The Problem of Atypical Neuroleptic Malignant Syndrome: A Case Report

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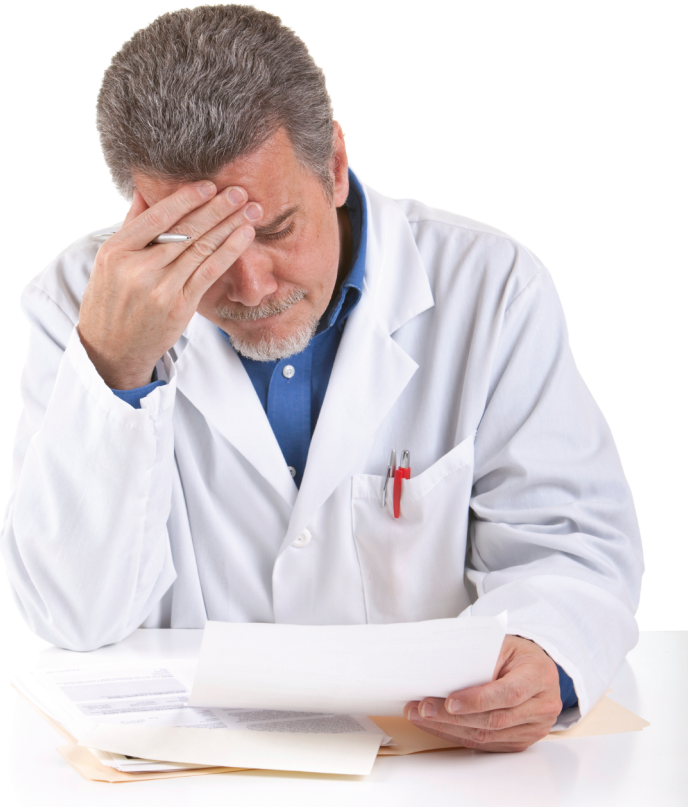
ABSTRACT

Neuroleptic malignant syndrome is a serious and potentially fatal adverse effect of antipsychotic medications. Although diagnostic criteria for neuroleptic malignant syndrome have been established and are widely accepted and used, it should be recognized that atypical presentations occur, particularly during treatment with atypical antipsychotics. However, it remains unclear whether these atypical presentations represent early or impending neuroleptic malignant syndrome. Furthermore, since neuroleptic malignant syndrome is a diagnosis of exclusion, careful consideration of other neuropsychiatric conditions should occur. Relying on creatine phosphokinase elevation may result in an incorrect diagnosis of atypical neuroleptic malignant syndrome. We wish to present a case of this diagnostic dilemma in a patient with catatonia.



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INTRODUCTION

Neuroleptic malignant syndrome (NMS) is a diagnosis of exclusion and other etiologies must be considered first.[1] To establish positive identification, a differential diagnosis relies on four major criteria; hyperthermia, rigidity (or other forms of EPS), autonomic disturbances and mental status changes.[1] Atypical NMS is defined as a presentation of three of the four signs.[2,3] In these cases, signs and symptoms arise after exposure to an antipsychotic agent (or may occur after withdrawal of a dopaminergic agent). The role of creatine phosphokinase (CPK) is important to detect and monitor NMS, although CPK is not specific to NMS.[1–3] We wish to report a case in which atypical NMS was carefully considered because of a bimodal CPK elevation.

CASE REPORT

A 76-year-old man was admitted to acute psychiatry for behavioral disturbances due to dementia (dementia with behavioral disturbances). He was transferred to a nursing home unit one week later. One month later, he fell during a transfer from wheelchair to bed. He reported that he hit his head on the floor or a locker. There were no obvious signs of trauma at that time. Within one day, he became hostile and combative. He could previously communicate, in short sentences, but became mute and was unresponsive to stimuli. He was transferred to the medical service for mental status changes. The patient became febrile (temperature, 102.6F; pulse, 91; respiratory, 16; blood pressure, 116/74).

Pertinent medication includes simvastatin 40mg once daily at bedtime (QHS), isoniazid 300mg once daily in the morning (QAM), quetiapine 25mg QHS, donepezil 10mg QHS, and divalproex 500mg once daily (QD).

The patient had hyperthermia, autonomic disturbance, and mental status changes, but rigidity was not reported. The CPK was elevated at greater than 1600U/L for three days after the fall. The "greater than 1600U/L" was the highest limit of CPK that could be measured by the hospital laboratory. The diagnosis of rhabdomyolysis was made and simvistatin was discontinued and not restarted. Simvastatin and isoniazid have a severe drug interaction, since both are metabolized via CYP-3A4.

