An unwell patient with Parkinson's disease: hyperpyrexia syndrome in a heatwave

Short title: Parkinson's heatwave hyperpyrexia syndrome

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Abstract

Hyperpyrexia syndrome in Parkinson's disease (PD) is a medical emergency requiring prompt action. This can be precipitated by numerous provoking factors, in particular withdrawal of dopaminergic medication.

We report a case of a patient with PD presenting with confusion, dramatic worsening of PD symptoms and pyrexia in the context of a heatwave, **potentially mediating its effect through dehydration and impaired medication absorption**. Precipitous cooling and conversion of dopaminergic medication to a rotigotine patch due to drowsiness led to her rapid improvement. The possibility of infection was covered however no source of infection or evidence of inflammatory response was found, but remained an important differential.

This case highlights the importance of recognising and managing hyperpyrexia syndrome in PD and the possibility of uncharacteristically hot weather being a cause.

Introduction

Hyperpyrexia syndrome is a medical emergency and may arise in an unpredictable and idiosyncratic manner. Whilst this can be precipitated by common physiological stressors such as acute infection, there are other factors to consider including abrupt cessation of dopaminergic medication. We present a case of h**yperpyrexia** syndrome occurring in the context of a heatwave.

Case presentation

An 82 year old female was admitted to hospital with a temperature of 39.4°C, heart rate 138, respiratory rate 26, and blood-pressure 159/95. She had been found indoors unwell during a heatwave with an ambient temperature between 26-29°C. She was unable to give any history and paramedic notes described increasing confusion, shaking and decreasing oral intake**.** Collateral history was sought to establish the circumstances prior to admission, ascertaining medication concordance (**with no missed doses reported)** and actively excluding a fall or long lie.

The patient had been diagnosed with idiopathic Parkinson's disease 14 years previously and the condition was well-controlled with regular specialist follow-up. She was prescribed co-beneldopa 12.5/50mg and 25/100mg tablets five times per day, co-beneldopa 25/100mg MR at night and an additional dose of dispersible co-beneldopa 12.5/50mg in the early afternoon. She had previous breast cancer and current venous leg ulcers. She lived with her husband and had carers twice daily.

No abnormalities were detected on chest x-ray and infection markers were consistently normal (WCC 7.8, CRP 8). Creatinine kinase (CK) was raised at 784 and lactate 1.39. Renal function was unchanged (Na 140, K 4.1, Cr77, urea 9.5). She was diaphoretic and hot to touch with severe coarse tremor of the right arm and head with blepharospasm. She was peripherally vasodilated with raised JVP. Her upper limbs and neck were stiff and she was unable to open her eyes or mouth. She was initially able to give single word answers but subsequently became obtunded with a GCS of 7 (E1 V1 M5).

Differential diagnosis

Recognising that overt signs of infection are often not present in older adults, a high index of suspicion was maintained for sepsis and empirical broad-spectrum antibiotics were initiated.

Examination demonstrated typical signs of PD (rigidity, tremor) but also new abnormal movements of the head and blepharospasm with delirium and subsequent coma. Autonomic instability was evident with sustained atrial fibrillation with fast ventricular response and diaphoresis. Treatment was instigated on a working diagnosis of a PD **hyperpyrexia** syndrome.

Outcome and follow up

Cooling was initiated by removal of leg dressings, application of cold compresses and proximity to an air conditioning unit. Due to drowsiness, regular dopaminergic medications were substituted for a 12mg/24h rotigotine patch. She remained pyrexial with a temperature >39°C for 12 hours (range 38.3 – 40.3C). Intravenous fluids were administered. Discussion was undertaken with the Intensive Care team for consideration of active cooling. However as the local unit used an invasive system (consisting of a centrally-inserted venous catheter) requiring intubation and ventilation, this was considered inappropriate due to her pre-existing frailty and escalation of treatment discussion that had occurred in clinic prior to admission.

