

Neuroleptic malignant syndrome in a case of extra-pontine myelinolysis: On the horns of dilemma

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SUMMARY Osmotic demyelination syndrome (ODS) and neuroleptic malignant syndrome (NMS) lead to severe neurological sequelae. Though currently thought to be different syndromes, literature suggests a relation between the two. We present the case of a 45-year-old male who was found to have chronic severe hyponatremia and underwent rapid correction of sodium and developed parkinsonism features. Magnetic resonance imaging (MRI) confirmed extrapontine myelinolysis (a type of ODS). The patient received haloperidol for agitated behavior and developed new features of rigidity, fever, tachycardia and elevated creatine phosphokinase (CPK) levels and thus neuroleptic malignant syndrome was suspected to overlap with ODS. We report this case highlighting the difficulty in differentiating the between ODS and NMS and their relationship.

Keywords extrapontine myelinolysis, neuroleptic malignant syndrome, hyponatremia, parkinsonism

To the Editor,

A 45-year-old alcoholic, hypertensive male receiving chlorthalidone presented to us with complaints of headache and altered sensorium after an episode of generalized tonic-clonic seizure (GTCS). On examination the notable findings were a Glasgow coma score (GCS) E4V2M5, poorly discernible speech, reactive pupils, with normal reflexes.

Initial investigations revealed hyponatremia (91 mEq/L), for which he received hypertonic saline with frequent electrolyte measurements. Over the next 2 days, sodium levels increased rapidly despite stopping all further correction ($[\text{Na}^+] = 97 \text{ mEq/L}$ at 24 h and 117 mEq/L at 48 h). The correction of sodium and further hospital course is depicted in Figure 1.

He suffered from 3 episodes of GTCS on the 3rd day of admission that were managed with benzodiazepines. Given the rapid rate of sodium correction and overt risk factors, a high suspicion of osmotic demyelination syndrome (ODS) was kept. Magnetic resonance imaging (MRI) of the brain on the fourth day revealed subtle hyperintensities in bilateral putamen, thalamus, and caudate lobe with a normal pons, consistent with extrapontine myelinolysis (EPM).

Post recovery from his seizures, he developed mutism and parkinsonism: slow shuffling gait, bradykinesia, resting tremors involving the oro-facio-lingual muscles, and cogwheel rigidity. With suspicion of organic delirium, he was prescribed low-dose haloperidol 0.5

mg on an as-needed basis. After 4 doses of haloperidol, on the 7th day of admission, he had worsening of sensorium (GCS: E3V1M4), fever, generalized rigidity, hyperreflexia, tachycardia beginning on the 9th day. Creatine phosphokinase (CPK) levels were elevated (by 2.5 times), with mild elevation of liver aminotransferases and leukocytosis. Due to recent haloperidol use, neuroleptic malignant syndrome (NMS) was suspected, and lorazepam with bromocriptine were initiated after withholding haloperidol. There was a gradual decrease in rigidity along with the resolution of fever, altered mentation, tachycardia after 3 days, and biochemical parameters also improved gradually. At discharge, he remained irritable with residual rigidity and bradykinesia for which he was prescribed quetiapine. At 3 months, he displayed residual parkinsonian features but was able to return to his job and perform his activities of daily living.

Rapid correction of hyponatremia can result in ODS (1). Patho-physiologically, it is characterized by oligodendrocyte damage and subsequent demyelination (2). Risk factors include chronic hyponatremia with very low levels of serum $[\text{Na}^+] < 105 \text{ mEq/L}$, rapid correction, alcoholism, hypokalemia *etc.* (3). Pons is commonly involved in ODS - called as central pontine myelinolysis (CPM), while half have extension beyond the pons resulting in EPM, and that may be the sole manifestation in up to 13% cases (4). The clinical presentation of EPM includes a myriad of movement disorders such as parkinsonism, dystonia, and catatonia.

