CASE REPORT

An uncommon adverse effect of levodopa withdrawal in a patient taking antipsychotic medication: neuroleptic malignant-like syndrome

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A patient with symptoms suggestive of neuroleptic malignant syndrome after levodopa withdrawal is described. The patient presented with persistent high fever, stupor, autonomic dysfunction, rigidity, and rhabdomyolysis. He was successfully treated with intravenous dantrolene, resumption of levodopa, and forced alkaline diuresis. Doctors should be aware of the risk of abrupt cessation of dopamine agonists.

Introduction

Neuroleptic malignant syndrome (NMS) is an idiosyncratic, potentially fatal complication of treatment with antipsychotic drugs that manifests as fever, muscle rigidity, and autonomic and mental dysfunction.[1] A similar clinical presentation has also been reported to develop after withdrawal from dopamine agonists.[2,3] Some authors have used the terms neuroleptic malignant-like syndrome (NMLS) or parkinsonism hyperpyrexia syndrome, as well as acute akinesia or the malignant syndrome in Parkinson disease, for such a condition.[4,5] The objective of this paper was to describe the first patient with NMLS in Hong Kong.

Case report

An 84-year-old Chinese man had chronic schizophrenia and was treated with chlorpromazine 50 mg at night for many years. Eighteen months prior to the index admission, chlorpromazine was replaced by olanzapine 20 mg daily as he had experienced extrapyramidal symptoms. He was also given levodopa 100 mg and benserazide 25 mg 3 times daily.

He was admitted to Tuen Mun Hospital, Hong Kong, for a fever of 39.5°C on 24 April 2010. He was conscious and did not have any specific symptoms. All medications, including olanzapine and levodopa, were stopped at admission as he was not permitted anything by mouth. Levodopa was not resumed subsequently as it was thought that levodopa offered no additional benefit to him. He was treated for urinary tract infection caused by *Escherichia coli* with intravenous co-amoxiclav (1.2 g every 8 hours). The fever was reduced initially. However, he developed a temperature of 40.1°C on day 3, together with stupor, sinus tachycardia, profuse sweating, and muscle rigidity. Computed tomography of the brain and lumbar puncture were within normal limits. Electroencephalography demonstrated generalised slowing (Fig 1). Creatine kinase (CK) level was elevated to more than 20 000 U/L (reference range, 50-200 U/L) on day 5. Levodopa 100 mg and benserazide 25 mg 3 times daily were reinstated. Five doses of intravenous dantrolene 20 mg every 12 hours and oral bromocriptine 2.5 mg 3 times daily were given (Fig 2). Dopamine (30 mg/h) was infused intravenously because of hypotension during treatment. Fever and rigidity gradually subsided on day 8 and day 10, respectively. He regained consciousness on day 11. However, his condition was complicated by hospital-acquired pneumonia. He was successfully treated with intravenous ticarcillin and clavulanic acid (3.2 g every 8 hours for 1 week), and was discharged from the hospital on day 27.

Key words
Antipsychotic agents; Dantrolene; Levodopa; Neuroleptic malignant syndrome; Substance withdrawal syndrome

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Discussion

The latest reports provide an incidence of NMS of 0.01 to 0.02%,[6] which is significantly lower than the previously estimated incidence of 3%.[7] This decrease likely reflects a more conservative prescribing pattern and a change in prescribing patterns towards atypical antipsychotics. The exact molecular pathogenesis of NMS remains elusive. However, there is strong circumstantial evidence that dopamine blockade plays a crucial role.[8] Therefore, NMLS can occur in patients undergoing dopamine agonist withdrawal.

There are no criteria for the diagnosis of NMLS. The patients reported have all presented with a constellation of typical symptoms and withdrawal of levodopa.

The differential diagnosis for this patient included NMS, serotonin syndrome, malignant hyperthermia, malignant catatonia, or generalised medical causes of central nervous system infection, systemic infection, seizures, acute hydrocephalus, heat stroke, acute dystonia, thyrotoxic storm, or drug overdose with phencyclidine, ecstasy, cocaine, or amphetamines.

