Neuroleptic Malignant Syndrome and Dantrolene. A Case Report

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Abstract

Neuroleptic malignant syndrome is a rare condition; manifestations include severe autonomic dysfunction, hyperthermia and muscle rigidity, among others. This may occur in response to drugs that interact with dopaminergic pathways. Diagnosis of this syndrome is mainly clinical since there is no specific laboratory test for this condition and it has a high mortality rate given its multiorgan involvement. This is a case report of a patient who developed neuroleptic malignant syndrome that was managed with supportive therapy and dantrolene.

Introduction

First description of neuroleptic malignant syndrome (NMS) was made in 1960 by Delay, who referred this event related to neuroleptics exposition as "akinetic hypertonic syndrome" [1]. This rare condition can be presented as an adverse reaction to the use of some antipsychotics and other medications, which interact with neuronal dopaminergic pathways. Clinical features include severe autonomic dysfunction, hyperthermia, and muscular rigidity, among others. Given its unusual presentation and a high mortality rate, it is important to make an opportune diagnosis in order to establish a prompt management [2-4]. In this case report, we present a patient with cancer who developed NMS after metoclopramide/haloperidol administration and his clinical evolution with treatment based on dantrolene and supportive measures.

Case Description

A 48-year-old male patient was admitted to our hospital with diagnosis of papillary cancer of unknown primary origin with metastatic compromise of the right eye tissues, cervical ganglia, thyroid and parathyroid glands. Patient was presented with pain and several edema along the right side of the face and neck associated with peripheral vertigo. Complimentary tests were made during first days and supportive measures were initiated based on methadone 10 mg OD/8h, morphine 6 mg IV/6h, amitriptyline 25 mg per day, and metoclopramide 10 mg IV/8h.

Twelve days after admission and after administration of metoclopramide, the patient turned anxious and disoriented with progression to psychomotor agitation. As vital signs were stable and no desaturation was present, he received supplementary oxygen by nasal cannula (SaO2 93%) and haloperidol 5 mg intramuscular; minutes later the patient turned aggressive, with visual and hearing hallucinations, paranoid delirium, muscular rigidity and diaphoresis. Midazolam intramuscular was initially administered without adequate response.

Patient status progressed to respiratory failure because of airway obstruction due to swelling of compromised neck tissues, trismus, and generalized rigidity; nasotracheal intubation guided by fibrobroncoscopy and admission to intensive care unit was decided (fig1). During transportation the patient presenting worsening of muscular rigidity, transient tonic clonic movements, tachycardia (160 bpm), hypotension (60/30 mmHg) with poor response to intravenous flu
This clinical scenario, led us to suspect a NMS and a bolus of dantrolene 20 mg IV in 20 minutes was administered, obtaining a dramatic positive response. Vasopressor infusion was suspended in less than eight minutes and cardiac frequency lowered to 90 bpm. A high rate of cold intravenous Ringer’s lactated was achieved (3000 ml/h) in combination with other cooling measures and dantrolene 20 mg /bicarbonate 1 mEq/Kg/h by continuous separate IV infusions was maintained over the next hour.

Hemodynamic stability of the patient was maintained without new requirements of vasopressors. Control arterial blood gases at 4 hours reported pH 7.37; pCO₂ 35mmHg; pO₂ 163mmHg; HCO₃⁻ 20mEq/L; EB -4.9; sO₂ 99% and lactic acid 2.4 mmol/L. Rhabdomyolisis occurred as evidenced by peak levels of CPK reached at first 24 hours after event. Despite of severe initial lactic acidosis was resolved during first 6 hours, high seric levels of transaminases persisted until two weeks (Fig. 2-4). During this period, extubation was achieved (7th day). The patient was discharged at 24th day without other complications.

Discussion

NMS is a serious, infrequent and morbid condition with a high mortality rate (10-20%) [2]. Its incidence reported around the world is variable (0.07% [3] – 2.2% [4]) because there are no accepted universal criteria and its exclusion diagnosis nature, among others [5]. The first approximation to diagnostic criteria and definition of NMS was an expert consensus meeting in 2011 that used Delphi’s methodology [6]. DSM-IV-TR criteria indicates that muscular rigidity and hyperthermia must be present after the administration of antipsychotic drugs before consider this diagnosis; probability increases when the elevation of the CPK is present [7]. Our patient presented these signs preceded by neurological symptoms. This observation is congruent with retrospective studies indicating that these neurological symptoms are present before systemic alterations in more than 80% of the cases [8,9].
Our case reflects a clear history of exposure to a medication that could precipitate NMS, with activation of a severe rhabdomyolysis as measured CPK levels show. Secondary acidosis with hyperlactatemia, liver dysfunction, and secondary kidney injury (fig 2-4) responded to medical treatment based on dantrolene and fluid management without requirement of renal support therapy.