The patient had a chest x-ray (CXR), urinalysis, and blood culture to rule out infection. The CPK remained elevated (>1600) for three days. The patient had episodes of hyperthermia for two more days (up to 102.9F). On the seventh day after the fall, the CPK was 1166mg/dL and the patient was afebrile. A psychiatry consult was requested because the patient remained mute, unresponsive, and resistant to care. He was seen by two of the authors (BTC and SAS), and was found to score 24 on the Bush Francis Catatonia Rating scale (BFCRS) and 50 on the Kanner scale (the component that measures catatonic signs that indicate syndrome severity)[4,5] A diagnosis of catatonia due to a general medical condition (dementia) was given. The prominent features included negativism, immobility, and mutism, and refusal to eat and drink. However, he did not have any significant rigidity (no tremor, cogwheeling, or waxy flexibility), only mild paratonia (Gegenhalten). NMS and atypical NMS were excluded. Quetiapine was continued and a trial of lorazepam was recommended.

The CPK dropped to 840 on Day 8, and 372 on Day 10. The catatonic signs did not improve after one day of lorazepam and higher doses were not used because sedation was reported after two 1mg oral doses.

The patient remained afebrile until 15 days after the fall. The patient's temperature increased to 101.8F, his pulse 84, his respiratory rate 20, blood pressure 120/70, and the CPK greater than 1600. The consultant saw the patient again. Although diagnosis of NMS and atypical NMS were excluded, the consultant advised discontinuing quetiapine, donepezil, and divalproex. A computed tomography (CT) scan of the head revealed mild diffuse cerebral and cerebellar volume loss and mild periventricular white matter low attenuation (i.e., consistent chronic small vessel ischemic disease). The next day (Day 16), the patient was seen and had improved (BFCRS, 24; Kanner, 40).[4,5] While the BFCRS went from 23 to 24, it was falsely elevated by some of the catatonic signs. Meanwhile, the KANNER went from 50 to 40, showing improviement. Clinically, the patient had improvement in stupor. He could carry on a brief conversation and maintained minimal self care. He still had catanonic signs, however. His CPK was 683. Further monitoring of the patient revealed no worsening in mental status or significant hyperthermia. CPK returned to the normal range (24–204U/L). He was discharged to a state nursing home 55 days after the fall. He continued to have severe cognitive impairment, with aggressive and impulsive behavior. His daily self care continued to deteriorate. He continued to have difficulty with speech, eating, and drinking. Nonetheless, signs of NMS did not return. He was discharged on the following regimen that included quetiapine 25mg QHS, without the return of hyperthermia, rigidity, mental status changes, or autonomic disturbances.

DISCUSSION

Atypical NMS remains a problematic entity.[1] Current reviews suggest that atypical NMS can be diagnosed with the presentation of three of the four cardinal signs of NMS.[1–3] Consequently, this puts greater emphasis on ancillary measures, such as CPK level. Unfortunately, in this case, catatonia due to general medical conditions, concurrent hyperthermia, and autonomic disturbances was felt to be a result of atypical NMS. The CXR revealed that the patient had atalectesis, which was the likely source of fever and autonomic changes.

Some clinical features that argued against NMS in this patient, were active negativism, the absence of rigidity, and intermittent hyperthermia (temperature elevation was only at night). Quetiapine was discontinued as a precaution.[6] Donepezil was discontinued because it had been reported to cause catatonia in a few cases. Valproic acid and lorezapam were discontinued because they might have contributed to sedation. Memantine was added to help catatonia, but later discontinued. Nonetheless, we did not diagnose atypical NMS despite the fact that the patient was on quetiapine and exhibited 3 of the 4 signs of NMS. The patient was rechallenged on quetiapine without the return of NMS signs.

The CPK elevation exhibited a double peak, that is an initial spike after the head injury and another

after the CPK had a considerable decrease. This bimodal pattern has been reported in the literature on head injury.[7] Consequently, we felt that in this case, the double peak of CPK was related to the head injury.[7] The head injury also contributed to the development of catatonic signs. While the mechanism of this double peak phenomenon of CPK is not known, our patient seemed to fit this profile. We feel caution is warranted in cases of atypical NMS, as this double peak of CPK may be misleading. Furthermore, this patient was in an institutional setting in which the head injury was well documented. Patients who present from community settings may not be able to provide this history. We feel this is an important case to review when considering a diagnosis of atypical NMS.

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