Neuroleptic malignant syndrome consists of a tetrad of mental status change, muscular rigidity, hyperthermia, and autonomic dysfunction associated with the use of neuroleptic agents. It has been estimated that 16% of patients with NMS develop the condition within 24 hours of initiation of antipsychotic treatment, 66% within the first week, and virtually all within 30 days.[1] For this patient, olanzapine was started 18 months prior to the index admission and was stopped a few days before the onset of the symptoms, making NMS a less likely diagnosis.

Serotonin syndrome is caused by the use of serotonergic drugs. The syndrome usually presents as agitated delirium but resembles NMLS in severe disease. Typical features of serotonin syndrome that are rarely seen in patients with NMLS include

一名服用抗精神病藥物的病人在停服左旋多巴後出現不尋常的不良反應：類抗精神病藥物惡性綜合症

一名病人在停服左旋多巴（levodopa）後出現類抗精神病藥物惡性綜合症的症狀。病人出現持續高燒、木僵、自主神經機能異常、強直及橫紋肌溶解症。為病人靜脈注射丹曲林(dantrolene)，再次施以左旋多巴及進行強迫性鹼性利尿法，最終成功醫治病人。醫生應留意多巴胺模擬劑突然停藥後出現的風險。

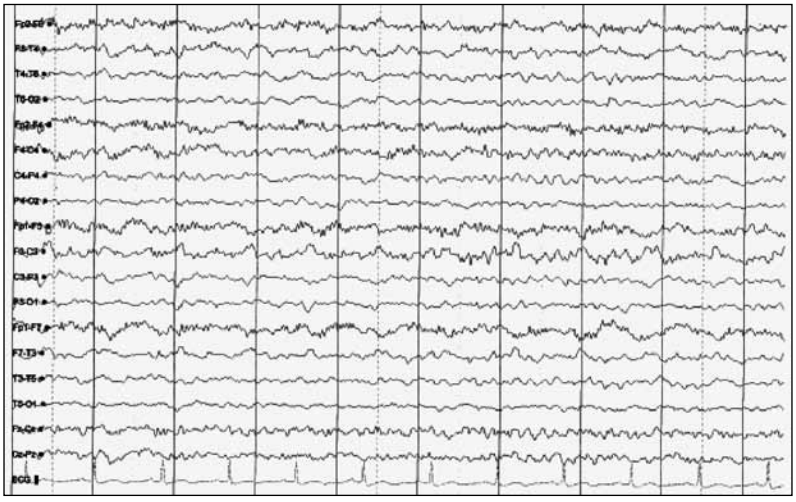

FIG 1. Electroencephalograph showing slow and symmetrical background with some non-specific slow waves