Differential diagnosis of NMS includes infectious, toxic (anticholinergic syndrome, serotoninergic syndrome, drug abuse), endocrine (pheochromocitome, thyrotoxicosis) and other psychiatric entities (catatonia, delirium, non convulsive epileptic state, among others.) Regarding the physiopathology of NMS, various hypothesis have related it with inhibition of dopaminergic pathways. This could explain the development of hyperthermia associated to blocking of its receptors in the hypothalamus and muscular rigidity by blockade of the same family of receptors at the corpus striatum. This theory is supported by other papers referring the fact that drugs like amantadine [10] and Bromocriptine [11], could be benefit.

Other authors have suggested a possible relation between NMS and primary defects of the escheletic muscle similar to malignant hyperthermia (MH), suggesting a possible common etiology between these two hypercatabolic disorders [12]. Unfortunately, ulterior studies have not confirmed this theory, and more yet have shown contradictory results. Caroff and Colleges discovered that 5/7 patients with NMS were susceptible of MH [13], as opposed to Krivosic-Horber who reported no demonstrable association [14]. Another possible explanation of NMS proposes an immunologic origin [15]. A systemic and massive response to tissue injury known as "acute answer phase" is classically developed with leukocytosis and elevation of muscular enzymes [16]. This phenomena also happens in MNS as we reported in this patient. When MNS development risk factors have been analyzed, it seems to be no relation with age, gender, time of exposition or dose of psychotropics [17]. Instead, polipharmony and the type of antipsychotic (first vs. last generation), have been associated as occurred in our patient where metoclopramide and haloperidol were used [18].

Management of NMS involves stopping of the probable causal drug, and suspending of other anti-serotoninergic drugs, even lithium and/or valproic-acid if concomitantly used [19]. Hydroelecrotical support by balanced fluids to achieve current established microcirculatory and metabolic goals and early decision for renal and ventilatory support are needed to assure survival and decrease the chance of bad outcomes. Electroshock therapy has been reported, indicated as the first line therapy when it is not possible to disregard catatonia or people who do not respond in the first week of treatment [20,21].

Dantrolene (a calcium blocker) has been used since 1976 [22] as the cornerstone for the treatment of human malignant hyperthermia and more recently for NMS with success. Coons et al has suggested that dantrolene could act as modulator of catabolic response seen in this syndrome [23].

It has been suggested that NMS is a neurogenic form of malignant hipertermia (MH), and the rol of the Ryanodine Receptor type 1 gene (RYR1) mutations could be envolved on the development of NMS [24]. The pathophysiology of NMS still elusive, however, the treatment of NMS with Dantrolene is known to be useful due to the restriction of neuronal hyperactivity because it reduces internal Ca++ flux within nerve cells, and limits the adverse effects of excessive SNS inputs on Ca2+ regulation within skeletal muscle [25]. In skeletal muscle, dantrolene sodium dissociates the excitation-contraction coupling, probably by interfering with the release of Ca++ from the sarcoplasmatic reticulum, being this associated with loss of grip strength and weakness of the extremities as well as drowsiness and dizziness. The biologic half-life after intravenous administration is between 4 to 8 hours, it bounds to plasma proteins, mostly albumin. The recommended prophylactic dose of is 2.5 mg/kg, the continous infusion begins at a minimum dose of 1 mg/kg, until symptoms subside or the maximum dose of 10 mg/kg has been reached. The adverse effects observed with high doses are depressant effect on gastrointestinal smooth muscles, there have been reports of thrombophlebitis following administration of intravenous dantrolene, and site reactions and tissue necrosis secondary to extravasation. Fatal and non-fatal liver disorders of an idiosyncratic or hypersensitivity type may occur with dantrolene sodium therapy [25,26].

Our patient received dantrolene and improved dramatically as we reported in spite of markers of acidosis and rhabdomyolysis that return to usual values 24-48 hours later.

In summary, we presented a case of NMS, a serious condition characterized by fast instauration of neurological, metabolic and hemodynamic compromises, that could be triggered by antyphsychotic drugs and other dopaminergic blockers. Classically, neurological symptoms precede systemic alterations resulting of value for diagnosis and exclusion of other etiologies. As unusual, NMS may be difficult to be diagnosed by physicians who not familiarized, with delays in adequate and focused treatment. Besides supporting therapies, dantrolene emerges as a highly effective alternative to blunt hypercatabolic response in advance to promptly return to hemodynamic stability and adequate systemic oxygen delivery. We would like to alert institutions around the world about availability of dantrolene or, at least, an inter-institutional collaborative network allowing rapid access to this drug.


References