Twenty-four hours later, the patient was apyrexial, bright and alert and motor symptoms returned to baseline. Oral medications for Parkinson's disease were recommenced and transdermal rotigotine stopped. Antibiotic choice was refined and a 5-day course completed, although no evidence of sepsis was established. Microbiological investigations comprising two sets of peripheral blood cultures, urine culture and respiratory swab for Covid-19, flu A+B and RSV were negative. The patient was established as medically fit for discharge on day 3 of admission with heatwave induced PD **hyperpyrexia** syndrome as the diagnosis, **with dehydration and poor oral intake whilst unwell contributing and potentially affecting medication absorption.**

Discussion

Numerous descriptions of acute syndromes have been depicted in PD, encompassing descriptors such as "Parkinson's disease hyperpyrexia", "acute akinesia" and "neuroleptic malignant-like syndrome". These are likely underpinned by an acute hypodopaminergic state which has been compared to the neuroleptic malignant syndrome (NMS) seen in individuals without PD; an idiosyncratic reaction to intentional dopamine blockade. In PD, individuals experience a pathological hypodopaminergic state which is augmented exogenously although imperfectly, and are exquisitely sensitive to sudden change in dopamine levels. Numerous precipitants have been documented, most frequently abrupt withdrawal of dopaminergic medication and infection, as well as failure of deep brain stimulation systems,[1] paralytic ileus and sodium abnormalities.[2] Hot weather has been described as a precipitant,[3] yet patients are not routinely counselled on strategies to mitigate this and is likely an increasing concern given climate change.

Hyperpyrexia syndrome is life-threatening, manifesting with cardiovascular and autonomic compromise that includes fever, tachycardia, tachypnoea and hypotension. Changes in consciousness can occur with delirium that may progress to coma and symptoms of PD invariably worsen, in particular causing severe rigidity that renders the patient immobile and increases the risk of complications such as pneumonia. Raised CK likely results from rigidity and is associated with rhabomyolysis risking renal failure and disseminated intravascular coagulation in severe cases. Although **hyperpyrexia** is fortunately rare, it is unpredictable. Older individuals and those with advanced disease appear to be at most risk.[4]

Treatment involves cooling, rehydration and ensuring normal dopaminergic supplementation is restored as quickly as possible. Altered consciousness or delirium may complicate the choice of medication route. Nasogastic tube can be considered where enteral absorption is not compromised or transdermal rotigotine is an option if diaphoresis does not compromise skin adherence. Limited

evidence exists for supplementary medication and is mostly inferred from the NMS literature; the use of dopamine-agonist bromocriptine is described,[5] similar to the effect of rotigotine started in our patient, as has dantrolene. Notably steroids have been recommended before, but these papers have since been retracted due to academic misconduct.[6] Serotonin syndrome can also present similarly and careful withdrawal of newly commenced serotonergic agents should be considered, in particular monoamine-oxidase inhibitors. The overlap of signs with sepsis is obvious and a high-index of clinical suspicion and prompt treatment of sepsis is appropriate, however this case highlights the importance of maintaining a wider differential.

Key points

- Hyperpyrexia syndrome in PD is a life threatening medical emergency and requires prompt comprehensive assessment and intervention.
- Precipitating factors can vary but commonly include cessation or variable concordance with dopaminergic medications and can be due uncharacteristically hot weather
- It is challenging to rule out sepsis which can frequently coexist and low threshold for empirical treatment should be considered.
- Ensuring restoration of normal or equivalent dopamine dosing through the best available route is key, through NG administration or conversion to rotigotine patch if needed (see http://pdmedcalc.co.uk/)
- Addressing any precipitating factors whilst rehydrating and actively cooling is important.
- Increasing dopaminergic dosing should be considered in refractory or severe cases, however specialist advice should be sought
- Further work is needed to understand the effect of environmental heat on people with Parkinson's and develop effective counselling to provide to patients. This is particularly important given the effect of climate change.

Written consent was sought from the patient for this publication

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