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CASE REPORT

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NEUROLEPTIC MALIGNANT SYNDROME DUE TO DONEPEZIL

ABSTRACT

Neuroleptic malignant syndrome (NMS), first described nearly five decades ago, is an idiosyncratic and life-threatening complication of treatment with drugs. NSM is characterized by fever, sever muscle rigidity and autonomic and mental status changes.

Many drugs may cause NMS, most of which are antipsychotic drugs. NMS can also be developed when dopaminergic drugs are suddenly withdrawn; in addition, there are other drugs that don't belong to any of the above categories that may cause NMS.

An 80 years old male patient was admitted to our Emergency Department for intermittent fever with onset from three days.
His medications included amlodipine, oral steroid, and donepezil, which was administered at the dose of 10 mg/day. At the time of admission, the patient showed stupor without other relevant signs at the physical exam.

Infectious diseases and systemic diseases were ruled out during the course. During the following ten hours after the admission, the patient experienced a further worsening of the fever to a stable level of 42°.

The neurological exam showed diffuse severe muscular stiffness and bilateral fixed miose.
A lumbar puncture was also performed that was negative. He died a few hours later.

An autopsy was also carried out and it did not show the reported results. Based on the findings in our patient and from the literature data, we hypothesize that the patient developed a NMS due to Donepezil.

This indicates that when we face with patients with altered mental state, fever, muscle stiffness and/or autonomous instability, an accurate medical history is required and we must consider Donepezil as a potential cause of suspected NMS.

LEARNING POINTS
- Neuroleptic malignant syndrome (NMS) is an uncommon and potentially fatal complication of neuroleptic treatment.
- Donepezil may cause an imbalance between the dopaminergic and cholinergic systems resulting in adverse neurological reactions because of its pharmacological properties
- Donepezil should be considered as possible cause of NMS

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INTRODUCTION

Neuroleptic malignant syndrome (NMS) is a rare and potentially fatal syndrome with hyperthermia, stiffness, autonomic instability and altered mental status. Although early symptoms of NMS may involve changes in mental state, the syndrome can progress gradually and culminate in fever and elevated CPK [(1)].

Although antipsychotics, such as chlorpromazine and haloperidol, are the main responsible, other drugs can be considered as the cause of NMS [(2)].

CASE REPORT

An 80 years old man with a past medical history of Addison disease, arterial hypertension and mild cognitive impairment, initially presented intermittent fever with onset from three days.
His medications included amlodipine, oral steroid, and donepezil, which was administered at the dose of 10 mg/day, started 15 days ago. All medications was autonomously administered. No other symptoms were reported and empiric therapy with piperacillin /tazobactam was started.
The patient was sent to the emergency department (ED) for further evaluation.

At the time of admission the patient showed stupor (Glasgow coma scale – GCS – 14; Eye 3, verbal 5, motor 6), without other relevant signs at the neurological, thoracic, cardiac and abdominal physical exam.
He had tachycardia, 130 beat per minute, with a rhythmic pulse.
His temperature was 38°C, while other vital signs were normal. Electrocardiogram and chest radiography were normal.
A trans-thoracic echocardiography only revealed hypertensive cardiopathy.
A brain CT scan was also performed without significant findings. Blood, urine, and sputum cultures were sent and then levofloxacin and parenteral fluids were started.

Steroid daily dose was increased to avoid acute Addison disease decompensation. No particular data emerged from the hematobiochemical and cultural examinations; in particular, the blood count, with formula, the C-reactive protein, renal and hepatic function, thyroid function, and the electrolytes were normal.
AdrenoCortico-Tropic Hormone (ACTH) and cortisol levels were not reduced. Culture tests from blood and urine were negative.

During ten hours after the admission, the patient experienced a further worsening of the fever to a stable level of 42°. At the neurological exam appeared diffuse severe muscular stiffness and bilateral fixed miose. Paracetamol, high dose aspirin, hydrocortisone, benzodiazepines, dantrolene and cold fluids were administered without benefits.

A comprehensive blood panel was repeated without sensitive changes, the creatinphosphokinase (CPK) was that was moderately increased (422 U/L– normal value 0-190 U/L). A total body CT scan was performed excluded infective localizations.

The patient, then, was transferred to the Infectious Disease ward where a lumbar puncture was performed, which was negative.
He died few hours later. An autopsy was performed without showing significant findings.
The patients' relatives approved the consensus of the case report.

DISCUSSION

We report the case of an immunocompromised patient with resistent fever. Fever is a common cause of hospitalization in elderly. The prompt recognition of its causes is mandatory, especially if chronic immunodepression concurs, to start an immediate antimicrobical therapy and prevent sepsis.

Consequently, a complete imaging and microbiological panel of exams has to be started.
In this case, no diagnostic evidence of infections or other possible organic causes of fever was found. Also temperature was not modified by antipyretic therapy.

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Therefore, they were excluded other possible diagnoses that could explain the symptoms of our patient. (**Tab.1**)

A donepezil induced acute neurological syndrome was hypothesized. The association of hyperthermia, muscle stiffness, autonomic instability, alteration of consciousness and high levels of CPK (albeit mild) allowed a diagnosis of malignant-like neuroleptic syndrome, despite the patient did not take antipsychotic treatment [(2)] Donepezil is useful for the treatment of dementia disorders, but the drug can cause an imbalance between the dopaminergic and cholinergic systems and these alterations may result in a dysregulation of dopaminergic, causing the onset of NMS [(3)].

The first and only case of NMS in donepezil monotherapy was described in 2003. [(3) (4) (5)]

TAB. 1
DIFFERENTIAL DIAGNOSIS OF NEUROLEPTIC MALIGNANT SYNDROME

Infectious
Meningitis or encephalitis or brain abscess
Postinfectious encephalomyelitis syndrome
Endocrine (Thyrotoxicosis or Pheochromocytoma)
Idiopathic malignant catatonia
Agitated delirium
Benign extrapyramidal side effects
Nonconvulsive status epilepticus
Structural lesions
Heatstroke
Anticholinergic delirium
Salicylate poisoning
Malignant hyperthermia
Serotonin syndrome
Substances of abuse

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CONCLUSION

Donepezil should be considered as possible cause of not responding fever in absence of other apparent conditions especially if cholinergic symptoms concur.

The NMS is considered a very rare condition in patients taking donezepil, observed only in post-marketing experience. To our knowledge, this case is the second one described in literature.

Although the NMS is a very rare condition, but potentially serious, it would be advisable to discontinue donepezil therapy for every patient who is admitted for fever of unknown origin.

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