

Parkinsonism-hyperpyrexia syndrome due to abrupt withdrawal of amantadine

To the Editor—We read with interest “An uncommon adverse effect of levodopa withdrawal in a patient taking antipsychotic medication: neuroleptic malignant-like syndrome” by Man.¹ The report was of an 84-year-old man who developed parkinsonism-hyperpyrexia syndrome (PHS) due to abrupt withdrawal of levodopa. We encountered another patient in May 2009 who developed PHS due to withdrawal of amantadine.

A 63-year-old man with progressive supranuclear palsy presented with confusion for 2 weeks. His past health included hypertension, ischaemic stroke, duodenal ulcer and left nephrectomy for renal stone and shrunken kidney. He was treated with amantadine, clonazepam, and benzhexol, but had no recent history of neuroleptic use. Physical examination revealed typical parkinsonian signs and dehydration. He was afebrile and his vital signs were stable. His Mini-Mental State Examination score was 16/30. Cranial computed tomography only showed atrophic changes. His white blood cell count (WBC) was $7.3 \times 10^9/L$ (reference range, $4.5-11.0 \times 10^9/L$) and his creatinine level was $208 \mu\text{mol/L}$ ($53-106 \mu\text{mol/L}$). He refused medications (including amantadine) after hospitalisation and amantadine was completely omitted for nearly 3 days.

On day 6, he suddenly developed tremor, muscle rigidity, fever of 40.8°C , diaphoresis, and sinus tachycardia of 140 beats/min. His Glasgow Coma Scale score dropped from 14/15 (E4, V4, M6) to 6/15 (E1, V2, M3). His WBC increased to $13.9 \times 10^9/L$, creatine kinase peaked at 1985 U/L (reference range, 50-200 U/L), sodium increased to 152mmol/L ($136-142 \text{mmol/L}$), and creatinine increased to $355 \mu\text{mol/L}$. Urine myoglobin was negative. Electroencephalography did not show any epileptic activity. Lumbar puncture excluded meningitis. Chest radiograph was normal. Sputum, urine, and blood cultures were all negative. A neurologist was consulted and the diagnosis of PHS was made.

The patient was treated in the intensive care unit with reintroduction of amantadine, intravenous fluids, intravenous dantrolene, levodopa/carbidopa, bromocriptine, paracetamol, and amoxicillin-clavulanate. He gradually recovered during the next

2 weeks.

This patient illustrates several points. Parkinsonism-hyperpyrexia syndrome is probably under-reported locally, partly because the clinical and laboratory features are non-specific. The diagnosis remains clinical and it is under-recognised due to its rare occurrence. Mild cases may be mislabelled as sepsis or worsening of parkinsonism. Although withdrawal of levodopa is still the most common cause of PHS, we should not forget other agents, including amantadine, dopamine agonists, and catechol-O-methyltransferase inhibitors.² Patients with Parkinson's disease are susceptible to PHS due to its inherent dopamine-depleted state, but PHS has also been reported in patients with atypical parkinsonism, for example multiple system atrophy³ and progressive supranuclear palsy. In this patient, hypernatraemia was another trigger for PHS. Cao and Katz⁴ have reported another patient in whom PHS was precipitated by hypernatraemia. Appropriate fluid replacement is essential for correction of electrolyte disturbance and prevention of renal failure secondary to rhabdomyolysis. Parkinsonism-hyperpyrexia syndrome is potentially fatal. Patients with parkinsonism should be warned of this possibility and advised against abrupt withdrawal of anti-parkinsonian medications. Finally, we do encounter some clinical situations where abrupt withdrawal of anti-parkinsonian medications is mandatory, for example, patients undergoing deep brain stimulation surgery. Rare cases of PHS have been reported.⁵ A high index of suspicion and prompt reintroduction of anti-parkinsonian medications postoperatively remain the mainstay of treatment for this rare complication.

YF Cheung, MRCP, FHKAM (Medicine)

Email: cyfz02@ha.org.hk

Department of Medicine, Queen Elizabeth Hospital, Hong Kong

Colin HT Lui, MRCP, FHKAM (Medicine)

Department of Medicine, Tseung Kwan O Hospital, Hong Kong

John HM Chan, FRCP, FHKAM (Medicine)

Department of Medicine, Queen Elizabeth Hospital, Hong Kong

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