

Neuroleptic Malignant-Like Syndrome (NMLS) in a patient with Parkinson's disease resolved with Rotigotine. A Case Report

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Summary. Neuroleptic Malignant-Like Syndrome (NMLS) is a rare, but potentially fatal complication of dopaminergic therapy in Parkinson's disease due to a sudden withdrawal of dopaminergic therapy. Here, we describe the case of a 79 years old woman, with 19 years history of Parkinson disease treated with L-dopa, dopamine agonists and MAO inhibitors, whose sudden withdrawal due to lack of therapeutic compliance, led to sudden onset of high fever, muscle rigidity, akinesia, autonomic dysfunction, impaired level of consciousness, respiratory distress and dysphagia with inability to take oral dopaminergic therapy. High blood levels of CPK and myoglobinaemia were found. The patient was treated with transdermal Rotigotine starting from a dose of 2 mg/24 hours, that was rapidly increased to 6 mg/24 hours, leading to resolution of the acute disturbances. (www.actabiomedica.it)

Key words: Neuroleptic Malignant-Like Syndrome (NMLS), Parkinson's disease, Rotigotine

Background

Malignant Hyperthermia (MH) and Neuroleptic Malignant-Like Syndrome (NMLS) are distinct conditions, that are often confused because of similar clinical features. Here MH and NMLS are defined as it follows (1).

Malignant hyperthermia is a rare, potentially fatal, autosomal dominant hereditary syndrome (incidence 1:50,000 adults), due to a defect of ryanodine receptor, a constitutive protein of calcium channel in the sarcoplasmic reticulum of skeletal muscle fiber). Ryanodine receptor protein is encoded in the region q12-13 of chromosome 19, and, if defective, cause an alteration of the transport of calcium in the sarcoplasmic reticulum. Clinical picture of MH is characterized by sudden onset of fever, altered mental status,

muscular rigidity. There are signs of increased CPK, myoglobinaemia, myoglobinuria, hyperkalemia, hypercalcemia and lactic acidosis. It occurs in genetically predisposed individuals, following the administration of inhaled anesthetics (halogen gases) and depolarizing neuromuscular blocking agents (succinylcholine) (2). Therefore MH is considered a myopathy due to altered calcium channel functioning. Mortality rate is 10%. Dantrolene is used in MH treatment as it inhibit ryanodine calcium channels.

Neuroleptic Malignant Syndrome (NMS) is a potentially fatal neurological emergency caused by neuroleptics drugs. It is composed of hyperthermia, extrapyramidal signs (severe rigidity and akinesia), autonomic nervous system impairment (tachypnea, tachycardia, hypertension, hypotension, incontinence) altered levels of consciousness (agitation, confusion, delirium,

stupor and coma), and respiratory disturbances. There is laboratory evidence of leukocytosis, rhabdomyolysis may follow, as increased CPK blood levels, myoglobinaemia and myoglobinuria, which leads to acute renal failure. Some authors have described "atypical" NMS cases, ie without some of main diagnostic clinical features such as hyperthermia, increased CPK blood levels and myoglobinaemia (3).

NMS incidence varies between 0.02% and 3.23% of patients treated with neuroleptics therapy, especially during the first weeks of treatment, but may result from drug dosage adjustments. Since newer atypical neuroleptics (clozapine, quetiapine, olanzapine) have been introduced cases presenting with overt clinical features were significantly reduced. For unknown reasons young males seem to be more susceptible to the syndrome. The pathogenesis of NMS is unknown. The main hypothesis is based on a dopaminergic deficit and a relative excess of glutamatergic transmission: "iperglutamatergic hypothesis" (4). A dopaminergic blockade with an inhibitory effect on the nigrostriatal system and hypothalamic area, explain muscle stiffness and thermoregulation disorders leading to hyperthermia (5). Treatment is based on removing causative neuroleptic medication, hydration, electrolyte imbalances and haemodynamic management, reducing body temperature and adequate skeletal muscle relaxant therapy (6). Dantrolene, bromocriptine, amantadine and apomorphine treatments are currently considered effective, with different mechanisms in managing muscular rigidity and hyperthermia (7). Patients should be transferred to an intensive care unit for close observation to avoid risk of complications such as myoglobinuria, dehydration, aspiration pneumonia and pulmonary embolism. Estimated mortality rate is around 20% (8).

Neuroleptic Malignant Syndrome-like the (NMLS) is a rare, but potentially fatal condition affecting Parkinson's disease patients on dopaminergic treatment. It is due to the sudden withdrawal of dopaminergic therapy, in case of polytherapy, even one only dopaminergic drug withdrawal may be causative of the syndrome (9, 10). It is a different clinical disorder distinct from NMS Clinically distinct from the NMS (11-13). Usually appears in patients who can not take and/or absorb dopaminergic therapy, other risk factors

are infectious diseases, immobilization or therapeutic changes in patients in advanced stages of disease (14). The diagnosis is based on patients clinical features, treatment is based on rapid and efficient resumption of dopaminergic oral therapy or by means of nasogastric tube. When oral drugs can not be administered, the use of subcutaneous Apomorphine represents a practicable and effective solution until motor improvement is observed and oral therapy may be restored.

Other drugs that have proven effective include bromocriptine, Dantrolene, amantadine and steroids.

In the present case report, we will review the diagnosis and treatment of this treatable condition.

Case

79 year old woman, with 19 years Parkinson's disease history, treated with levodopa (625 mg/day), pramipexole (2.1 mg/day) and rasagiline (1 mg/day). In her past clinical history Arterial hypertension, chronic atrial fibrillation, angina pectoris (treated with nitrates), left hip fracture.

