Parkinsonism hyperpyrexia syndrome caused by abrupt withdrawal of ropinirole

Introduction

The parkinsonism hyperpyrexia syndrome is a rare but potentially fatal complication seen in patients with Parkinson's disease. It is characterized by mental status changes, muscle rigidity, hyperthermia and autonomic dysfunction. Mortality of up to 4% has been reported but an additional one-third of patients have permanent sequelae. The treating physician should be mindful of two very similar and serious conditions: neuroleptic malignant syndrome and serotonin syndrome.

Parkinsonism hyperpyrexia syndrome may be indistinguishable from neuroleptic malignant syndrome except that it occurs in patients with pre-existing parkinsonism and is often referred as neuroleptic malignant-like syndrome. This is the first reported case where withdrawal of the dopamine-receptor agonist ropinirole alone has led to parkinsonism hyperpyrexia syndrome, despite the patient continuing to take levodopa and a monoamine oxidase inhibitor.

Discussion

Parkinsonism hyperpyrexia syndrome is a neuroleptic malignant-like syndrome seen in patients with Parkinson's disease. It is a rare (0.3% of Parkinson's disease patients/year) but a potentially lethal form characterized by mental status changes, muscle rigidity, hyperthermia and autonomic dysfunction (Newman and Grosset, 2009).

Parkinsonism hyperpyrexia syndrome is under-reported, partly because the clinical and laboratory features are non-specific. Mild cases may be mislabelled as sepsis or worsening of parkinsonism. High fever is the most frequent clinical manifestation of parkinsonism hyperpyrexia syndrome, followed by worsening of parkinsonism and then altered levels of consciousness.

Levenson (1985) suggested a definition of neuroleptic malignant syndrome using the sum of three major or two major and four minor criteria in an appropriate clinical setting (*Table 1*) and these criteria can also be helpful in diagnosing a neuroleptic malignant-like syndrome condition, i.e. parkinsonism hyperpyrexia syndrome.

The major differential diagnosis is serotonin syndrome and the differences are highlighted in *Table 2*. Serotonin syndrome may have additional clinical features such as myoclonus, hyperreflexia, seizures and mood alteration (restlessness, elevated mood). This overlap may relate to the impact that elevated serotonin levels have on lowering dopamine levels. Serotonin syndrome may resolve quickly but can be potentially fatal. Like parkinsonism hyperpyrexia syndrome, the rarity and seriousness of serotonin syndrome precludes large randomized trials (Mills, 1997).

Rapidly switching between dopamine agonists may also lead to parkinsonism hyperpyrexia syndrome as does dehydration and metabolic disturbances. The dose of ropinirole that this patient was on pre-event was low and the preparation a long-acting one (starting dose is 2 mg once daily), indicating that acute illness, rapid changes in the Parkinson's disease treatment regimen and dehydration might have contributed to the development of parkinsonism hyperpyrexia syndrome.

Although withdrawal of levodopa is still the most common cause of parkinsonism hyperpyrexia syndrome, other agents can be implicated, including amantadine, dopamine agonists and catechol-O-methyl-transferase inhibitors (Kipps et al, 2005).

An EMBASE search performed by the ropinirole drug manufacturer in July 2013 specifically to check for ropinirole withdrawal features did not yield any reference to parkinsonism hyperpyrexia syndrome.

Table 1. Diagnostic criteria for neuroleptic malignant syndrome

Criteria	Feature
Major	Fever, rigidity, and elevated creatine kinase level
Minor	Tachycardia, abnormal blood pressure, tachypnoea, altered consciousness, diaphoresis and leukocytosis

Case Report

A 67-year-old man with an 8-year history of Parkinson's disease was admitted with an episode of collapse at home. He was found to have postural hypotension and nitrite-positive urine dip. The labile blood pressure was attributed to his multiple anti-parkinsonian medications (4 mg ropinirole once a day, 100/25 mg co-careldopa 5 times a day and 10 mg selegiline once a day). He only received trimethoprim for his urinary tract infection and no new medication was added. During the admission his ropinirole was tapered off over 3 days.

