# DYSKINESIA-HYPERPYREXIA SYNDROME IN PARKINSON’S DISEASE: A HEAT SHOCK-RELATED EMERGENCY?

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**ABSTRACT**

**BACKGROUND**

Dyskinesia hyperpyrexia syndrome (DHS) has been reported as a medical emergency in patients with advanced Parkinson’s disease (PD). The few previously published cases have emphasized the role of high dopaminergic daily dose and complex concomitant polytherapy as a risk factor for DHS.

**CASES**

We report three patients with advanced PD and Levodopa-Carbidopa intestinal gel (LCIG) who developed DHS during a seasonal heatwave.

**CONCLUSIONS**

In this context of climate warming, advanced PD patients, especially when treated with high dopaminergic daily dose (i.e. under LCIG), are a cohort at risk for DHS. In the event of heatwaves, onset of fever and appearance/worsening of severe dyskinesia must be evaluated with the utmost care in order to prevent a DHS emergency in PD.

# INTRODUCTION

Non-physiological dopaminergic stimulation can cause Dyskinesia-Hyperpyrexia syndrome (DHS), a rare medical emergency associated with Parkinson’s Disease (PD)1-5. DHS is characterized by severe contin­uous dyskinesia, rhabdomyolysis and hyperthermia that may progress to men­tal state alteration, renal and cardiac failure and death. Here we report three patients with advanced PD and optimal control of motor fluctuations under Levodopa-Carbidopa Intestinal Gel (LCIG) infusion. They all developed DHS during summer heatwaves (Supplementary Figure S1).

**CASE 1 (July 2015, 2nd decade, external temperature 38-40°C, max average temperature ≥ 34°)**

A 77-year-old man with a 17-year history of PD underwent LCIG infusion in 2012 because of severe motor fluctuations. Before LCIG he had mild dyskinesia, which did not worsen after the infusion. He also suffered from orthostatic hypotension and hyperhidrosis episodes. In the year preceding DHS, motor fluctuations had been fully controlled with LCIG (1500 mg/day) and dyskinesia were minimal (Unified Parkinson’s disease rating scale, UPDRS IV, items 32-33 = 2). His treatment also included pramipexole (1.05 mg/day), amantadine (200 mg/day) and sertraline (50 mg/day). During a heatwave in July 2015, at age 80, he developed severe continuous generalized choreo-dystonic dyskinesia (UPDRS IV32-33= 8) followed by confusion and lethargy.

At admission in the Intensive Care Unit (ICU), his temperature was 42°C, he had leucocytosis (14,200 per mm3), iperCKemia (16040 U/L), elevated liver enzymes (AST = 389 U/I, ALT=450 U/I), renal failure (creatine = 2.1 mg/dl) and high plasma osmolality (309 mEq/l). He had increased C-reactive protein (6.8 mg/dL, normal value < 0,3 mg/dL) and procalcitonin (4.1 ng/mL, normal value <0.5 ng/mL). A total body CT scan revealed cholecystitis and pericholecystic effusion. Cerebrospinal fluid examination was negative, including bacteriological cultures.

Treatment was started with intravenous fluids, antipyretics, and antibiotic (piperacilline and tazobactam). Because of severe diurnal continuous dyskinesia persisting at a milder intensity when stopping the infusion at night, LCIG was tapered and pramipexole was gradually suspended (Table 1, Supplementary Figure S1). This action did not produce remission of dyskinesia. His clinical conditions worsened over the following days because of right basal pneumonia and renal failure. Switching to meropenem and colistine antibiotic therapy was unsuccessful. Laboratory investigations revealed 18,100 leukocytes, creatinine=3.78 mg/dl, myoglobin >900 ng/ml and CK = 2747 U/I. He died of multiple organ failure at five days after being admitted to the hospital.

**CASE 2 (July 2016, 1st decade, external temperature 36-38°C, max average temperature ≥34°)**

On July 2016, a 76-year-old woman with advanced PD and chronic ischemic heart disease developed fever (38°) requiring antibiotic treatment. Over the year preceding DHS, she had been treated with LCIG (1200 mg/day), pramipexole (1.05 mg/day), venlafaxine (75 mg/day) and zolpidem (10 mg/day). LCIG provided full control of motor fluctuations and minimal dyskinesia occurring for few hours in the evening (UPDRS IV32-33 =1). She also suffered from orthostatic hypotension and nocturnal visual hallucinations (successfully treated with clozapine 25 mg/day). At day 3 after the onset of fever, her temperature reached 41°C and she developed uncontrollable continuous dyskinesia persisting also at night and causing admission to the ICU. At examination, she had stupor, severe generalized choreo-dystonic dyskinesia (UPDRS IV32-33 =8) with only a mild bilateral akinetic-rigid syndrome. She also had severe respiratory distress and tachycardia. Her blood test revealed severe dehydration, leukocytosis (18,000 per mm3), hyperCKemia (2967 U/I) and hypernatremia (160 mEq/L). Later that day, she developed acute pulmonary oedema and she died, before any change in her PD medications would have been done.

