A fatal case of neuroleptic malignant syndrome after paralytic bowel in a patient taking antiparkinson medications.

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Introduction

Neuroleptic Malignant Syndrome (NMS) is an idiosyncratic, rare and potentially fatal condition frequently associated with the withdrawal of an antipsychotic medication (1). Synonyms are Neuroleptic Malignant-Like Syndrome (NMLS), Acute Akinesia, Malignant Syndrome in Parkinson's disease, Parkinsonism Hyperpyrexia Syndrome. The following symptoms are often described: persistent high temperature, stupor, rigidity, autonomic and mental dysfunction and rhabdomyolysis. Some authors report a similar condition associated to withdrawal of dopamine agonists' administration (2, 3).

Paralytic Bowel (PB) is a condition frequently impairing the medications' absorption, even in the absence of modifications of the normal daily intake (4, 5). The occurrence of NMS caused by PB has not been found so closely in literature, but there is a relationship between NMS and gastroparesis (6).

The present case report describes the first case of NMS diagnosed in Italy in a PD patient on therapy with LD and amantadine who, due to the concomitant development of paralytic bowel, experienced drugs' malabsorption thus finding himself in the same conditions of a substantial withdrawal of dopamine agonists' therapy. The intrinsic risk of fatal outcomes of such a circumstance is emphasized hereto.

Case and methods

A patient aged 72, affected by Parkinson's Disease (PD) since many years, bedridden for nonunion of femoral fracture, came to the emergency department of our hospital complaining of temperature over 39.5^{0}C degrees since four days, accompanied by diffuse abdominal pain, distention and constipation. Patient's relatives reported normal intake of daily medications, consisting in levodopa and amantadine for the treatment of PD. The examination conducted at admission in the emergency department revealed the following clinical picture: hyperpyrexia with axillary temperature 39.8^{0}C, mild sinus tachycardia (112 bpm), blood pressure at 178/93 mmHg, oxygen saturation (SaO2) on pulse oximetry of 93% and respiratory rate of 20. Mild dyspnea was appreciated without crackles or rhonchi on auscultation, although a vesicular sound was a little bit increased in intensity. Abdominal bloating arose from physical examination. Furthermore, mixed alkalosis was confirmed by Arterial Blood Gas (ABG) analysis, while laboratory test results showed the following clinically significant abnormalities: increased total Creatine Phosphokinase (CPK) up to 614 mIU/mL (n.r. 24-200); increased Lactate Dehydrogenase (LDH) up to 1034 IU/L (n.r. 200-480); increased myoglobin up to 142 ng/mL (n.r. 0-112); severe hypokalemia with serum potassium concentrations of 2.6 mEq/L; and an elevated White Blood Cells count (WBC) value of 12.000.

In the following days, chest and abdominal x-rays, urine culture, viral tests and multiple blood cultures were performed, all showing negative results. Ceftriaxone prophilaxis (1 gr twice a day) and fluid therapy were started and normal intake of domiciliary medication was continued. Despite the therapies, the patient was stable for three days without showing any improvement in the general clinical condition. Temperature was continuous and resistant to nonsteroidal anti-inflammatory drugs

(NSAIDs) and corticosteroids. After a further four days, laboratory tests showed clear rhabdomyolysis with worsening of general medical conditions accompanied by the development of the initial diuresis contraction to oligo-anuria. Because of persistent elevated temperature and worsening of clinical condition we performed a contrast enhanced computerized tomography (CT) scan of chest and abdomen, showing the presence of paralytic bowel. Due to the negativity of all cultural tests and the non-responsive temperature also associated with moderate increase of muscular enzyme and normal levels of reactive C protein (RCP), it was decided to administer dantrolene therapy (1mg/Kg iv) for three days, suspending the calcium channel blockers, which led to a prompt remission of temperature. Intense fluid resuscitation was given as a supportive therapy, under serial monitoring and correction of electrolytes disturbance. Nevertheless, in the following days oligo-anuria endured and no response to either fluid therapy, electrolytes correction and furosemide has been observed. Creatinine values gradually increased, resulting in renal failure with a stable CPK. Patient's relatives refused to dialyze the subject and exitus, due to irreversible cardiac arrest, occurred nine days after admission.

DISCUSSION

Neuroleptic Malignant Syndrome (NMS) is a rare and potentially fatal complication occurring in patients treated with antipsychotic drugs (1), causing temperature, muscular rigidity, altered mental status, autonomic and mental dysfunction and rhabdomyolysis. Although this syndrome is mainly associated with treatments based on several classes of neuroleptics, NMS has also been reported as a possible reaction to a sudden withdrawal and abrupt reduction of antiparkinsonian drugs, especially dopamine (3, 7). Indeed, PD itself may be considered as a significant risk factor for

NMS. In fact, besides the withdrawal of dopaminergic drugs, occurrence of this syndrome in PD patients has also been related to other conditions such as dehydration, intercurrent infection, use of cholinesterase inhibitors, rapid switchover from bromocriptine to pergolide, constipation, and enteral nutrition (3, 8), as well as to the deterioration of parkinsonian symptoms alone (3, 9). Furthermore, it has been demonstrated that low levels of dopamine metabolite (homovanillic acid) in the cerebrospinal fluid may correlate with the possibility of developing NMLS regardless of the dosage of levodopa (3, 10).

