Tidsskriftet
DEN NORSKE LEGEFORENING

A man in his fifties with increasing motor fluctuations, sleep impairment and altered mental status

NOE Å LÆRE AV

INGRID NYSVEEN

E-mail: inysve@gmail.com
Department of Neurology
Innlandet Hospital, Lillehammer
*Current address:
Department of Neurology
Oslo University Hospital, Rikshospitalet
Ingrid Nysveen is a specialty registrar in neurology.
The author has completed the ICMJE form and declares no conflicts of interest.

MIRZA JUSUFOVIC

Department of Neurology
Oslo University Hospital, Rikshospitalet
Mirza Jusufovic, MD PhD, specialist in neurology and researcher.
The author has completed the ICMJE form and declares no conflicts of interest.

SVEIN MARTIN LUTH

Regional Psychiatric Centre - Gjøvik
Innlandet Hospital, Gjøvik
Svein Martin Luth is a senior consultant and specialist in psychiatry.
The author has completed the ICMJE form and declares no conflicts of interest.

VIDAR GUNDERSEN

Department of Neurology
Oslo University Hospital, Rikshospitalet
and
Institute of Clinical Medicine
University of Oslo
Vidar Gundersen, MD PhD, senior consultant and specialist in neurology, and associate professor.
The author has completed the ICMJE form and declares the following conflicts of interest: He has received consultancy fees from Abbvie.

INGER MARIE SKOGSEID

Department of Neurology
Oslo University Hospital, Rikshospitalet
Inger Marie Skogseid, MD PhD, senior consultant and specialist in neurology, and researcher.
The author has completed the ICMJE form and declares the following conflicts of interest: Her employer has received funds from the Research Council of Norway, and she has received lecture fees from Medtronic, Desitin Pharma, Boston Scientific and the Movement Disorders Society

BACKGROUND/CASE PRESENTATION

A man in his fifties with advanced Parkinson´s disease was admitted with increasing motor fluctuations including dyskinesias, as well as hallucinations and delusions. After reduction of oral dopaminergic treatment, the dyskinesias improved, but the psychotic symptoms persisted. They were perceived as levodopa-induced, despite concurrent prominent bradykinetic-rigid symptoms. Dopaminergic treatment was therefore discontinued. He subsequently developed hyperthermia, severe generalised rigidity and akinesia, and autonomic instability. Parkinsonism-hyperpyrexia syndrome was diagnosed, and continuous intraduodenal levodopa/carbidopa infusion was initiated. Despite this, he had several episodes of respiratory distress requiring mechanical ventilation, as well as bradycardia and a single asystole. Although motor and autonomic dysfunction slowly improved, severe akinetic-rigid and neuropsychiatric symptoms persisted, with poor response to increased levodopa. On vital indication, electroconvulsive therapy was performed with clear improvement of mobility and mental state. A hip fracture requiring surgery necessitated discontinuation of ECT, which failed to show equivalent effect when resumed. His condition was considered terminal and all active treatment ceased, resulting in death a few weeks later.

INTERPRETATION

Parkinsonism-hyperpyrexia syndrome can develop if dopaminergic treatment is reduced abruptly and excessively. Coexistence of confusion and/or psychosis and clear bradykinetic-rigid symptoms should alarm the clinician. Dopaminergic treatment should not be discontinued, but given intraduodenally. ECT can be effective if started sufficiently early and administered frequently.

A man in his fifties with advanced Parkinson's disease showed a sudden and marked exacerbation of motor symptoms, and altered mental status. Therapeutic intervention produced only transient improvement. The cause was a rare and serious condition related to both the underlying disease and its treatment.

The patient was admitted to the neurological department of the local hospital for adjustment of his Parkinson's disease medication owing to increasing motor fluctuations – bradykinesia and rigidity alternating with dyskinesias – as well as anxiety and impaired sleep. He had been diagnosed with Parkinson's disease 8 years earlier and since then been treated with dopaminergic drugs. At the time of admission, he was taking the dopamine receptor agonist pramipexole 1.05 mg × 3, the monoamine oxidase B (MAO-B) inhibitor rasagiline 1 mg and levodopa/carbidopa/entacapone 200/50/200 mg × 7 daily. Levodopa had been added to pramipexole a year after diagnosis, and the catechol-O-methyltransferase (COMT) inhibitor entacapone added four years later due to motor fluctuations. Two months prior to admission, the MAO-B inhibitor had been changed from selegiline 10 mg to rasagiline 1 mg, and one month prior to admission, levodopa/carbidopa/entacapone had been increased from six to seven doses daily.