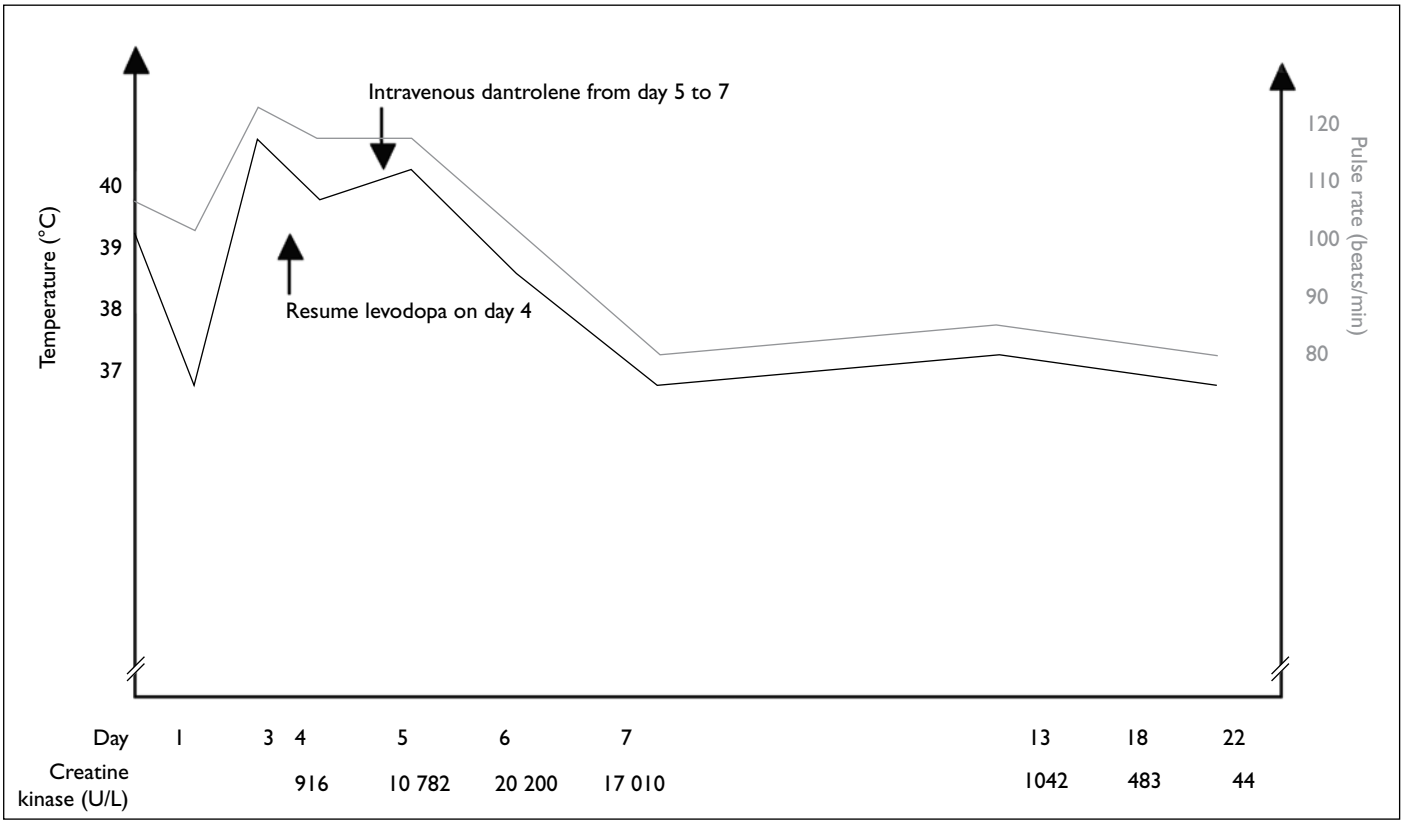

FIG 2. Schematic diagram showing the patient's temperature and pulse rate during the hospital stay, and the period of administration of key drugs

shivering, hyper-reflexia, myoclonus, and ataxia. A prodrome of nausea and vomiting in serotonin syndrome is not described in NMLS. Rigidity and hyperthermia are often less severe than in patients with NMLS.[9]

Malignant hyperthermia is a rare genetic disorder that is distinguished from NMLS by its clinical setting, for example, the use of potent halogenated inhalational anaesthetic agents and succinylcholine.

Malignant catatonia is an acute and progressive mental excitement with fever and continuous motor activity resulting in exhaustion. Most patients with malignant catatonia have a prodrome of behavioural and personality changes or frank schizophrenic symptoms lasting from 2 weeks to 2 months.[10] A useful approach to distinguish this syndrome from NMLS or NMS is to conceptualise malignant catatonia as an exhaustion syndrome, caused and maintained by relentless psychomotor excitement, lasting several days to weeks in duration, which results in alterations in autonomic function. These alterations, which include fever, profuse perspiration, and rapid pulse, coupled with a patient's refusal to eat and drink, lead to progressive and rapid weight loss, dehydration, hypotension, and deterioration in the patient's general condition.

