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CASE REPORT

Ziprasidone-related neuroleptic malignant syndrome in a patient with Parkinson's disease: a diagnostic challenge

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A case of neuroleptic malignant syndrome (NMS) in a patient with Parkinson's disease (PD) is presented. The syndrome was precipitated by the atypical antipsychotic, ziprasidone. The challenge of recognizing NMS in a patient with underlying parkinsonian symptoms, where prominent symptom overlap can occur, is discussed. Copyright © 2004 John Wiley & Sons, Ltd.

KEY WORDS — neuroleptic malignant syndrome; parkinson's disease; ziprasidone; antipsychotic agents; dopamine

INTRODUCTION

Neuroleptic malignant syndrome (NMS) is a potentially fatal disorder characterized by fever, autonomic instability, altered level of consciousness and severe rigidity. Laboratory studies often reveal elevated serum creatine kinase (CK) levels, leukocytosis and abnormalities of liver function (Carbone, 2000). NMS was first described as an adverse reaction to dopamine blocking agents (Delay and Deniker, 1965). Often associated with the use of high-potency neuroleptics, it also can occur with therapeutic doses of the newer atypical neuroleptics such as clozapine and olanzapine (Caroff and Mann, 1998).

To highlight a challenging diagnostic dilemma, a case of neuroleptic malignant syndrome precipitated by the atypical neuroleptic, ziprasidone, in a patient with Parkinson's disease (PD) is presented. There is prominent symptom overlap between NMS and PD, and every case of NMS reported in Parkinson's patients to date, except one, has been precipitated by withdrawal of antiparkinsonian medication (Ueda *et al*., 1999; Gordon and Frucht, 2001). The one case report of NMS in PD precipitated by neuroleptic medication was secondary to haloperidol administration (Ryken and Merrell, 1989). In addition, there is only one prior case report of NMS secondary to administration of ziprasidone in any patient (Murty *et al*., 2002), and none in PD prior to this report. Ziprasidone is a combined serotonin and dopamine receptor antagonist that is reported to have minimal motor, cognitive, weight gain, prolactin related or anticholinergic side effects (Seeger *et al*., 1995).

CASE REPORT

G.T. is a 52-year-old Caucasian female with a 6-year history of idiopathic PD who presented to the Emergency Department in January 2003 for evaluation of tremors and rigidity worsening over the past 7–10 days. She had been stable on carbidopa/levodopa 25/100 (one tablet three times a day) and pramipexole (0.5 mg three times a day). Six months prior, she began to experience some psychotic symptoms, including the delusion that her husband was having an affair, auditory hallucinations of the phone

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ringing, and visual hallucinations of bright lights and a small white dog running around her house. She had no prior history of psychotic symptoms. She was started on quetiapine 100 mg at night, which improved these symptoms, but it was discontinued after 2 months because of generalized edema. She then was started on aripiprazole 10 mg per day, but this was discontinued after 3 weeks because of the worsening of her parkinsonian symptoms. Then 2 weeks later and 10 days prior to presentation, she was started on ziprasidone 20 mg twice a day. There was a slight improvement in her psychotic symptoms, but she once again experienced a worsening of her tremor and rigidity to the point where she was unable to walk or care for herself. Her decline in functioning contributed to her becoming depressed, and she was started on sertraline 25 mg twice a day 1 week prior to presentation. Additional medications at presentation included simvastatin 20 mg at bedtime, albuterol two puffs twice a day as needed, mentelukast 10 mg at bedtime and levothyroxine 25 mcg twice a day.

On examination, her temperature was 36.3°C, blood pressure 170/96, pulse 119, respirations 20 and oxygen saturation 98% on 2 l oxygen by nasal cannula. She was bradykinetic, almost mute and profusely diaphoretic. She had masked facies and a decreased blink reflex. There was severe axial and appendicular rigidity (right side greater than left and lower extremities greater than upper), coarse resting tremor of the upper extremities, and prolonged spasms of the lower extremities. Gait could not be assessed. Motor exam revealed severe cogwheeling. Cranial nerves II–XII were intact. She was not oriented to place or time. She was delusional and reported both auditory and visual hallucinations. The remainder of her general and neurological examination was normal.

