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Postoperative rhabdomyolysis due to neuroleptic malignant syndrome associated with droperidol and metoclopramide

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Dear Editor,

Neuroleptic malignant syndrome (NMS) is a rare, idiosyncratic, and potentially fatal complication of neuroleptic use, with a prevalence of 0.02–2.4% [1]. NMS is an important differential diagnosis of hyperthermia in the perioperative period, with a mortality rate of 5–20% [2]. Early recognition is essential for proper management, impacting morbidity and mortality [2]. In this article, we report a postoperative rhabdomyolysis secondary to NMS, associated with the use of droperidol and metoclopramide. Additionally, we review the most recent diagnostic criteria and treatment protocols for NMS.

A female patient, 28 years old, 53 kg, 158 cm, was admitted for bilateral mammoplasty with breast implant. She denied previous diseases or addictions, except for an adverse reaction to intravenous metoclopramide, described as a behavioural change, with agitation and a feeling of imminent death. There were no reports of abnormal movements or changes in muscle tone at that time. She used oral hormonal contraceptives.

The surgery was performed under sedation and a thoracic epidural anaesthesia, lasting 2 hours. She received midazolam 15 mg as a pre-anaesthetic medication. Induction was performed with fentanyl 100 µg and droperidol 10 mg. A thoracic epidural anaesthesia was performed at T7–T8 level with 2% lidocaine (100 mg) and 0.5% bupivacaine (175 mg). For hemodynamic stabilization, IV etilefrine (20 mg) was needed. The patient remained on spontaneous ventilation with a face mask during the procedure. She received antibiotic prophylaxis with cefazolin 2 g and prophylaxis for postoperative nausea and vomiting with metoclopramide 10 mg. The procedure was uneventful, and the patient was referred to a post-anaesthetic recovery room with no complaints and stable.

After 2 hours, the patient evolved with sinus tachycardia (maximum heart rate of 140 bpm), tachypnoea (maximum respiratory rate of 21 inspirations per minute), and hyperthermia (maximum axillary temperature of 41°C), which sustained for about 24 hours, in addition to blood pressure variation between 100/60 and 130/80 mmHg. The patient complained of severe myalgia. Her mental status was described as normal, but her muscle tone was not recorded.

There was a progressive increase in creatine kinase (CK) levels, from 1231 IU L^{-1} (after 6 hours), to 3306 IU L^{-1} (after 12 hours), and 9702 IU L^{-1} (after 24 hours of the procedure). Renal function remained unchanged over the period. After supportive therapy with antipyretics and hyperhydration, the patient improved completely and was discharged home on the fifth postoperative day.

The patient sought a referral centre for malignant hyperthermia (MH) for further investigation. Physical/neuro-

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logical examination and electroneuromyography were normal. The baseline CK serum level was normal (69 IU L^{-1}). The molecular study for myopathies (next-generation sequencing panel with 208 genes) did not detect pathogenic variants in the coding regions and exon processing sites of the analysed genes, in particular those linked to MH susceptibility (*RYR1*, *CACNA1S*, *STAC3*). Cardiorespiratory exercise test demonstrated aerobic capacity within the normal range, but with signs suggestive of cardio circulatory limitation assessed by early lactate threshold and oxygen consumption-reduced load ratio, compatible with a sedentary lifestyle. A biopsy of the quadriceps femoris was performed under sedation and regional anaesthesia for the standard test for susceptibility to MH, the *in vitro* muscle contracture test with halothane-caffeine, with a negative result. The patient signed an informed consent form for the investigation. Written consent was obtained from the patient to publish all detailed personal and clinical information.

We report a patient who presented a postoperative hyperthermic syndrome with tachycardia, tachypnoea, blood pressure oscillation, and rhabdomyolysis associated with the use of medications with dopamine receptor antagonist effects (droperidol and metoclopramide). After extensive investigation, MH and rhabdomyolysis associated with underlying myopathy were ruled out, leading to a diagnosis of NMS by exclusion.

The pathophysiology of NMS involves a sudden decrease in dopaminergic activity in the central nervous system, which is usually triggered by neuroleptics or by the abrupt withdrawal of antiparkinsonian drugs [1, 2]. Among the most frequently used antipsychotics in clinical practice, butyrophenones (haloperidol and droperidol) seem to present a greater risk of NMS due to the potent blockade of postsynaptic D_2 receptors in the nigrostriatal system [3]. This effect is potentiated by the association of other drugs with an antidopaminergic effect, such as metoclopramide, as used in the present report.

TABLE 1. Diagnostic criteria for neuroleptic malignant syndrome (adapted from Gurrera *et al*., 2017 [5])

Diagnostic Criteria Score	Points
Exposure to dopaminergic antagonists (or withdrawal of dopaminergic agonists) within the past 72 hours	20
Hyperthermia (oral temperature > 38°C on at least 2 occasions)	18
Rigidity	17
Altered mental status (reduced or fluctuating level of consciousness)	14
Elevation of CK (≥ 4 times the upper normal limit)	10
Autonomic dysfunctions, defined as at least 2 of the following alterations: • Elevation in blood pressure (systolic or diastolic ≥ 25% of baseline values) • Blood pressure fluctuations (≥ 20 mmHg in diastolic or ≥ 25 mmHg in systolic within the past 24 hours) • Diaphoresis • Urinary incontinence	10
Hypermetabolism, defined as (both criteria): • Elevation in heart rate (≥ 25% of baseline values) • Elevation in respiratory rate (≥ 50% of baseline values)	5
Exclusion of other aetiologies (infectious, toxic-metabolic, and/or neurological)	7
Total	100

