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Neuroleptic malignant syndrome – a case report

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ABSTRACT

Neuroleptic malignant syndrome (NMS) is rare, but potentially lethal complication associated with the use of neuroleptic agents. NMS is most often observed after high-potency first-generation neuroleptic agents. NMS is characterised by a distinctive clinical syndrome including: hyperthermia, muscular rigidity, mental status change, autonomic disability. The most common laboratory finding is elevated serum CK. The management of patients with NMS demands aggressive care and discontinuing of the causative agent.

A 49-year-old patient with recurrent depressive disorders is presented. NMS developed following the increase in haloperidol dose and concomitant use of olanzapine. The treatment with bromocriptine and lorazepam resulted in a prompt recovery.

Key words: neuroleptic malignant syndrome, hyperthermia, elevated serum CK

CASE REPORT

A 49-year-old patient was admitted to the Department of Internal Diseases with a 3-day history of fever. The patient had been treated psychiatrically for 9 years due to recurrent depressive disorders. One week prior hospitalization, the Patient underwent an episode of severe depression with psychotic symptoms (i.a. catatonia). He was treated with fluoxetine (20 mg/day), haloperidol (1 mg/day) and aripiprazole (10 mg/day). He refused bilateral electroconvulsive therapy (ECT). The patient developed higher temperature and muscle stiffness following the increase in haloperidol dose (from 1 to 2 mg/day) and concomitant use of olanzapine (10 mg/day) .

Physical examination on the day of admission revealed fever (39°C), elevated blood pressure (160/95 mmHg), tachycardia (115 beats per minute), tachypnea (30 breaths per minute) and saturation of 95% at ambient air. Neurologic examination exposed reduced level of consciousness and rigidity. Laboratory investigation showed leucocytosis (white blood count of 15,67 x 10^3/L), hypokalemia (3,3 mmol/L), aspartate transaminase level elevation (105 U/L), alanine transaminase level elevation (79 U/L). Furthermore, creatine kinase level was markedly elevated (2185 IU/l), with normal CK MB fraction and cardiac troponin levels. Additionally, a low serum iron concentration was observed (34 ug/dl). An electrocardiogram revealed no acute ischemic changes. Brain imaging studies showed no pathological changes (Figure 1). Lumbar puncture excluded central nervous system infection. Focal lesions were not visible in abdominal ultrasonography.

Taking into account the clinical picture, neuroleptic malignant syndrome (NMS) was diagnosed. Haloperidol was discontinued. The patient was treated with lorazepame (1 mg every six hours) and bromocriptine (2,5 mg every eight hours). Supportive care was performed – electrolyte imbalance was aligned, euvolemic state was maintained using intravenous fluids. Paracetamol and cooling blankets were used to lower fever. Low molecular weight heparins were prescribed for prevention of deep venous thrombosis.

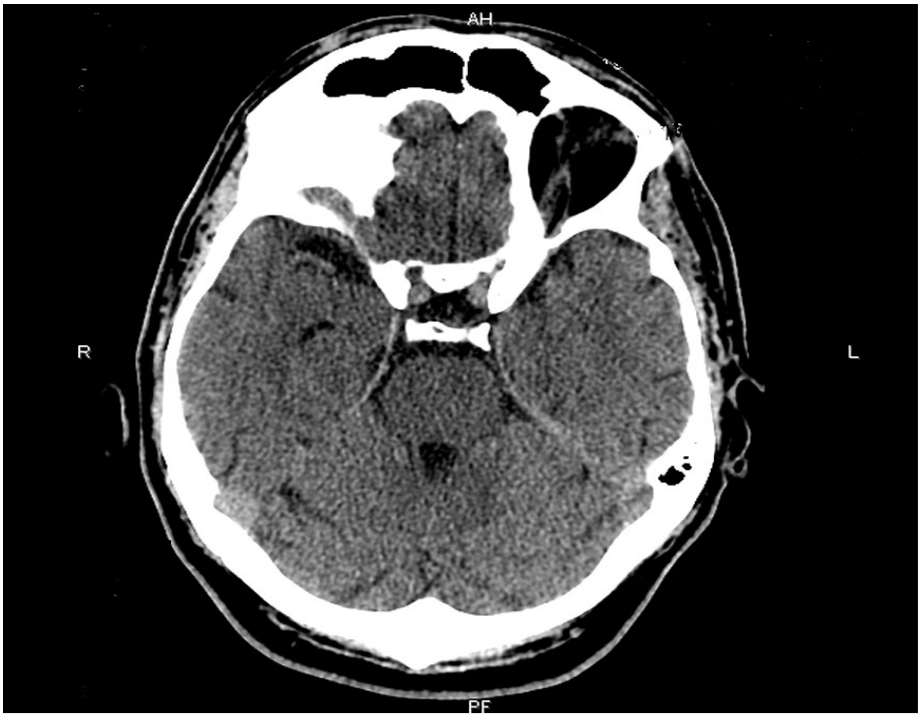

Figure 1. Head CT scan - no pathological changes are detectable within the structures of the cerebral hemispheres and the cerebellum

Within a few days, the patient became afebrile, NMS symptoms withdrew and CK level decreased (Figure 2). The bromocriptine and lorazepam were tapered off. The patient was transferred to the Department of Psychiatry for further psychiatric treatment. The psychiatrics prescribed mirtazapine (45 mg/day), venlafaxine (300 mg/day), queatiapine (600 mg/day) and chlorprothixene (100 mg/day) due to its lower reported rate of NMS. After 6 weeks, his psychotic symptoms improved and he was discharged from hospital.