Upon admission, he was oriented to time and place, but had a monotone speech melody and showed marked rigidity. He was perceived as undertreated. Levodopa/carbidopa was added in a slow release formulation 25/100 mg at bedtime, and after 72 hours he was discharged for three weeks of residential rehabilitation.

Parkinson's disease is characterised by progressive degeneration of neurons in the substantia nigra. Dopamine is formed from levodopa in the end terminals of these neurons in the striatum, and is then degraded by the enzymes MAO-B and COMT. The neurons form part of networks with the thalamus and cortex, which have key roles in modulating motor function as well as cognitive, emotional and autonomic processes (Figure 1).

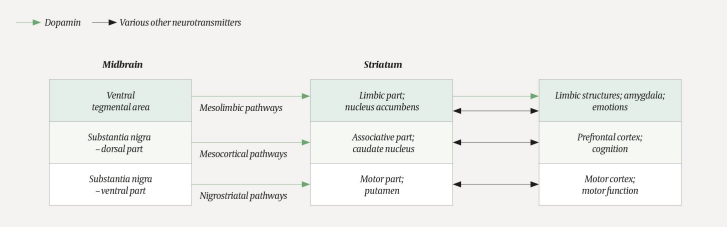

Figure 1 *Simplified schematic overview showing the connections from dopaminergic neurons in the midbrain to the striatum and cortex. The connections between the striatum and cortex are part of complex networks that also include other basal ganglia and thalamic nuclei and involve a number of different neurotransmitters.*

In advanced Parkinson's disease, the capacity for reuptake, synthesis and storage of dopamine is low because of the few remaining nigrostriatal neurons. The drug levodopa has a short half-life and, when taken orally, must be transported first across the duodenal wall into the bloodstream and then across the blood-brain barrier before it can be converted to dopamine in the brain. The pronounced neuronal loss combined with the pharmacokinetics of orally administered levodopa result in fluctuations of the brain dopamine levels roughly in line with serum levodopa levels. This contributes to fluctuations in motor and non-motor symptoms (1, Figure 2). Empirical evidence suggests that MAO-B and COMT inhibitors, and dopamine receptor agonists in slow release formulations, are less helpful in evening out these fluctuations in patients with advanced Parkinson's disease. For patients who continue to receive oral dopaminergic treatment, frequent levodopa dosing is thus often the best strategy (2).

Six weeks later, the patient was readmitted to the local hospital after several weeks in which he had been noisy and disruptive and had accused acquaintances of withdrawing money from his bank account. He was oriented to time and place, but showed generalised dyskinesia and was very talkative. A too high total dosage of dopaminergic medications was now suspected. Pramipexole was discontinued and doses of levodopa/carbidopa/entacapone were reduced from 200/50/200 mg × 7 to 125/31.5/200 mg × 7 daily. Treatment with rasagiline was continued. Quetiapine 50 mg was added to reduce anxiety and promote sleep. Improvement in the dyskinesias and behavioural disturbances was observed, and he was discharged with planned follow-up by a home nurse.

This patient required a high total dose of dopaminergic medication to maintain acceptable motor function. However, this can lead to periods of excessive dopaminergic stimulation of the striatum, resulting in motor overactivity with dyskinesias, as well as altered cognitive and emotional function with impulsive behaviour, hypomania and psychotic symptoms (Figure 2).