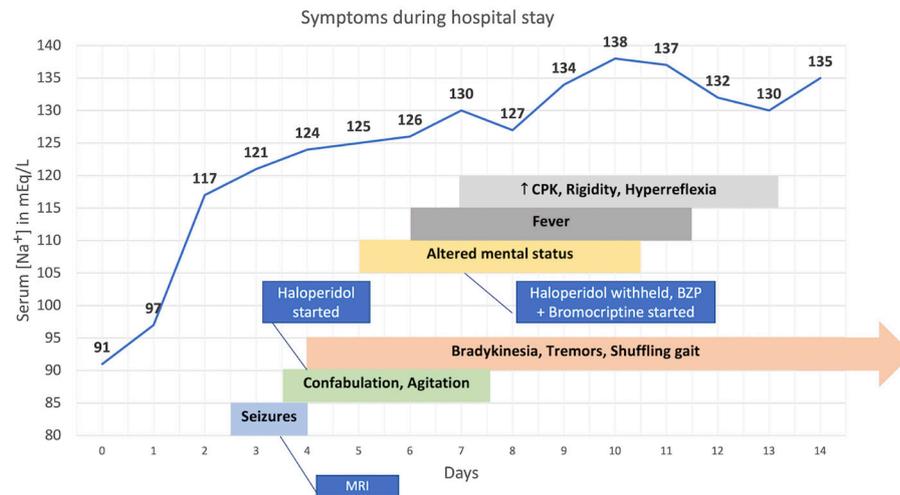


Figure 1. Hospital course of the patient showing the trend of serum sodium [Na⁺] levels with time, and the temporal correlation between the symptomatology of EPM and NMS, along with the exposure to haloperidol. BZP, benzodiazepines; CPK, creatine phosphokinase; MRI, magnetic resonance imaging.

Our patient's hospital stay was complicated by fever, worsening mental status, generalized rigidity and persistent tachycardia following haloperidol use. NMS is a distinct clinical syndrome occurring after use of dopaminergic antagonist agents, presenting with a tetrad of altered mental status, fever, rigidity, and autonomic dysfunction. Two dilemmas arose in the present case – first, whether the clinical picture suggested NMS or catatonia; and secondly – should we consider NMS secondary to the haloperidol use or due to EPM.

Differentiating between the NMS and catatonia has remained an enigma, and some authors consider the two illnesses to lie on a spectrum (5). NMS diagnosis is considered more likely when fever, rigor, tremors, laboratory evidence of muscle injury, leucocytosis, and diaphoresis are found. In contrast, catatonia is favored when features of negativism, posturing, waxy flexibility, stereotypy, stupor, or agitation are present (6). In our patient the symptomatology was more suggestive of NMS.

To address the second difficulty, we reviewed the literature and identified two reports describing ODS presenting as NMS (7,8). The first report described a patient on long term quetiapine therapy and developed altered mental status, fever, stiffening, raised CPK values after rapid correction of hyponatremia and an MRI brain found T2 hyperintensities in the caudate nucleus and putamen. The second report describes a hypertensive male with chronic alcoholism and pancreatitis who developed NMS 1 day after receiving neuroleptics for alcohol withdrawal, and an MRI showing prominent findings of CPM with EPM. In both of these reports, patients were exposed to neuroleptics, but NMS seemed unlikely because of specific features like stable doses, use of atypical antipsychotics, compounded by imaging findings consistent with EPM. Although NMS following antipsychotic use is an idiosyncratic reaction, a parenteral

route of administration, higher individual doses, and the total dose of drug administered have been linked to increased risk of NMS (9).

NMS is a diagnosis of exclusion and can occur even after a single dose of typical antipsychotics. However, an erroneous diagnosis of NMS can result in delayed recognition of other serious medical disorders with similar symptoms and may inhibit future antipsychotic treatment because of unwarranted concerns about recurrent episodes (7). We conclude that EPM may clinically mimic NMS, making differentiation between superimposed NMS and pure EPM difficult.

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