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CASE REPORT

There is more to this fever than meets the eye: A case of neuroleptic malignant-like syndrome (NMLS) secondary to withdrawal of procyclidine and L-dopa on a background of long-standing flupenthixol depot use

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This case report highlights the risk of development of Neuroleptic Malignant-Like Syndrome secondary to withdrawal of procyclidine with brief withdrawal of L-dopa and long-term typical antipsychotic depot. The patient responded to reintroduction of procyclidine, sedation and supportive treatment. The mechanism and management of NMS and NMLS is also reviewed. This case emphasises that any changes in antipsychotic and antiparkinsonian medications should be undertaken with extreme caution and patient should be closely monitored for development of NMLS after alteration in these medications.

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Introduction

Although neuroleptic malignant syndrome (NMS) is typically a complication of treatment with neuroleptic drugs, it can also occur following the withdrawal of L-dopa or dopamine agonists: neuroleptic malignant-like syndrome (NMLS) (sometimes called parkinsonism hyperpyrexia syndrome) (Toru *et al*. 1981; Taylor *et al*. 2018). NMS is an emergency which presents with symptoms of confusion, muscular rigidity, fever and autonomic instability. It is a rare and idiosyncratic response to antipsychotic medications, seen in 0.5–1% of patients exposed to antipsychotics (Anath *et al*. 2004). The pathophysiology of NMS is not adequately explained, although it is thought that it may be associated with a sudden decrease in central dopamine activity in the mesocortical, nigrostriatal, mesolimbic and hypothalamic pathways (Langan *et al*. 2012). The management of NMS includes supportive care, removal of the precipitating medication (or reinstatement of L-dopa or dopamine agonist), and in some cases, dantrolene or bromocriptine may be indicated (Langan *et al*. 2012). Rotigotine patch can be considered in patients with difficulties of oral administration and/or absorption (Fiore *et al*. 2014). Subcutaneous apomorphine is another option for patients where oral administration could be problematic (Lattanzi *et al*. 2006). There is evidence for the use of benzodiazepines, for example, lorazepam, diazepam and clonazepam as treatments for NMS (Pileggi *et al*. 2016). Some authors have reported that patients resistant to maximum medical therapy may benefit from instillation of intrathecal baclofen (Wait *et al*. 2009). Less often, administration or withdrawal of drugs that do not affect the dopamine system has been associated with a NMLS (Spivak *et al*. 1996).

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Case report

A 67-year-old female with a history of paranoid schizophrenia and drug-induced parkinsonism was admitted to hospital with reduced mobility. Her medications included flupentixol depot injection 50 mg given intramuscularly 4-weekly (unchanged for over 20 years), carbidopa/levodopa (Sinemet Plus 25/100 mg two tablets, twice daily and Half Sinemet CR 25/100 mg once daily) and procyclidine 5 mg three times daily. She had no history of prescribed or recreational serotonergic drugs. Carbidopa/levodopa and procyclidine were stopped as part of the medication optimisation, as they were felt unlikely to be benefiting her parkinsonism. The carbidopa/levodopa was restarted after 1 day due to worsening tremor.

Approximately 72 hours after the medication review, the patient spiked a temperature of 39.0 °C, developed tachycardia up to 122/minute and had

tachypnoea up to 48 breaths/minute. Her urine dipstick was positive for leucocytes, blood and protein. White cell count was elevated at 18.5×10^9/l with a neutrophilia (17×10^9/l). She had an acute kidney injury (urea 27 mmol/l, creatinine 157 umol/l and eGFR of 29 ml/minute (previously normal)). The initial diagnosis was urinary sepsis, with pre-renal acute kidney injury, and piperacillin/tazobactam and intravenous (IV) fluids were started. There was no clinical evidence of constipation contributing to malabsorption of oral medications.

Over the next 24 hours, she deteriorated and became markedly rigid with recurrent spasms and a reduced Glasgow Coma Scale (GCS) level to 9. She was persistently pyrexial with a temperature of 40.4 °. Creatinine kinase level was checked because of rigidity, and it was elevated at 2609 U/l, indicative of rhabdomyolysis. A diagnosis of NMLS was made secondary to the withdrawal of her anticholinergic medication (procyclidine). The patient was then commenced on IV lorazepam at regular intervals, and procyclidine was given via a nasogastric tube; IV fluids were continued. Blood culture and urine culture results were negative and her antibiotics were stopped. She improved over the next 72 hours, became afebrile, muscle spasms ceased and her GCS improved. Her renal function also recovered and the patient returned to her baseline clinical condition. No clinical sequelae of NMLS were identifiable on discharge.