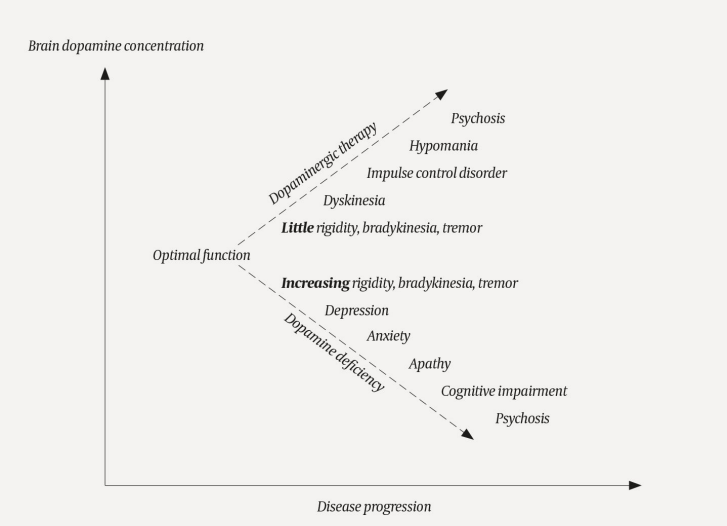

Figure 2 *Simple schematic overview of motor, emotional and cognitive symptoms in progressive Parkinson's disease. Fluctuations in symptoms occur as a result of gradually increasing brain*

dopamine deficiency and periods of excessive stimulation from dopaminergic drugs.

The doses of all dopaminergic antiparkinsonian drugs can be converted into levodopa-equivalent daily doses (LEDD) and added together, as shown in Table 1 (3). Our patient's total LEDD upon his first discharge from hospital was 2 352 mg, and such a high dose may have contributed to his motor overactivity. In line with the guidelines for treatment of psychotic symptoms in Parkinson's disease, the dopamine agonist was discontinued first (2). However, his total LEDD was also greatly reduced, to 1 339 mg per day.

Table 1

Conversion of dopaminergic antiparkinsonian drugs to daily levodopa-equivalent doses (LEDD) in a patient with Parkinson's disease.

Accepted conversion factor for dopaminergic medications		Highest dose, mg (upon first hospital discharge)	Reduction, mg (during second admission)
Levodopa	1	1 400 • 1.00 = 1 400	875 • 1.00 = 875
Entacapone	Levodopa • 0.33	1 400 • 0.33 = 462	875 • 0.33 = 289
Levodopa slow release	0.75	100 • 0.75 = 75	100 • 0.75 = 75
Rasagiline	100	1 • 100 = 100	1 • 100 = 100
Pramipexole	100	3.15 • 100 = 315	-
Total LEDD		2 352	1 339

A few days after returning home, the patient was admitted to the local hospital for the third time (day 1). He had rigidity in the neck and all extremities, and could only move them a little in response to simple commands. His general condition was reduced, and his consciousness fluctuating. When awake, he had periods of incomprehensible speech and inappropriate laughter. Neurological and general examinations were otherwise normal, as were the blood tests performed on arrival. That same evening, the duty neurologist was summoned after a nurse found the patient lying on the floor. The doctor observed reduced awareness and pronounced rigidity of the neck and extremities. Short-term improvement of the rigidity was seen after 10 mg intravenous diazepam.

When assessed by the consulting neurologist on day 2, the patient was judged to have psychosis with paranoid delusions. Levodopa was considered to possibly still be contributing to this, and therefore levodopa/carbidopa/entacapone were discontinued. To rule out other causes, such as autoimmune encephalitis or a malignant brain tumour, lumbar puncture was performed on day 2 and brain MRI and EEG on day 3. These examinations did not reveal any definite pathological findings. Rasagiline and quetiapine were discontinued on day 3. The patient did not improve, and on day 5 antipsychotic treatment with clozapine 25 mg was started. On day 7, levodopa/carbidopa/entacapone were restarted with dose escalation over the next few days.

Levodopa was discontinued abruptly owing to the suspicion that medication-induced dopaminergic overstimulation was causing the psychosis. However, the patient had at that time no motor signs of overstimulation, and in such cases other causes of psychosis must be considered. Regardless, abrupt discontinuation of levodopa is not recommended in patients with Parkinson's disease, because of the high risk of a severe deterioration of motor function. It became clear after a few days that dopaminergic drugs had to be reinstated, but these were escalated slowly to avoid exacerbation of the psychotic symptoms. Clozapine, an antipsychotic with established efficacy against psychosis in Parkinson's disease, was also administered (4).

