Neuroleptic malignant syndrome: the diagnostic dilemma

Abstract
Neuroleptic malignant syndrome (NMS) is a life-threatening, often fatal idiosyncratic reaction to neuroleptic or other drug therapies that antagonise the central dopaminergic neurotransmission. The clinical presentation of NMS is very heterogeneous. The lack of specific levels of symptom severity in currently used diagnostic criteria dims the diagnosis of NMS. Therefore differential diagnosis is of priority, because NMS is a diagnosis of exclusion. The aim of this paper is to present a complex clinical picture in a patient that after a differential diagnostic exclusion of other medical conditions and intoxications is diagnosed as NMS. Case reports such as these help raise awareness of this clinical issue.

Keywords: Antipsychotic Agents. Dopamine. Anti-N-Methyl-D-Aspartate Receptor Encephalitis.

Introduction
Neuroleptic malignant syndrome (NMS) is a life-threatening, often fatal idiosyncratic reaction to neuroleptic or other drug therapies that antagonise the central dopaminergic neurotransmission.[1-6] Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5)[7] distinguishes four groups of criteria for the diagnosis of NMS. The first set of criteria includes the development of severe muscle rigidity and an increase in body temperature after administration of neuroleptic medication. The second group of criteria includes accompanying symptoms which complete this complex neuropsychiatric syndrome: Fluctuations in the level of consciousness (from confusion to coma), mutism, signs of dysregulation of the autonomic nervous system (sweating, dysphagia, tremor, incontinence, tachycardia, elevated or labile blood pressure, tachypnoea), and abnormalities in the laboratory analysis results (leukocytosis, elevated creatine kinase [CK]). The third criterion for the diagnosis is the exclusion of other medical conditions that can lead to the appearance of the same signs and symptoms (intoxication with other substances, other medical conditions). Fourth, it is necessary to exclude other mental illness (i.e. mood disorders or psychosis with catatonic phenomena).

It is believed that 0.5% to one per cent of patients exposed to anti-dopaminergic medication develop this condition,[8] with an incidence of 0.01% to 0.02%.[9,10] It is most common in the use of potent first-generation antipsychotics (butyrophenones, phenothiazines). Although synthesised in order to “produce” a small number of neurological side effects, time has shown that atypical antipsychotics can cause NMS, although often in a milder form with lower mortality.[11] Displayed are the cases of NMS after administration of clozapine,[12] risperidone,[13] olanzapine,[14] quetiapine,[2] and aripiprazole,[2] Also, there were cases of this syndrome after administering an antiemetic metoclopramide,[15,16] tricyclic antidepressants,
Neuroleptic malignant syndrome

Neuroleptic malignant syndrome (NMS) is a serious and potentially life-threatening condition that occurs most commonly in patients taking antipsychotic medications. It typically presents with symptoms such as hyperthermia, muscle rigidity, altered consciousness, and autonomic instability. Early detection and treatment are crucial to prevent serious complications and improve outcomes.

The aim of this paper is to present a complex clinical picture in a patient after a differential diagnostic exclusion of other medical conditions and intoxications diagnosed as NMS.

Case report

Patient aged 23, male, admitted to the Clinic for Psychiatric Disorders due to psychotic decompensation. The patient has been mentally changed from his twentieth year of life, when he first contacted a psychiatrist. The changes manifested themselves in the form of indisposition, tension, fears, occasional obsessive thoughts and compulsive actions. He was treated with fluoxetine with a daily dose of 40 mg and low doses of risperidone (up to 2 mg per day). During the treatment the patient had not regularly taken the therapy and occasionally used marijuana and alcohol. The patient was born prematurely in the seventh month of a high-risk pregnancy. Early psychomotor development was normal. In his personal history there were no other significant diseases, injuries, seizures, and allergies. There was no information about neuropsychiatric heredity.

On the day of admission to the psychiatric ward, the patient was of disorganised behaviour under the influence of delusions and acoustic hallucinations, in an obvious psychomotor restlessess, uncooperative, because of which he was physically restrained. In a routine laboratory blood analysis, which had been done before administering the therapy, the following discrepancies were found: Erythrocyte sedimentation rate (ESR) 18 mm/hr (reference value 2-12), serum iron (Fe) 5.6 mmol/L (10-30.4), C-reactive protein (CRP) 10 mg/dL (0-5), CK 1720 U/L (38-171). During the first three days of hospitalisation he was treated intramuscularly with antipsychotic haloperidol at a total daily dose of 15 mg and diazepam at a dose of 30 mg. On the third day, a routine laboratory analysis of blood showed an increase in the number of leukocytes 14.2 x 10^9/L (3.5-10 x 10^9) with granulocytosis (85.1% [43.0-76.0]), an increase in the value of total bilirubin 23.4 umol/L (5.1 to 20.5), and direct bilirubin 6.5 umol/L (0-3.4), CRP 35.3 ng/L (0-5), CK 2955 U/L (38-171), whereas the level of serum Fe was decreased (7 mmol/L [10 to 30.4]). Although physical examination has not shown the presence of clinical signs of infection or hyperbilirubinaemia, because of the perceived differences in the values of laboratory parameters, the antipsychotic was discontinued and an antibiotic is introduced in the therapy with antipsychotic haloperidol at a total daily dose of low doses of risperidone (up to 2 mg per day). During the hospitalisation at Neurology Clinic where the treatment is continued.

Lithium, phenelzine,[17-19] and after the sudden suspension of levodopa in patients with Parkinson’s disease. Early detection and treatment of NMS under the principles of good clinical practice significantly improves the outcome.