CK – creatine kinase

Over the years, the diagnostic criteria for NMS have undergone changes. In 2000, the Revised Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association (DSM-IV-TR) established that, for the diagnosis of NMS, it would be necessary to have muscle rigidity and hyperthermia (mandatory criteria), in addition to at least one of the following clinical changes: autonomic instability (represented by sweating, dysphagia, tremor, urinary incontinence, tachycardia and/or blood pressure fluctuations) or mental status changes (fluctuations in levels of consciousness, confusion, mutism, and/or coma) [4]. The main laboratory alterations linked to NMS are leukocytosis and those resulting from muscle rigidity/rhabdomyolysis, such as elevations in serum aldolase, lactate dehydrogenase (LDH), transaminases, myoglobin, and CK, in addition to myoglobinuria [4]. Following the DSM-IV-TR criteria, our patient had hyperthermia, tachycardia, blood pressure oscillation, and laboratory alteration indicative of rhabdomyolysis; however, muscle stiffness, which is present in NMS as a "cogwheel sign", was not researched/reported. We emphasize that, in the context of hyperthermic syndromes and rhabdomyolysis, it is important for the anaesthesiologist to always investigate muscle tone.

In 2011, new diagnostic criteria for NMS were published following an international consensus formed by 17 medical specialists [5]. Each item of this criteria has a specific score, for a total of 100 points; NMS diagnosis needs scores greater than or equal to 74 (sensitivity 69.6%, specificity 90.7%) (Table 1) [5]. According to these new criteria, the patient in our report had a borderline score of 70 points (exposure to dopaminergic antagonists in the last 72 hours: 20 points, hyperthermia > 37.8°C [2 measurements]: 18 points, CK elevation: 10 points, autonomic dysfunction: 10 points, hypermetabolism: 5 points, exclusion of other aetiologies: 7 points). Mental status change was absent. The score was compromised by the absence of inquiry into the muscle stiffness (17 points). Alongside the well-established clinical and laboratory manifestations and the various diagnostic scores reported in the literature, atypical presentations in NMS are described, which consider the elevation of creatine kinase levels as one of the main criteria [1].

TABLE 2. Dopaminergic drugs for neuroleptic malignant syndrome

Drug	Dose	Route	Frequency
Bromocriptine	2.5–10 mg	Enteral	3 times per day
Levodopa with carbidopa or benserazide	100 mg	Enteral	3–4 times per day
Amantadine	100 mg	Enteral	3–4 times per day

Administer up to one week after symptom resolution.

Due to the diagnosis of NMS being one of exclusion, the differential diagnoses must include many situations, such as anticholinergic, adrenergic, and serotonergic syndromes; systemic (sepsis, tetanus) and central nervous system infections (meningitis, encephalitis, and ventriculitis); malignant and central hyperthermia; exogenous poisoning by licit (alcohol, monoamine oxidase inhibitors, tricyclic antidepressants, serotonin, or dual reuptake inhibitors) and illicit drugs (methamphetamine, cocaine); and endocrine or metabolic conditions (pheochromocytoma and thyrotoxicosis) [1, 2]. The diagnosis of NMS cannot be made in the absence of the use of neuroleptics or withdrawal of dopaminergic in the last 72 hours, or when there is the use of other medications that justify the symptoms (phencyclidine derivatives) or the presence of psychiatric disorders or other neurological conditions that explain the symptoms (mood disorders with catatonia, Cotard's delusion) [2]. At least in this one case, our findings indicate that having NMS is not necessarily associated with MH susceptibility during anaesthesia. Conversely, whether people with MH susceptibility are at risk for NMS when treated with neuroleptics remains an open question.

NMS treatment involves general clinical support measures (hydration with crystalloids, airway control, and oxygen therapy) associated with dopaminergic replacement and immediate withdrawal of antipsychotics (Table 2) [2]. In the case of agitation, benzodiazepines are the medication of choice. Because it is a hyperthermic syndrome resulting from hypermetabolism, the prescription of antipyretics is ineffective, and physical cooling measures should be adopted (application of cold compresses and/or ice, in addition to thermal blankets) [2]. The patient must be admitted to the intensive care unit so that they can be monitored and investigated for other differential diagnoses. Prophylaxis for pulmonary thromboembolism is indicated. Neurology and psychiatry teams and, in suspected cases, poison control centres must be activated. Dantrolene (1 mg kg^{-1}, IV, qid, for 24–48 hours) is used, despite being considered palliative, because it acts only peripherally at the muscular level, controlling the symptoms of muscular rigidity. In refractory cases, the use of non-depolarizing neuromuscular blockers and electroconvulsive therapy (ECT) should be considered [2]. In the present report, only supportive treatment was performed with hyperhydration and suspension of antidopaminergic medications. The patient had a favourable course, possibly because of their good general health and young age, close monitoring, and appropriate interventions. In the case of doubts regarding the clinical management and/or differential diagnosis of conditions that progress with hyperthermia and hypermetabolism in the perioperative period, the attending physician can contact reference centres for malignant hyperthermia.

In conclusion, because NMS is a serious and potentially fatal condition, in addition to knowing its classic clinical manifestations, the anaesthesiologist should have a high degree of suspicion in the face of incomplete or atypical presentations of the disease, especially in the postoperative period and when associated with medications that lead to a decrease in dopamine levels in the CNS.

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