On day 9, the patient became febrile (38.5 °C), with increasing somnolence and rigidity. Blood tests showed leucocytosis 13.5 · 10^9/l (reference range 3.5–10 · 10^9/l) and CRP 102 mg/l

(0–5 mg/l), increasing to 144 mg/l the following day.
Creatine kinase (CK) peaked at 414 U/l (40–280 U/l). Auscultation of the lungs revealed crackles and mucus accumulation. Chest X-ray and urine dipsticks were normal. Penicillin G 5 million IU × 4 was started for possible pneumonia. This was later changed to cefotaxime 2 g × 3. On day 10, a nasogastric tube was inserted due to dysphagia. This was used to administer soluble levodopa/benserazide corresponding to a LEDD of 800–900 mg. CRP and leucocyte count decreased over the next few days, but the patient continued to have a temperature of about 38 °C, heavy sweating (diaphoresis), tachycardia and pronounced rigidity. Neuroleptic malignant syndrome caused by clozapine was now suspected, and clozapine was therefore discontinued on day 12.

Neuroleptic malignant syndrome (NMS) is a rare but potentially life-threatening condition that may occur with the use of dopamine receptor-blocking antipsychotics. It was first described in 1960 in a patient treated with haloperidol (5). The cardinal symptoms are altered mental status, pronounced muscle rigidity, fever and impairments in autonomic function, such as the regulation of sweating and body temperature, heart rate, blood pressure and respiration. Over 90 % of those affected have increased CK levels in blood, and 75 % have polymorphonuclear leucocytosis (6).

Patients with Parkinson's disease can develop signs and symptoms similar to those of neuroleptic malignant syndrome if dopaminergic medications are reduced abruptly and excessively, even without the use of antipsychotics. A number of terms are used in the literature to refer to this condition, including parkinsonism-hyperpyrexia syndrome, neuroleptic malignant-like syndrome and acute dopamine-depletion syndrome (6). The term parkinsonism-hyperpyrexia syndrome (PHS) will be used in this article.

On day 15, the patient developed acute respiratory distress with excess respiratory mucus. His oxygen saturation fell to 70 %, and he twice received non-invasive ventilatory support in the intensive care unit. On day 22 he was transferred to a university hospital owing to severe and persistent motor and neuropsychiatric symptoms as well as unstable respiratory function. Upon arrival at the neurological observation unit, he was afebrile and could breathe independently, but failed to respond verbally. He had apraxia of eyelid opening, tremor in the right arm, prominent neck rigidity with fixed torticollis, and generalised dystonia and rigidity.
The clinical picture was consistent with neuroleptic malignant syndrome, but he had had only limited exposure to antipsychotics. Because of the rapid and extensive reduction of dopaminergic treatment earlier in the disease course, parkinsonism-hyperpyrexia syndrome was considered a more appropriate diagnosis. To restore dopaminergic stimulation, the dose of levodopa administered via nasogastric tube was gradually increased, and from day 24 a dopamine agonist was reintroduced in the form of rotigotine sustained-release patches. The patient now had tachycardia, diaphoresis, increased respiratory rate, excessive mucus production and a fall in oxygen saturation to <85 % despite oxygen delivery via a mask.
CT thorax on day 24 showed pulmonary embolism. Subcutaneous enoxaparin 40 mg × 1 was changed to dalteparin 7 500 IU × 2, and he received 24 hours of non-invasive ventilatory support in the intensive care unit. He had several episodes of severe bradycardia (20 beats/min). On day 25 he had a brief asystole, and was resuscitated with a precordial thump and ten compressions.
From day 25, he showed some improvement in motor function and was able to respond to verbal commands. On day 35, due to persistent and prominent akinetic-rigid symptoms, the patient underwent a percutaneous endoscopic gastroduodenostomy (PEG), and continuous intraduodenal infusion of levodopa/carbidopa (Duodopa) 1 900/475 mg per day by pump was started. Over the next few weeks, it gradually became possible to mobilise the patient, and he was able to stretch out his arms and maintain a sitting position for brief periods.

Continuous intraduodenal levodopa infusion should be considered for patients with advanced Parkinson's disease who have motor fluctuations despite optimised oral

medication. A percutaneous endoscopic gastroduodenostomy is performed, and an internal jejunal probe inserted under endoscopic surveillance through the PEG opening past the ligament of Treitz. Our patient was given continuous Duodopa owing to signs of dopaminergic understimulation at night and because high single doses of levodopa resulted in motor fluctuations and a fall in blood pressure.