**CASE 3 (August 2017, 1st decade, external temperature 38-40°C, max average temperature ≥33°)**

A 79-year-old woman with a 30-year history of PD was successfully treated with LCIG (1250 mg/day) for 9 years because of disabling motor fluctuations. She also suffered from post-prandial orthostatic hypotension. Her UPDRS IV32-33 on LGCI was 2 due to mild dyskinesia affecting facial muscles, especially in the evening. She was hospitalized on August 2017 because of a 4-days history of fever associated with pharyngodynia, hyporexia, dehydration and generalized severe choreo-dystonic dyskinesia. Involuntary movements mildly persisted also at night. She had two febrile episodes in the previous two months, successfully treated with antibiotics. At admission her temperature was 39.5°C and she had the following laboratory findings: 11,900 leucocytes, CK = 1967 U/I, creatinine = 1.97 mg/dL, serum sodium = 159 mEq/L. C-reactive protein = 3.1 mg/dL, procalcitonin = 2.3 ng/mL. Chest X-rays, blood and urine cultures were negative. She was hydrated with 5% dextrose solution (2000 ml/day), treated with ceftriaxone 2g/day and LCIG dose was progressively reduced (about 50%), because of severe dyskinesia (UPDRS IV32-33=8). Over the following days, body temperature, CK levels, serum creatinine, sodium and kidney function returned to normal levels. Severity of dyskinesia was also greatly reduced (UPDRS IV32-33=2). She was discharged after six days of hospitalization.

# DISCUSSION

PD patients may experience severe acute complications often associated to change of their medications or systemic diseases. The most common described emergency is Parkinsonism-Hyperpyrexia Syndrome (also known as acute akinesia)6, which may be caused by dopaminergic drugs withdrawal or abrupt reduction, interruption of Deep Brain Stimulation, traumatic injury, infectious or gastrointestinal diseases. PD patients experiencing Parkinsonism-Hyperpyrexia Syndrome develop severe akinetic state with transient unresponsiveness to dopaminergic treatment.

DHS is a poorly described and undereported acute complication in PD patients with an opposite clinical spectrum (dyskinesia) but under similar precipitating systemic factors (infectious diseases, trauma, dehydration). In all reported cases1-5, including ours (Table 1, n= 8 patients), DHS occurred in patients with long duration PD and it was associated to a trigger event. Most of the subjects were treated with high doses of dopaminergic drugs (half of them with LCIG). A distinctive feature of DHS is the relationship with high ambient temperature, described in a patient with recurrent DHS over 3 summers2 and in our three cases. All our patients, suffering from DHS during summer, showed the same sequence of clinical-pathological events: sustained hyperthermia and impaired thermoregulation, dehydration, dyskinesia, rhabdomyolysis and alteration of mental state. In all cases, ambient temperature was much higher than the seasonal average. A clear source of infection was only demonstrated in case 1 from our series, pointing out the additional role of other factors for DHS, such as impaired thermoregulation and dehydration.

Considering the few data available on this rare emergency, we can just speculate on a pathophysiological mechanism for DHS. Here we propose that DHS is a multifactorial phenomenon in which hyperpyrexia (caused by systemic diseases or trauma), high ambient temperature and impaired thermoregulation (further worsened by dehydration during summer heatwaves) may contribute to full development of the clinical picture. In addition, a high daily dose of levodopa, as used in advanced PD under LCIG, might sustain this vicious circle.

Preclinical studies have suggested that ambient temperature strongly influences dopaminergic transmission and dopamine receptor sensitivity. Over 32°C, systemic injection of apomorphine fails to elicit any significant fall in core temperatures7. Furthermore, rats exposed to heat stress (ambient temperature=45±0.5°C) demonstrate a significant increase of dopamine and glutamate in the systemic circulation and hypothalamus along with signs of hypothalamic inflammation8. Moreover, abnormal thermoregulation9, which is part of the spectrum of dysautonomia in PD, might trigger DHS, further enhancing the effect of high ambient temperature on dopaminergic receptors. This hypothesis is further supported by the presence of autonomic impairment in our cohort of PD patients with DHS.