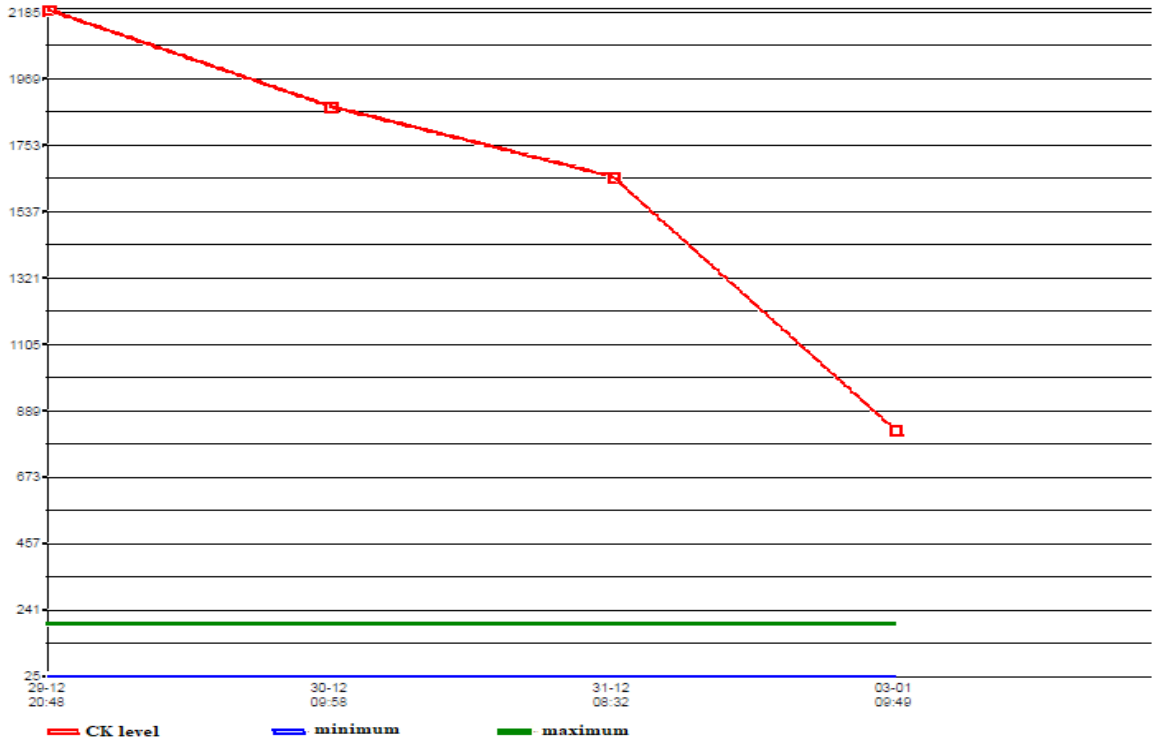

Figure 2. The declining CK level

DISCUSSION

Neuroleptic malignant syndrome (NMS) is a life-threatening psychiatric emergency and the most dangerous complication associated with the use of neuroleptic agents [1]. NMS is most often observed after high-potency first-generation neuroleptic agents (e.g., haloperidol). However, Caroff et al. [2] reported that every class of neuroleptic drugs may cause NMS, including second-generation antipsychotic medications (e.g., clozapine, olanzapine) or even antiemetic drugs (e.g., promethazine, metoclopramide).

Incidence rates for NMS range from 0,02 to 3 percent among patients treated with neuroleptic drugs. Modi et al. [3] and Margetić and al. [4] suggested that in recent years, there has been a tendency for less frequent occurrence of NMS due to the use of smaller doses of neuroleptics, avoidance of polytherapy and greater awareness of the disease among physicians. Mortality has recently been estimated at between 10 and 20 percent.

Berardi et al. [5] systematized the following NMS risk factors:

- acute catatonia
- extreme agitation
- recent or rapid dose escalation of neuroleptics
- switch from one psychiatric agent to another
- parenteral administration of neuroleptics
- antiparkinson medication withdrawal

It is unclear whether other commonly listed clinical conditions represent the risk factors of NMS (e.g., concomitant use of lithium or other psychiatric drugs, high-potency agents and depot formulation, dehydratation).