After a month, the patient was moved back to the local hospital, still suffering from prominent rigidity and a tendency to airway obstruction. He was intubated the night after the transfer and was tracheostomised on day 3. He remained on a ventilator for ten days. Following decannulation, he was anxious and hallucinating, and had little capacity for meaningful communication. Further adjustments to his medication were difficult without exacerbating his motor or psychiatric symptoms.

A psychiatrist was therefore consulted on the indication for electroconvulsive therapy (ECT). The patient was unable to consent, but a decision was made to initiate ECT treatment on vital indication. The first three treatments were administered once a day and the patient tolerated the general anaesthesia reasonably well. He showed rapid improvement, and the psychiatrist was able to obtain the patient's consent from the second treatment onwards.

Positive effects of ECT have been described previously in cases of treatment-refractory motor symptoms, severe depression and psychosis in Parkinson's disease (7). ECT is also used to treat refractory neuroleptic malignant syndrome (8), and there are reports of efficacy in cases of parkinsonism-hyperpyrexia syndrome (9). The therapy is initially administered with short intervals between sessions, with a gradual transition to maintenance therapy, as when treating depression. ECT is performed under general anaesthesia, which can be challenging in patients with autonomic instability. Transient memory impairments may occur, but the treatment otherwise has few adverse effects.

With maintenance therapy every 2–3 days the patient showed significantly less rigidity and had periods of improved mental status. But when, after nine sessions, the treatment interval was increased to 4–5 days, he deteriorated between sessions. He was more mobile, but showed a lack of caution and sustained several fractures as a result of falls. Surgery for a femoral neck fracture led to a two-week pause in the ECT after 12 sessions. By the time treatment was resumed, he was back to his pre-ECT state. While some effect of the treatment was seen, the patient deteriorated rapidly when the interval was increased to seven days. ECT was discontinued after 36 sessions.

The patient was discharged to a nursing home three months after being transferred from the university hospital. After a few months, his condition was judged to be terminal. Active treatment, including intraduodenal levodopa infusion, was then discontinued. He died shortly afterwards.

Discussion

This case report describes a serious and protracted clinical course with a fatal outcome, resulting from an abrupt failure of dopaminergic stimulation of striatal neurons and their connections to motor, emotional, cognitive and autonomic brain areas. We consider the rapid dose reduction and subsequent discontinuation of dopaminergic drugs to be the main precipitating event in this patient with advanced Parkinson's disease, and believe the correct diagnosis to be parkinsonism-hyperpyrexia syndrome. Antipsychotics (quetiapine, clozapine) were administered briefly and in such small doses that they could not have been the main cause of the dopaminergic failure, as they are in cases of neuroleptic malignant syndrome. The patient's psychotic symptoms were interpreted to be a sign of drug-induced dopaminergic overstimulation, which was why levodopa was greatly reduced and eventually discontinued. But the patient showed at the same time a pronounced worsening of akinetic-rigidity. This combination of symptoms should alarm the clinician, and should raise suspicion of parkinsonism-hyperpyrexia syndrome.

It is important to be aware that psychosis can occur in Parkinson's disease independently of the use of dopaminergic drugs and is more common in cases of advanced disease and with

concomitant cognitive impairment (4). High doses of dopaminergic drugs increase the risk of psychosis (4). In cases of psychosis plus motor signs of dopaminergic overstimulation (dyskinesias), the use of dopamine agonists, MAO-B inhibitors and COMT inhibitors should be discontinued (in that order), while the frequency of levodopa dosing can be increased (2). Great caution must be exercised if considering a reduction in levodopa dose. Levodopa should never be greatly reduced or abruptly discontinued in a patient with advanced Parkinson's disease. If oral administration is not possible, levodopa must be administered via nasogastric tube.

Parkinsonism-hyperpyrexia syndrome can also be prevented by ensuring that patients with Parkinson's disease and motor fluctuations have timely access to advanced treatments such as deep brain stimulation or pump-delivered therapy. For patients undergoing deep brain stimulation, it is essential to avoid acute battery failure; battery replacement must be treated as an emergency.