Exposure to high ambient temperature is a natural risk that continues to increase with the rising of global temperature and 30% of the world population is currently exposed to potentially deadly heat for 20 days or more per year10. In the context of global climate warming, PD patients with a long disease duration and a high daily dopaminergic dose should be considered a high-risk cohort for DHS. We suggest that over heatwaves, onset of fever and appearance/worsening of severe dyskinesia should be a red flag for DHS. Timely treatment with rehydration, antipyretic measures, circulatory support, together with a reduction of antiparkinsonian drugs might be crucial for a favourable outcome.

**AUTHOR ROLES**

1.  Research project: A. Conception, B. Organization, C. Execution;

2.  Statistical Analysis: A. Design, B. Execution, C. Review and Critique;

3.  Manuscript: A. Writing of the first draft, B. Review and Critique;

# MS: 1B, 1C, 3A

# MM, MD, RA, MM: 1C, 3B

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# GC: 1A, 1B, 1C, 3B

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ETHICAL COMPLIANCE STATEMENT

We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this work is consistent with those guidelines. We also guarantee that patients or their legal representatives have given their consent to anonymously report their clinical reports in accordance with current ethical standards.

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**SUPPLEMENTARY FIGURE S1.** Unified Parkinson’s disease rating scale (UPDRS) items 32-33 for dyskinesia in each of the three reported patients, before Dyskinesia-Hyperpyrexia Syndrome (T0), at the time of Dyskinesia-Hyperpyrexia Syndrome (T1) and after recovering from it (T2) (only in patient 3 who survived). Cutaneous temperature (CT), ambient temperature (AT) and Levodopa and daily dosage of and Levodopa-Carbidopa intestinal gel (LCIG) are shown.

**Table 1: Clinical features of our cases with Dyskinesia-Hyperpyrexia syndrome and previously reported cases.**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | Age/  Gender | Season | PD duration  (years) | Suspected Trigger | Medication (Daily dose) | Treatment | Outcome |
| Case 1 | 80/M | Summer | 17 | Infection/ Summer heatwave | LCIG = 1500 mg  Pramipexole= 1 mg  Amantadine = 200 mg  Sertraline = 50 mg | Pramipexole and AMA withdrawn  LCIG dose reduction = 700 mg  Antibiotics | Death |
| Case 2 | 76/F | Summer | 18 | Infection/ Summer heatwave | LCIG = 1200 mg  Pramipexole= 1 mg  Clozapine = 25 mg  Venlafaxine = 75 mg  Zolpidem = 10 mg | Antibiotics | Death |
| Case 3 | 79/F | Summer | 30 | Infection/ Summer heatwave | LCIG = 1250 mg | LCIG reduction (675 mg)  Rehydration  Antibiotics | Recovered |
| Gil-Navarro et al, 2010 | 68/F | NA | 12 | NA | Levodopa = 750 mg  Pramipexole = 4 mg  Amantadine = 200 mg | Pramipexole tapered off Quetiapine 25 mg | Recovered |
| Taguchi et al 2015 | 70/F | Fall | 13 | Drug change (pramipexole IR→ER) | Levodopa = 600 mg  Pramipexole = 3 mg  Selegiline= 5 mg | Reduction of dopaminergic drugs | Recovered |
| Herreros- Rodriguez et al, 2016 | 83/F | 3 consecutive Summers | 25 | Summer heatwave | Levodopa = NA | LCIG=1310 mg | Recovered |
| Acebrón Sánchez- Herrera et al,  2017 | 66/F | Summer | 16 | Trauma/recent medication change (ropinirole for RLS) | LCIG = 1450 mg  Amantadine = 200 mg  Ropinirole = 8 mg  Safinamide= 100mg | LCIG reduced  Amantadine, ropinirole and safinamide stopped  Midazolam i.v. | Recovered |
| Baek et al, 2017 | 74/F | Spring | 23 | Trauma (rib fracture) | Levodopa = 375 mg  Amantadine = 200 mg  Pramipexole = 1 mg | Pramipexole stopped  Levodopa reduced to 300 mg | Recovered |

ER= extended release; F = female; IR = immediate release; i.v. = intravenous; LCIG = Levodopa-Carbidopa Intestinal Gel; M= male; NA= not available; PD = Parkinson’s diseas