterior-parietal lobe and was diagnosed as having a stroke, from the medical side. He was treated with aspirin (75 mg), amlodipine (5 mg), and atorvastatin (20 mg) through naso-gastric tube feeding.

All patients were initially challenged with inj. lorazepam 4 mg intra-muscularly for one day; on non-improvement, the dose was escalated up to the maximum tolerable dose (10–16 mg) and duration (1–2 days) as per guideline[3] (**Table 1**). However, none of them showed any sign of improvement; rather, Case A had a history of falls due to excessive sedation. The unwillingness of the patient's relatives and difficulty obtaining consent from the catatonic patient for modified ECT were ethically challenging for administering ECT. Lorazepam was stopped for all after three days of the lorazepam trial. All of them were started on memantine following the failed lorazepam trial, and they significantly improved with memantine (20–25 mg), as evidenced by the change in BFCRS score over the course (**Table 1**). In Cases A and B, catatonic symptoms reappeared after the stoppage of memantine. Our patients reported satisfactory motor functioning in follow-up.

Discussion

N-methyl-D-aspartate (NMDA) hyperactivity indirectly influences Gamma-aminobutyric acid (GABA)-A function in the frontal lobe, as well as excess glutamate and hyperactivity of glutamate receptors in the parietal lobe, which are hypothesized to produce catatonia-like symptoms.[6] Hyponatremia produces swelling of the astrocyte membrane, thus disrupting the normal glutamate metabolism of astrocytes and leading to an increase in glutamate in extracellular fluid.[7] The catatonic symptoms in Case A may have resulted from this mechanism. Brain parenchyma ischemic injury may also result in glutamate excitotoxicity,[8] which may explain the catatonic symptoms in Cases B and C. Memantine, used in cognitive disorders, acts by blocking NMDA receptors, thus reducing abnormal glutamatergic hypertransmission, and[9] yielded a better outcome in our cases. Given the explainable pathomechanism underlying the development of catatonia in our cases, the improvement of catatonic symptoms with a glutamate antagonist (memantine), and their reappearance on its stoppage, we argue glutamate hyperactivity as an underlying mechanism of catatonia in our cases. The use of conventional modalities like benzodiazepines is limited in the presence of respiratory compromise and drowsiness, and there is a lack of consensus regarding their long-term use. Aside from a relatively long response time,[4] memantine

has beneficial effects on cognition and is devoid of other limitations of conventional modality.[9] Also, it has an extra edge over other glutamate antagonists by being more selective in binding to NMDA receptors and having a lower chance of causing psychosis as an adverse reaction.[4]

In addition, previous reviews have highlighted that memantine can provide better sensory-motor recovery, improved behavioral outcomes, and preservation of neuroplasticity in patients with ischemic stroke by increasing BDNF levels and enhancing angiogenesis.[10]

Conclusion and Clinical Implications

The limitation of our study is that it was observational without control or comparison with conventional modality, and we cannot draw any conclusions about its superiority over conventional therapy. However, we suggest memantine as another treatment option for catatonia where glutamate excitotoxicity is presumed to be the underlying pathomechanism.

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