Initial laboratory evaluation revealed her blood sugar, electrolytes, BUN, creatinine and CBC with differential were all within normal limits. Creatine kinase (CK) was 363 IU/l (normal range 30–140). An electrocardiogram revealed sinus tachycardia with nonspecific ST segment changes, and the chest x-ray was normal. Her EEG was notable for the continuous occurrence of slow wave activity. Blood and urine cultures were obtained and later reported as negative. After arrival, the patient complained of headache, subjective hyperthermia, anxiety and shortness of breath. She became mildly agitated and was given lorazepam 0.5 mg and an albuterol/atrovent nebulizer treatment, which improved her respiratory status.

Initially, the patient was considered to have a psychosis superimposed on PD, and NMS was not entertained. However, when her CK was reported back as 363 IU/l, the diagnosis of probable NMS was made on the basis of the elevated CK, along with severe rigidity, altered mental status, near-mutism, tachycardia, elevated blood pressure, diaphoresis and a history of neuroleptic use (Levenson criteria) (Levenson, 1985). Normal saline was started i.v. at 100 cc/h, and dantrolene 1 mg/kg was given i.v. Pramipexole was discontinued, and the patient was admitted to the Neurological Intensive Care Unit. CK levels with MB fractions were obtained every 8 hours. CK peaked 24 h after admission at 1176 IU/l, with an MB fraction of 15.0 ng/ml. Troponin was consistently less than 0.3 ng/ml, indicating that the CK elevation was not of cardiac origin. The patients' temperature also peaked 24 h after admission at 37.8°C. Adequate urine output was maintained.

A regimen of carbidopa/levodopa SR 25/100 three times a day and one-half tablet of regular carbidopa/levodopa 25/100 three times a day was started and ziprasidone was discontinued. The patient's rigidity and tremor diminished substantially. Her anxiety and agitation was managed with alprazolam 0.25 mg three times a day. A psychiatry consultation was obtained regarding her continued visual hallucinations. Olanzapine 5 mg at bedtime was started, and the patient was subsequently transferred to a psychiatric unit 72 h after admission for further management of her psychotic symptoms. These symptoms and her confusion slowly resolved, her CK decreased to <20 IU/l by hospital day 13, and she was discharged on hospital day 18 to outpatient follow up.

DISCUSSION

The need for prompt and careful recognition of NMS, a potentially life-threatening illness, is clear. However, early detection is not easy, especially if the full syndrome is not present or if the signs are obscured by a concomitant medical or organic brain disease (Lazarus, 1985; Clark *et al*., 1986). In this patient, the diagnosis was complicated by the fact that her tremor, rigidity and altered mental status were initially considered to be manifestations of her underlying PD.

In addition to infection, the differential diagnosis of NMS includes heat stroke, serotonin syndrome and toxicity from other medications (Carbone, 2000). Central nervous system infection was excluded in this patient by cerebrospinal fluid analysis, and systemic infection was ruled out by negative blood and urine cultures. Heat stroke was ruled out because the patient

had not been exposed to any environmental precipitants, was not febrile on admission, and her electrolytes were within normal limits. The symptoms of serotonin syndrome resemble NMS and include mental status changes, myoclonus, rigidity, hyperreflexia and autonomic instability. Serum CK may be elevated. However, the syndrome usually develops within hours or days after the addition of a new serotonergic agent or change in dose (Sternbach, 1991; Bodner *et al*., 1995). The patient presented here was taking only a low, constant dose of a single medication that increases serotonin activity (sertraline), and was taking no other medications known to cause NMS-like symptoms.

The first step in effective management of NMS requires early recognition of the syndrome which, as indicated by this case report, can indeed be complicated in patients with underlying PD.

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