Ideally, we would have preferred to change the patient to an oral atypical agent, but given that she had a history of treatment-resistant psychosis and poor concordance with oral medications, this was not a feasible treatment option. This patient had previously developed an acute dystonic reaction with oral risperidone leading to its discontinuation, which out ruled risperidone or paliperidone as an alternative depot. She tolerated the continuation of flupentixol well without recurrence of symptoms – she had received this depot for over 20 years previously without event. It is possible that the depot predisposed this patient to the development of this condition and made her more susceptible to NMS when procyclidine and L-dopa were withdrawn.

Discussion

Syndromes similar to the NMS following withdrawal of dopaminergic drugs have been described since the 1980s with a mortality rate of up to 4% and with an additional one-third of patients developing permanent sequelae (Newman *et al*. 2009). Other names used for this condition are NMLS, parkinsonism hyperpyrexia syndrome and acute akinesia or the malignant syndrome in Parkinson's disease (Onofrj & Thomas, 2005). It can be considered distinct from NMS and usually occurs in patients unable to take or absorb their dopaminergic medications, often due to compliance issues and concurrent illness (Mizuno *et al*. 2003). NMLS has generally been described in patients with idiopathic Parkinson's disease, but there are few case reports in patients with secondary parkinsonism (Mizuno *et al*. 2003; Newman *et al*. 2009). Our case is slightly different to those previously described, in that there was iatrogenic modification of a complex regimen of medications which likely contributed to the development of this syndrome: namely, the abrupt discontinuation of procyclidine and L-dopa on a background of long-standing typical antipsychotic use. It was unlikely to be malignant catatonia which is one of the differentials as there were no prodromal behavioural symptoms of psychosis, agitation and catatonic excitement developing over weeks (Fleischhacker *et al*. 1990; Oruch *et al*. 2017). Likewise, it was unlikely to be a serotonin syndrome as the patient took neither prescribed nor recreational serotonergic drugs.

The likely aetiology of NMLS was the withdrawal of L-dopa and procyclidine, with the typical antipsychotic depot (the dose of which had not changed for 20 years) likely predisposing rather than precipitating the episode. Based on this understanding, we reinstated the flupentixol depot following the resolution of this episode. She tolerated the continuation of flupentixol well without recurrence of symptoms. It is possible that the depot predisposed this patient to the development of this condition and made her more susceptible to NMS when procyclidine and L-dopa were withdrawn.

The treatment for NMLS is similar to that of NMS: supportive therapies such as active cooling, fluid resuscitation and benzodiazepines are first line. Dantrolene or bromocriptine may be indicated in some cases (Onofrj & Thomas, 2005; Langan *et al*. 2012; Fiore *et al*. 2014). Rotigotine patch, benzodiazepines and baclofen may benefit select patient groups (Wait *et al*. 2009; Fiore *et al*. 2014; Pileggi *et al*. 2016). It is important to consider the differential of NMLS in all patients with parkinsonism who are febrile, especially if they become persistently hyperpyrexic and have an altered mental status, and in patients who have had a recent change to cholinergic medications (Gurrera *et al*. 2011) (Table 1). The most important point is that this group of patients may have concurrent illnesses/comorbidities, and differentiation between sepsis and NMLS might be difficult. Early recognition of NMLS is key to commencing appropriate therapy and to prevent morbidity and mortality from this condition.

Finally, this case emphasises the fact that any changes in antipsychotic and antiparkinsonian

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Table 1. *Neuroleptic malignant syndrome diagnostic criteria: expert panel consensus*

Diagnostic criterion	Priority score
Exposure to dopamine antagonist, or dopamine agonist withdrawal, within past 72 hours	20
Hyperthermia (>100.4 °F or >38.0 °C on at least two occasions, measured orally)	18
Rigidity	17
Mental status alteration (reduced or fluctuating level of consciousness)	13
Creatine kinase elevation (at least four times the upper limit of normal)	10
Sympathetic nervous system lability, defined as at least two of the following:	10
Blood pressure elevation (systolic or diastolic ≥25% above baseline)	
Blood pressure fluctuation (≥20 mmHg diastolic change or ≥25 mmHg systolic change within 24 hours)	
Diaphoresis	
Urinary incontinence	
Hypermetabolism, defined as heart-rate increase (≥25% above baseline) and respiratory-rate increase (≥50% above baseline)	5
Negative work up for infectious, toxic, metabolic or neurologic causes	7
Total	100

medications should be undertaken with extreme caution and patient should be closely monitored for the development of NMLS after alteration in these medications, for a number of days. Where antipsychotic medications are co-prescribed, it is important to consider holding them, while the NMLS is being treated and to carefully weigh up the risks/benefits of reinstatement once the episode has resolved.

Conflict of interest

All authors have no conflicts of interest to disclose.

Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committee on human experimentation with the Helsinki Declaration of 1975, as revised in 2008. The authors assert that ethical approval for publication of this case report was not required by their local Ethics Committee.

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Consent

Consent was obtained from the patient prior to the submission of case report.

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