The incidence of parkinsonism-hyperpyrexia syndrome is uncertain. In a Japanese case series, the incidence was estimated to be 2–3 % in cases of advanced parkinsonism (10). The condition may also occur without prior adjustment of dopamine receptor-stimulating or -blocking drugs, or interruption of deep brain stimulation. Causes may include infection, dehydration, ileus, or surgery (11). The prognosis is poor, but improves with early diagnosis and adequate treatment. In the Japanese study, 67 % of patients regained their previous functional level, while mortality was 4 % (10).

If parkinsonian-hyperpyrexia syndrome is suspected, the patient must receive prompt and adequate treatment with dopaminergic drugs as well as supportive care to counteract autonomic failure and serious complications. If the response is insufficient, ECT may be considered in addition. A significant clinical response may be seen after a few sessions, but the effect often diminishes rapidly without further treatments. The duration of the effect and the usefulness of maintenance treatments have not been well established, but a transient response can help stabilise the patient (8). Our patient had been critically ill for almost three months prior to the start of treatment and unfortunately did not experience a lasting effect. Maintenance therapy was nevertheless continued to some degree, given the absence of any other treatment options.

The key message in this article is that physicians must exercise great caution if they deem it necessary to reduce dopaminergic drugs in patients with Parkinson's disease, especially in cases with comorbid intercurrent disease or other acute challenges. Psychosis in Parkinson's disease must not invariably be viewed as a symptom of dopaminergic overstimulation. In cases of altered mental status or psychosis and simultaneous worsening of rigidity and bradykinesia, parkinsonism-hyperpyrexia syndrome must be suspected.

REFERENCES:

1. LeWitt PA. Levodopa therapy for Parkinson's disease: Pharmacokinetics and pharmacodynamics. Mov Disord 2015; 30: 64–72. [PubMed][CrossRef]

2. Ferreira JJ, Katzenschlager R, Bloem BR et al. Summary of the recommendations of the EFNS/MDS-ES review on therapeutic management of Parkinson's disease. Eur J Neurol 2013; 20: 5–15. [PubMed][CrossRef]

3. Tomlinson CL, Stowe R, Patel S et al. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. Mov Disord 2010; 25: 2649–53. [PubMed][CrossRef]

4. Ffytche DH, Creese B, Politis M et al. The psychosis spectrum in Parkinson disease. Nat Rev Neurol 2017; 13: 81–95. [PubMed][CrossRef]

5. Delay J, Pichot P, Lemperiere T et al. A non-phenothiazine and non-reserpine major neuroleptic, haloperidol, in the treatment of psychoses. Ann Med Psychol (Paris) 1960; 118: 145–52. [PubMed]

6. Rajan S, Kaas B, Moukheiber E. Movement Disorders Emergencies. Semin Neurol 2019; 39: 125–36.

[PubMed][CrossRef]

7. Andersen K, Balldin J, Gottfries CG et al. A double-blind evaluation of electroconvulsive therapy in Parkinson's disease with "on-off" phenomena. Acta Neurol Scand 1987; 76: 191–9. [PubMed][CrossRef]

8. Rosenquist PB, Youssef NA, Surya S et al. When all else fails: The use of electroconvulsive therapy for conditions other than major depressive episode. Psychiatr Clin North Am 2018; 41: 355–71. [PubMed][CrossRef]

9. Ozer F, Meral H, Aydin B et al. Electroconvulsive therapy in drug-induced psychiatric states and neuroleptic malignant syndrome. J ECT 2005; 21: 125–7. [PubMed][CrossRef]

10. Takubo H, Harada T, Hashimoto T et al. A collaborative study on the malignant syndrome in Parkinson's disease and related disorders. Parkinsonism Relat Disord 2003; 9 (suppl 1): S31–41. [PubMed][CrossRef]

11. Mizuno Y, Takubo H, Mizuta E et al. Malignant syndrome in Parkinson's disease: concept and review of the literature. Parkinsonism Relat Disord 2003; 9 (suppl 1): S3–9. [PubMed][CrossRef]

Published: 19 October 2020. Tidsskr Nor Legeforen. DOI: 10.4045/tidsskr.19.0765
Received 24.11.2019, first revision submitted 23.3.2020, accepted 15.6.2020.