Delayed diagnosis of parkinsonism hyperpyrexia syndrome resulting in death: a case report

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ABSTRACT
A 68-year-old woman with a history of Parkinson disease was admitted for *Escherichia coli* urinary tract infection and physical deconditioning. She was subsequently found to have a history of rheumatoid arthritis and iatrogenic Cushing syndrome with adrenal insufficiency. The patient developed high fever, fluctuating blood pressure, hypertonia, progressive confusion, and recurrent generalised tonic-clonic seizures. She was kept nil by mouth, and levodopa was withheld for 2 days. Blood test showed elevated creatine kinase level. Diagnosis of parkinsonism hyperpyrexia syndrome was made after consultation with neurologists, and levodopa was resumed. However, her condition did not improve and she died eventually. This case highlights the precipitating factors of parkinsonism hyperpyrexia syndrome and the importance of early recognition of the disease. Care must be taken in avoiding sudden withdrawal of levodopa in patients with Parkinson disease.

Key words: Hyperthermia, induced; Levodopa; Muscle hypertonia; Parkinson disease; Seizures

CASE PRESENTATION
In February 2017, a 68-year-old woman was admitted to our hospital with physical deconditioning. She had a 10-year history of Parkinson disease and osteoporosis. She was followed up by a private neurologist. The usual dosage of oral levodopa with benserazide (Madopar) was 125 mg four times per day. Before admission, she had a 1-month trial of increasing oral Madopar dosage to 250 mg four times per day for bilateral lower limb weakness. Minimal improvement was observed and the dosage was reduced to 125 mg four times per day. In the past 3 months, her mobility had declined gradually from walking unaided to bedbound. She had repeated falls and poor appetite.

Physical examination showed normal vitals, full score in the Glasgow Coma Scale, dehydration, and four limb muscle power of grade 3 in the Medical Research Council scale. Baseline blood test results were normal, except for increased white cell count (20.2 x10^9/L) with predominant neutrophils. Results of chest radiography, electrocardiography, and computed tomography of the brain were normal.

Urine culture yielded *Escherichia coli*. She was given amoxicillin with clavulanic acid for the provisional diagnosis of urinary tract infection leading to functional decline. Two days after admission, she was hypoglycaemic with a blood glucose level of 3.7 mmol/L and mild confusion. Patient’s relatives and medical record from her private doctor revealed that the patient had taken oral steroids for rheumatoid arthritis prescribed by a private rheumatologist but subsequently lost to follow-up. She had taken over-the-counter oral steroid for 4 years. Clinically, she also had Cushingoid features. Three days after admission, a clinical diagnosis of adrenal insufficiency was made, and the patient was started on oral hydrocortisone 10 mg twice per day.
One week after admission, she developed high fever and progressive confusion. Results of repeated computed tomography of the brain and lumbar puncture were normal. The patient was given a meningitic dose of ceftriaxone and acyclovir. Oral hydrocortisone was increased to 20 mg twice per day. Her usual medication of Madopar was continued all along.

Two weeks after admission, she developed recurrent generalised tonic-clonic seizures with up-rolling eyeballs, followed by a continuous tonic posture. She had persistent fever, four-limb hypertonia, and bilateral flexed wrists. The patient’s Glasgow Coma Scale score decreased to 12. Electroencephalography result was normal. Blood tests showed elevated creatine kinase level to 852 U/L (reference range, 26-192 U/L). She was given phenytoin and intravenous hydrocortisone. She was kept nil by mouth including medications for 2 days in view of recurrent seizure with impaired conscious level.

Neurologists were consulted in view of persistent fever, recurrent seizure, and abnormal posture. The diagnosis of parkinsonism hyperpyrexia syndrome was made. A Ryle’s tube was inserted, and Madopar 250 mg five times per day was commenced. Oral bromocriptine 2.5 mg twice per day was started. Nonetheless, fever persisted despite resumption of levodopa for >1 week. She developed fluctuating hypotension subsequently required on and off fluid challenge and low-dose inotropic support. Repeated sepsis work-up result was negative. Renal function was normal (creatinine, 55 µmol/L). Rechecked creatine kinase level peaked at 1339 U/L. Antibiotic was changed to meropenem. The hypotension was attributed to autonomic instability. On day 25 of admission, the patient had sudden cardiac arrest and was resuscitated but died 1 day later.

**DISCUSSION**

In the present case, multiple precipitating factors were identified for the parkinsonism hyperpyrexia syndrome, including change in levodopa dosage before admission, dehydration, *E. coli* urinary tract infection, sudden withdrawal of levodopa when patient was kept nil by mouth, and sudden withdrawal of steroid before the history of steroid use was known. Creatine kinase level was only mildly elevated.

Parkinsonism hyperpyrexia syndrome or neuroleptic malignant syndrome is characterised by the tetrad of mental status change, muscular rigidity, hyperthermia, and autonomic instability. It is a rare complication of Parkinson disease. Unlike neuroleptic malignant syndrome which is due to anti-psychotic agents, parkinsonism hyperpyrexia syndrome is most commonly due to sudden withdrawal of levodopa in patients with Parkinson disease. The pathological mechanism is a sudden suppression of central dopaminergic activity. Common precipitating factors include infection, dehydration, hot weather, and stroke. Withdrawal or malfunction of deep brain stimulation device is also a potential cause. Common complications of parkinsonism hyperpyrexia syndrome may include aspiration pneumonia, disseminated intravascular coagulation, deep vein thrombosis, pulmonary embolism, acute renal failure, and rhabdomyolysis.

The disease carries significant mortality and morbidity. In a large collaborative study in Japan, full recovery occurred in 68.7% of patients, and the remaining 31.3% of patients failed to recover to their pre-morbid status. Parkinsonism hyperpyrexia syndrome can also occur in other diseases that involve monoaminergic system, such as multiple system atrophy.

Common findings of parkinsonism hyperpyrexia syndrome include elevated creatine kinase level to >1000 U/L, leukocytosis, normal brain imaging, and normal lumbar puncture. Treatment consists of prompt resuming levodopa, supportive care, bromocriptine, and dantrolene. Careful history taking is important in diagnosis and early treatment to prevent mortality. The National Health Service provides guidelines for peri-operative management of levodopa, including dosage conversion of oral levodopa to rotigomine patches. Early recognition of parkinsonism hyperpyrexia syndrome and avoiding sudden withdrawal of levodopa are key to preventing mortality from the disease.

**CONFLICTS OF INTEREST**

All authors have disclosed no conflicts of interest.
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ETHICS

The patient was treated in accordance with the Declaration of Helsinki. The patient’s relatives provided informed consent for the treatment/procedures and consent for publication.

REFERENCES