The typical laboratory abnormality in NMLS is elevated serum CK level, which is often higher than 1000 IU/L and can be as high as 100 000 IU/L. Other common findings include leukocytosis, mild elevation in alkaline phosphatase, liver transaminases, and lactate dehydrogenase, hypocalcaemia, and metabolic acidosis. The treatment for NMLS is to resume dopamine agonists immediately. Supportive therapy is the next most important step. Volume resuscitation should be aggressive. Serial monitoring and correction of electrolyte disturbances is critical. Physical cooling should be implemented for extreme hyperthermia. Pharmacological therapy is based on case reports and clinical experience. There is no general consensus on specific pharmacological treatment. Owing to its efficacy in malignant hyperthermia, dantrolene, a direct-acting skeletal muscle relaxant, has been used in the treatment of NMS/NMLS. There are conflicting results about its use, however.[11,12] One important point is that dantrolene should not be co-administered with calcium channel blockers to avoid cardiovascular collapse. Other pharmacological agents that have been reported to be useful for the treatment of NMLS are benzodiazepines, bromocriptine, amantadine, and methylprednisolone pulse therapy.

Complications of NMLS include rhabdomyolysis, renal failure, respiratory failure, sepsis, disseminated intravascular coagulation, and seizures. There is no reported mortality rate for NMLS. However, the reported mortality rate for NMS is 10 to 20%,[13] which probably also applies to NMLS due to the close resemblance of the two syndromes.

Conclusion

Neuroleptic malignant-like syndrome is a potentially fatal disease. Diagnosis relies on a high index of suspicion and early detection of the typical symptoms and signs with supportive laboratory results. The scenario in this report emphasises the necessity for strict compliance with levodopa treatment, especially during acute illness and hospital admission. Early diagnosis is important for avoiding complications.

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References

1. Strawn JR, Keck PE Jr, Caroff SN. Neuroleptic malignant syndrome. Am J Psychiatry 2007;164:870-6.
2. Reutens DC, Harrison WB, Goldswain PR. Neuroleptic malignant syndrome complicating levodopa withdrawal. Med J Aust 1991;155:53-4.
3. Akcali A, Savas L. Malignant syndrome of two Parkinson patients due to withdrawal of drugs. Ann Acad Med Singapore 2008;37:77-8
4. Onofrj M, Thomas A. Acute akinesia in Parkinson disease. Neurology 2005;64:1162-9.
5. Mizuno Y, Takubo H, Mizuta E, Kuno S. Malignant syndrome in Parkinson's disease: concept and review of the literature. Parkinsonism Relat Disord 2003;9 Suppl 1:S3-9.
6. Stübner S, Rustenbeck E, Grohmann R, et al. Severe and uncommon involuntary movement disorders due to psychotropic drugs. Pharmacopsychiatry 2004;37 Suppl 1:S54-64.
7. Levenson JL. Neuroleptic malignant syndrome. Am J Psychiatry 1985;142:1137-45.
8. Mann SC, Caroff SN. Central dopamine hypo activity and the pathogenesis of the neuroleptic malignant syndrome. Psychiatr Ann 2000;30:363-74.
9. Lejoyeux M, Fineyre F, Adès J. The serotonin syndrome. Am J Psychiatry 1992;149:1410-1.
10. Castillo E, Rubin RT, Holsboer-Tachsler E. Clinical differentiation between lethal catatonia and neuroleptic malignant syndrome. Am J Psychiatry 1989;146:324-8.
11. Sakkas P, Davis JM, Janicak PG, Wang ZY. Drug treatment of the neuroleptic malignant syndrome. Psychopharmacol Bull 1991;27:381-4.
12. Reulbach U, Dütsch C, Biermann T, et al. Managing an effective treatment for neuroleptic malignant syndrome. Crit Care 2007;11:R4
13. Shalev A, Hermesh H, Munitz H. Mortality from neuroleptic malignant syndrome. J Clin Psychiatry 1989;50:18-25.