The patient was admitted to the hospital for suspected bronchopneumonia associated with hyperthermy up to 40°C, severe akinesia, increased values of creatine kinase (CPK) 2596.0 U/l (reference values 25-170 U/l), CK-MB 8.4 ng/ml (reference values from 0.6 to 6.3 ng/ml), Myoglobin 1805.50 ng/mL (reference values from 14.3 to 65.8 ng/ml), lactate dehydrogenase (LDH) 785 U/l (reference values 220-450 U/l), aspartate aminotransferase (AST) 86 U/l (reference values 7-35 U/l), alanine aminotransferase (ALT) 21 U/l (reference values 5 - 35 U/l), Gamma Glutamine transferase (GGT) 68 U/l (reference values 0-40 U/l), alkaline phosphatase 333 U/l (vr <270), sodium 155 mEq/l (vr 130-150), Calcium 7.1 mg/dl (8.1 to 10.5 vr), White Blood Cell 10.47 10³/ul (vr 4 to 10.8). Glasgow Coma Scale on hospital admission was (GCS): 7. Acute renal failure was observed with creatinine values of 1.7 mg/dL (0.6-1.1), and BUN 79 mg/dL (vr 10-50). Urinalysis: PH 7.5 (5.5 to 6.5), protein 200 mg/dL (vr 0-20), Haemoglobin 1.00 mg/dL (absent), Ketone 5 mg/dL (absent) Erythrocytes 1674 n/uL (vr 0-15), Leukocytes 1228 n/uL (vr 0-18), Bacteria 24,655 n/uL (0-8000). Chest X-Ray showed

“diffuse interstitial bronchial pattern with basal left interstitial infiltrates”. E.K.G.: Sinus rhythm at 95, RBBB.

Hemogasanalysis (21% oxygen therapy) pH 7.422, pCO₂ 28.4 mmHg, pO₂: 57, SO₂: 93.3%. Vital signs: PA: 100/50 mmHg, HR 95 arrhythmic.

Neuroleptic malignant-like syndrome was suspected because of both the clinical picture and the urinary infection and poor compliance to dopaminergic therapy; therefore patient was treated with intravenous acetaminophen (as needed), methylprednisolone (40 mg/ml 1 fl bid for 2 days, then 20 mg/ml 1 bid for 3 days, and further reduced to 20 mg/ml 1 fl die for 2 days), levofloxacin (500 mg/100 ml 1FL ev/day for 5 days) meropenem (1000 mg/ml 1FL tid for 5 days) and rehydration.

Nasogastric tube positioning to administer oral dopaminergic therapy was difficult, and it caused a lesion of the pharyngeal mucosa.

Apomorphine was not considered because of evidence of coronary artery disease treated with nitrates.

Therefore patients was strted on transdermal Rotigotine 2 mg/24 hours, fas for the well known drug efficacy and tolerability (15) . Dosage was increased of 2 mg every two hours up to 6 mg/24 hours, without side effects. Then clinical course was favourable, with complete remission of both hyperthemia and muskle rigidity. After 48 hours patient was alert, cooperative, and able to take oral therapy. A total 312.5 mg L-Dopa oral dose was started, half dosage compared to what was previous patient intake, in home care regimen. Patient was discharged after eight days with complete recovery of the critical clinical conditions, CPK, myoglobin, and transaminase renal function back to normal parameters. UPDRS section III at discharge was 58. Therapy L-Dopa therapy (312.5 mg/day), Rotigotine transdermal patch 6 mg/24 hours were prescribed whereas Pramipexole (2.1 mg/day) and Rasagiline (1 mg/day) were suspended.

Discussion

The NMS and the NMLS are distinct clinical entities, the first is associated with dopaminergic blockade during treatment with antipsychotic, where-

as NMLS may occur in case of sudden dopaminergic therapy withdrawal.

Conditions leading to leading NMLS maybe various: poor therapeutic compliance, intercurrent infections, stress and dehydration. A prompt clinical diagnosis is critical to establish efficacious L-Dopa therapy to prevent untoward consequences and reduce mortality.

We have learned from literature review that there is no standard therapy for NMLS, but there are several factors that may influence the choice of the dopaminergic drug: the cause of the akinetic crisis, patient state of consciousness, actual patient therapy, the course of the disease, patient's age, and comorbidities (16, 17, 18).

There is no agreement on the pathogenesis or therapy of this syndrome, early diagnosis is critical to patient serviva.

In this case, immediately after diagnosis, there were difficulties due to administartion route and comorbidites: oral L-Dopa was not considered because nasogastric tube positioning was difficult and apomorphine was excluded on the clinical history of coronary artery disease treated with nitrates (19). We chose treatment with rotigotine patch for transdermal route administration, and it has proved to be effective in this case.

Rotigotine is a dopamine agonist D₃, D₂, D₁, with transdermal formulation used in the Parkinson's disease; today it seems to be the dopaminergic drug that is more close to the physiology of the continuous and constant dopaminergic stimulation (20-23).

It is important to consider NMLS in all patients with Parkinson's disease presenting with hyperpyrexia and sensory disturbances, especially in course of acute intercurrent illness or hospitalization, in these cases preventive optimization of dopaminergic therapeutic dosages and route of administration may avoid NMLS occurrence. Correct dose scheme and timing of administration of dopaminergic drugs are critical to prevent NMLS occurrence too.

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