According to the National Organization for Rare Disorders, the main diagnostic features of NMS are (11):

- Neuroleptics within 1 to 4 weeks;
- Hyperthermia (above 38°C);
- Muscle rigidity;
- At least five of the following:
  - Change in mental status
  - Rapid heartbeat (tachycardia)
  - Low or high blood pressure (hypo- or hypertension)
  - Excessive sweating (diaphoresis)
  - Excessive saliva production (sialorrhea)
  - Tremor
  - Incontinence
  - Increased creatine phosphokinase, or increased urinary myoglobin
  - Increased number of white blood cells (leukocytosis)
  - Increased concentrations of metabolic acids in blood and urine
  - Exclusion of other drug-induced psychiatric or systemic illness.

With respect to these criteria, which are substantially shared, the clinical picture discussed hereto looked somewhat atypical, given the absence of both neuroleptic drugs' assumption (apparently not accompanied by any withdrawal of dopaminergic drug administration) and concomitance of at least five of the abovementioned conditions. The diagnostic pattern for the identification of the paralytic bowel was therefore complicated, thus requiring the execution of an abdomen CT scan.

CONCLUSIONS

Malabsorption of drugs may simulate and substantially coincide with assumption withdrawal, even in the absence of modifications in the drugs' daily administration. Physicians involved in the treatment of PD patients should take into consideration the event of dopaminergic drugs' malabsorption due to PB as a possible cause of NMS, as in the case reported hereto. Although somehow atypical, a clinical picture basically attributable to NMS should suggest to timely investigate the bowel functionality and status, in order to exclude malabsorption issues, thus avoiding delayed NMS diagnosis which may potentially entail fatal outcomes for the patient.

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References

1. Thomas A, Onofrj M. Akinetic crisis, acute akinesia, neuroleptic malignant-like syndrome, Parkinsonism-hyperpyrexia syndrome, and malignant syndrome are the same entity and are often independent of treatment withdrawal. Mov Disord. 2005 Dec;20(12):1671; author reply 1671-2.
2. Fiore S, Persichino L, Anticoli S, De Pandis MF. A neuroleptic malignant-like syndrome (NMLS) in a patient with Parkinson's disease resolved with rotigotine: a case report. Acta Biomed. 2014 Dec 17;85(3):281-4.
3. Wei L, Chen Y. Patient Prefer Adherence. Neuroleptic malignant-like syndrome with a slight elevation of creatine-kinase levels and respiratory failure in a patient with Parkinson's disease. 2014 Feb 27;8:271-3. doi: 10.2147/PPA.S59150. eCollection 2014.
4. Pfeiffer RF[1]. Parkinsonism Relat Disord. 2011 Jan;17(1):10-5. doi: 10.1016/j.parkreldis.2010.08.003. Epub 2010 Sep 15. Gastrointestinal dysfunction in Parkinson's disease.
5. C. J. Suresh Chandran. Ann Indian Acad Neurol. 2008 Oct-Dec; 11(4): 248–250. Maglinant syndrome in Parkinson's disease without dopaminerergic drug withdrawal.
6. Justyna Dutkiewicz, Stanisław Szlufik, Michał Nieciecki, Ingeborga Charzyńska, Leszek Królicki, Piotr Smektała, andAndrzej Friedman. J Neural Transm (Vienna). 2015; 122(12): 1659–1661. Small intestine dysfunction in Parkinson's disease.
7. Berman BD; Neuroleptic malignant syndrome: a review for neurohospitalists. Neurohospitalist. 2011 Jan;1(1):41-7. doi: 10.1177/1941875210386491
8. Grace JB, Thompson P. Neuroleptic malignant like syndrome in two patients on cholinesterase inhibitors. Int J Geriatr Psychiatry. 2006;21:192-194.
9. Hashimoto T, Tokuda T, Hanyu N, Tabata K, Yanagisawa N. Withdrawal of levodopa and other risk factors for malignant syndrome in Parkinson's disease. Parkinsonism Relat Disord. 2003;9:25-30.
10. Ueda M, Hamamoto M, Nagayama H, Okubo S, Amemiya S, Katayama Y. Biochemical alterations during medication withdrawal in Parkinson's disease with and without neuroleptic malignant-like syndrome. J Neurol Neurosurg Psychiatry. 2001;71:111-113.

11. http://rarediseases.org/rare-diseases/neuroleptic-malignant-syndrome/

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