Three days post admission the patient was found in a 'confused, rigid and hallucinating' state with a temperature of 40.2°C. He had increased tremor and stiffness, profuse sweating, tachypnoea and tachycardia. Review of his drug chart and collateral history from the nursing staff confirmed his adherence to his usual anti-Parkinson's disease medications during his hospital stay.

A diagnosis of parkinsonism hyperpyrexia syndrome was made. He was cooled via external ice packs and cold intravenous saline. A nasogastric tube was inserted, an additional dose of his usual co-careldopa was given and ropinirole was restarted. The creatine kinase was 845 U/litre (50–200 U/litre) and urine showed blood on dipstick. The patient started recovering over the next few hours and his muscle tone and temperature returned to baseline over the next few days.

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Table 2. Comparison of neuroleptic malignant and similar syndromes (parkinsonism hyperpyrexia syndrome) and serotonin syndrome

	Neuroleptic malignant syndrome	Serotonin syndrome
Onset	Acute (minutes to hours)	Sub-acute (days)
Resolution	Gradual (average 9 days)	Improves in <24 hours
Physical examination	Altered sensorium (90%)	Altered sensorium (50%)
	Muscle rigidity (90%)	Muscle rigidity (50%)
	Autonomic dysfunction (90%)	Autonomic dysfunction (50–90%)
	Hyperthermia (90%)	
Laboratory abnormalities	Elevated creatine kinase level (90%)	Elevated creatine kinase level (20%)
	Elevated hepatic transaminase levels (75%)	Elevated hepatic transaminase levels (10%)
	Leukocytosis (90%)	Leukocytosis (15%)

From Mills (1997)

Parkinsonism hyperpyrexia syndrome has also been reported in patients with atypical parkinsonism, for example multiple system atrophy and progressive supranuclear palsy (Konagaya et al, 1997). It is important to note that deep brain stimulation does not protect the patient from parkinsonism hyperpyrexia syndrome (Factor, 2007).

Medical complications of parkinsonism hyperpyrexia syndrome can be chronic and irreversible, including renal failure from rhabdomyolysis, respiratory failure from decreased chest wall compliance, aspiration pneumonia, and other complications of immobility (Newman and Grosset, 1999).

More recently, dopamine agonists have been shown to produce behavioural addictions, with an estimated 14–17% combined prevalence of impulse control disorders such as pathological gambling, compulsive eating, compulsive buying, and hypersexuality in dopamine agonist-treated patients for all indications (e.g. restless legs syndrome).

Dopamine agonist withdrawal syndrome is defined as a severe, stereotyped cluster of physical and psychological symptoms that correlates with dopamine agonist withdrawal in a dose-dependent manner, causes clinically significant distress or social or occupational dysfunction, are refractory to levodopa and other Parkinson's disease medications, and cannot be accounted for by other clinical factors (Rabinak and Nirenberg, 2010). BJHM

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LEARNING POINTS

- Any elevation of body temperature during the course of anti-parkinsonian drug treatment should be considered as parkinsonism hyperpyrexia syndrome until proven otherwise.
- This is the first reported case of parkinsonism hyperpyrexia syndrome associated with withdrawal of ropinirole alone and highlights the fact that parkinsonism hyperpyrexia syndrome can develop despite the use of other anti-Parkinson's disease drugs. Parkinsonism hyperpyrexia syndrome has been reported with withdrawal of other dopamine agonists and non-dopaminergic medications.
- In a patient who is 'nil by mouth' a nasogastric tube must be placed to administer regular Parkinson's disease medications. The rotigotine transdermal patch and apomorphine as subcutaneous injections are other options.
- The monoamine oxidase-B inhibitors such as selegiline should be used with caution when combined with other antidepressants, including tricyclics and selective serotonin-reuptake inhibitors, because of the risk of causing serotonin syndrome.
- Dopamine agonists have a stereotyped withdrawal syndrome that can lead to profound disability in a subset of patients.