The occurrence of septicaemia, melaena, and haematemesis further complicated the clinical course and treatment. After three months, in the neurological findings, sequelae were noted – anisocoria, generalised mild to moderate hypotrophy, contracture of the lower extremities (ankles) on both sides. The patient was discharged from the Neurology Clinic with the diagnosis of NMS without prescribed psychopharmacotherapy. During the hospitalisation at Neurology Clinic he had not been given any kind of specific therapy for NMS.

Discussion

NMS is a medical emergency that requires prompt recognition and treatment due to the still high mortality. Mortality rate due to NMS before 1984 amounted to 40%, and while decreasing in recent decades it is now estimated at about ten per cent.[3,20] A higher risk of death is for people younger than 20 and older than 60. Also, the mortality rate is increased by the presence of organic brain disorders, mental retardation, substance abuse, and numerous NMS complications. The almost universal ones are rhabdomyolysis and renal failure, whereas aspiration
pneumonia, pulmonary embolism, respiratory distress syndrome, sepsis, disseminated intravascular coagulation, and myocardial infarction are often present.[20] According to literature, 79% of patients with NMS make a full recovery, while possible consequences might present themselves as cognitive disorders, muscle atrophy, contracture, and focal neurological disturbances.[21]

The mechanism of NMS occurrence is unclear. Most researchers pointed out that the non-infectious hyperthermia is caused by interruption of dopaminergic neurotransmission in the hypothalamus, hyperfunction of the autonomic nervous system as a result of dopamine antagonism, while the imbalance at the level of striatal dopamine receptors results in muscle rigidity, with the consequent myoglobinuria and increased levels of serum CK due to muscle catabolism.[1,20] However, the development of NMS in patients treated with atypical antipsychotics, including partial dopamine agonists, indicates that in the development of NMS, there are a number of other neurotransmitter systems involved. So far, the identified risk factors include clinical, systemic, and metabolic factors: Agitation, dehydration, physical restraining, pre-existing abnormalities in dopamine activity or function of dopamine receptors in the central nervous system (CNS), hyponatraemia, lack of Fe.[3,22-24] Practically all case series have reported physical exhaustion and dehydration immediately prior to the occurrence of NMS.[3,20,25] Pharmacological risk factors are the use of highly potent conventional antipsychotics, parenteral administration, faster dose escalation, and higher total dose.[1]

The clinical presentation of NMS is very heterogeneous. The lack of specific levels of symptom severity in currently used diagnostic criteria dims the diagnosis of NMS. Therefore differential diagnosis is of priority importance, because NMS is a diagnosis of exclusion.[3] (Table 1)

This presented case was not typical. The dilemma remains whether this patient really developed NMS. In fact, after application of the Naranjo adverse drug reaction (ADR) probability scale,[26] the obtained score was two, that indicates the possibility of the connection of an undesirable effect after the administration of the drug. However, after extensive diagnostics a number of medical conditions were excluded, and the diagnosis of NMS was set in accordance with the criteria currently applicable, classification of disease- when there are no criteria for other disorders, this rare diagnosis is set.

Our patient had risk factors: He was a young man, extremely agitated and dehydrated, with low levels of serum Fe. Among other risk factors that were present there were: Physical restraining and a history of abuse of psychoactive substances. He already had increased CK (1720 U/L) on admission, which might be explained by the high level of motor activity within extreme psychomotor agitation. On the third day CK was increased to 2953 U/L, but without the presence of clinical evidence of NMS. On the other hand, CRP was increased upon arrival, and its value tripled on the third day of the treatment, with the development of leukocytosis with granulocytosis. Despite the absence of clinical signs of infection and neuroleptic syndrome, after registered deviations in the values of CK and an increase in markers of inflammation, on the third day of treatment antipsychotic was discontinued with the introduction of antibiotic therapy and intensive parenteral rehydration. However, paradoxically on the fifth day of hospitalisation, the patient developed muscle rigidity, hyperthermia, and autonomic dysfunction, while at the same time the laboratory blood result report registered a drop of CK to 692 U/L. Practically the whole time the patient had normal renal function, which excludes massive rhabdomyolysis. Also, calm liver enzymes represent an atypical finding which does not fit the diagnosis of NMS. The patient was transferred to the Neurology Clinic because of the fluctuation of consciousness, and after a thorough three months’ diagnostics and non-specific treatment, he was discharged with the diagnosis of NMS.

It is questionable whether in this case, despite the normal values of the analysis of CSF, there was room for additional diagnostics, for example in the direction of anti-N-Methyl-D-Aspartate (NMDA)-receptor encephalitis.[27] Also, the question is whether the described case, as well as all the other cases of NMS, are truly idiosyncratic reactions to antipsychotics or a reflection of impotence of official medicine which does have its limits? How accurate are our official classification systems of disease?

| Table 1: Differential diagnosis of neuroleptic malignant syndrome (NMS) |
|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|
| Infections               | Psychiatric or neurological disease | Substance intoxication | Endocrine disorders | Environmental factors   |
| Meningitis or encephalitis | Idiopathic malignant catatonia | Anticholinergic delirium | Thyrotoxicosis       | Heat stroke             |
| Brain abscess            | Structural lesions of the midbrain | Salicylate poisoning    | Pheochromocytoma     |                         |
| Tetanus                  | Benign extrapyramidal syndrome | Malignant hyperthermia (inhalation anaesthetics) |                         |                         |
| Sepsis                   | Non-convulsive status epilepticus | Serotonin allergy syndrome |                         |                         |
|                          |                                        | Substance abuse (cocaine, amphetamines, lysergic acid diethylamide (LSD)) |                         |                         |
|                          |                                        | Withdrawal syndromes    |                         |                         |
It seems that we need more research of aetiology and pathophysiology of NMS in order to improve the diagnostics of this clinically heterogeneous and complex syndrome. Permanent exchange of clinical experience is also essential, especially in the field of rationalisation of the use of antipsychotic therapy.

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**References**