The pathogenesis of NMS is indistinct. Current scientific theories assume:

- dopamine receptor blockade – that is why blockade of central dopamine receptor in the hypothalamus may lead to hyperthermia and dysautonomia, while interference with nigrostriatal dopamine pathways can cause parkinsonian-type symptoms and rigidity
- genetic predisposition – suggested by familial clusters of NMS, probably because of the presence of the dopamine D2 receptor genes
- disrupted modulation of the sympathetic nervous system - because of dopamine antagonists destabilize normal dopamine regulation therefore NMS is manifested in increased muscle tone and metabolism, ineffective heat dissipation and labile blood pressure [6,7].

NMS is characterized by a distinctive clinical syndrome. The following tetrad of NMS symptoms is commonly reported:

1) HYPERTHERMIA - typically body temperatures of more than 38 °C, but temperatures greater than 40 °C are also common, without other obvious causes of fever
2) MUSCULAR RIGIDITY – it applies to all muscle groups, stable resistance through all ranges of movement or 'lead-pipe rigidity' or cogwheel phenomenon, other motor abnormalities: tremor, dystonia, opisthotonus, trismus, chorea and other dyskinesias
3) MENTAL STATUS CHANGE – predominantly an agitated delirium with confusion, also encephalopathy with stupor and coma, catatonic signs and mutism are seen
4) AUTONOMIC DISABILITY – tachycardia, high or labile blood pressure, tachypnea or even dysrhythmias, sweating, sialorrhea

Laboratory abnormalities include primarily:

- ELEVATED SERUM CK (greater than 1000 international units/L) - the degree of CK elevation correlates with muscular rigidity, disease severity and prognosis, it is connected with muscle damage.

Other laboratory findings are common but nonspecific and include: leukocytosis (white blood count from 10,000 to 40,000/mm^3), mild elevations of lactate dehydrogenase, alkaline phosphatase and liver transaminases, myoglobinuria, rhabdomyolysis, electrolyte disorders, metabolic acidosis, a low serum iron concentration.

To confirm the diagnosis the following diagnostic test are required: brain imaging studies and lumbar puncture (to exclude structural brain disease and infection). Some physicians also perform electroencephalography to exclude status epilepticus. Apart from CK serum, patient's general health condition should be assessed: blood morphology, electrolytes, transaminases, D-dimers, creatynine, urea, coagulation test, urinalysis and electrocardiogram [8, 9, 10].

The international diagnostic criteria for NMS (2011) are based on positive clinical and laboratory findings and the exclusion of alternative causes, and each item is given a priority score for its relative importance in contributing to the diagnosis. No threshold score has been defined for making a diagnosis of NMS. Brain imaging studies are typically normal, as in the presented case. Also, cerebrospinal fluid is usually normal, but a nonspecific elevation in protein has been reported. In electroencephalography generalized slow wave activity is seen in NMS patients.

Gurrera et al. [11] suggested the following neuroleptic malignant syndrome diagnostic criteria:

diagnostic criterion	*priority score*
exposure to dopamine antagonist, or dopamine agonist withdrawal, within past 72 hours	20
hyperthermia	18
rigidity	17
mental status alteration (reduced or fluctuating level of consciousness)	13
creatine kinase elevation (at least 4 times the upper limit of normal)	10
sympathetic nervous system lability, defined as at least 2 of the following: ▪ blood pressure elevation (systolic or diastolic ≥25 percent above baseline) ▪ blood pressure fluctuation (≥20 mmHg diastolic change or ≥25 mmHg systolic change within 24 hours) ▪ diaphoresis ▪ urinary incontinence	10
hypermetabolism, defined as heart-rate increase (≥25 percent above baseline) and respiratory-rate increase (≥50 percent above baseline)	5
negative work-up for infectious, toxic, metabolic, or neurologic causes	7
	Total: 100

The mean priority score indexes each criterion according to its relative importance in making a diagnosis of NMS according to an expert panel. Although, no threshold score has been defined and validated for us in making a diagnosis of NMS. According to Carbone et al. [12] and Caroff et al. [13] studies, differential diagnosis of NMS includes:

- serotonin syndrome
- malignant hyperthermia
- malignant catatonia
- central nervous infections (e.g., encephalitis, meningitis)
- seizures
- acute hydrocephalus
- drug intoxication (e.g., cocaine, amphetamines, ecstasy, lithium)
- pheochromocytoma
- acute porphyria
- tetanus
- heat stroke
- thyrotoxicosis

The management of patients with NMS includes:

- ✓ discontinuing of the causative agent or other potential contributing drug
- ✓ aggressive and supportive care:
  - maintaining cardiorespiratory stability
  - euvolemic state (intravenous fluids)
  - lowering fever (e.g., cooling blankets)
  - lowering blood pressure (e.g., clonidine or nitroprusside)
  - prevention of deep venous thrombosis (e.g., heparin or low molecular weight heparin)
  - benzodiazepines (e.g., lorazepam) to control agitation
- ✓ medical therapy
  - dantrolene – skeletal muscle relaxant, to treat malignant hyperthermia
  - bromocriptine – dopamine agonist, to restore lost dopaminergic tone
  - amantadine – as an alternative to bromocriptine

Most episodes of NMS resolve within 2 weeks, as in presented case [14, 15, 16, 17, 18].

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