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Neuroleptic malignant syndrome: a case report and discussion

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ABSTRACT

Neuroleptic malignant syndrome (NMS) is an emergent, life threatening condition most often seen as an iatrogenic complication of neuroleptic or antipsychotic treatment. It is characterized by a tetrad of clinical features: mental status changes, fever, muscle rigidity and autonomic instability, although it is not necessary for all of them to be present at a same time for working diagnosis to be made. This paper will deal with the case of a 29-year old male patient diagnosed with schizophrenia who developed NMS, presented as a generalized tonic-clonic seizure and high fever, after 191 days of in-hospital treatment. After 13 days of hospital treatment in the Intensive Care Unit of Clinical Hospital Dubrava, the patient is in a hemodynamical and proper quantitative mental state and discharged for further psychiatric treatment at his parent hospital institution.

Key words: neuroleptic malignant syndrome, neuroleptics, creatine kinase

Case report

After 191 days of in-hospital treatment, a 29 year old male patient is transferred from a psychiatric institution to our Emergency Department (ED) under a working diagnosis of epileptic status. According to his medical history, he was a former intravenous drug addict with diagnosed schizophrenic disorder and chronic bronchitis. He was treated with clozapine (500mg divided into 3 daily doses), fluphenazine (5mg twice a day), with a depot formulation of fluphenazine (25mg intramuscularly) and biperiden (from 5mg), lorazepam (7.5mg orally divided into 3 daily doses) and nitrazepam (5mg once daily). The patient was conscious, psychomotorically agitated, non-verbal, febrile 38.4 °C, mild tachycardic with 1500 ml of urine retention. Other neurological and general physical statuses were inconspicuous. With brain imaging studies we excluded acute intracranial events, and with lumbar puncture we excluded a central nervous system infection. With regard to the fever, high creatine phosphokinase (CPK), significant hyponatremia and a history of treatment with antipsychotics, a working diagnosis of NMS was set and the patient was admitted to the ICU 8 hours after his initial loss of consciousness. The initial laboratory results showed: CPK 6308 IU/L, CPK MB 70 IU/L sodium 113 mEq/L , potassium 3.7 mEq/L, mildly elevated transaminases, leukocytosis 10,700/mm3 , Hgb 12.8 g/dL, with other routinely used tests in a reference range. Immediately upon admission, psychiatric treatment was discontinued, the patient was sedated with the continuous intravenous administration of midazolam. Supportive measures, including heavy intravenous administration of isotonic crystalloid solution with electrolyte recovery and antipyretics with extracorporeal cooling measures, were also initiated. Over the next few days high CPK values were detected, with a maximum value of 323,400 IU/L detected 24 hours after the onset of symptoms. The patient's myoglobin value was 8130 ng/mL, and an increase in inflammatory parameters (CPR 179.5 mg/L, L 11,200/mm3) along with high fever was noted. On day four, the patient became afebrile, sedation therapy was discontinued, the patient regained consciousness and vital parameters were normal, but the patient was still without adequate verbal contact, responding to painful stimuli with disapproval. On day eight, the patient became febrile again, his axillary temperature measured up to 39.4 °C with profuse sweating and hypersalivation and there was a minor increase in CPK and myoglobin. Samples were taken for blood and urine culture (later the cultures were sterile) and an empirical antibiotic therapy with ciprofloxacin at a dose of 400 mg intravenously 2x1 was initiated. The next day the patient became afebrile, with normal vital functions and established verbal contact. The patient's further course of stay passed without additional complications and the patient was in a proper quantitative mental state, in good general condition, hemodynamically stable and was discharged on day 13 for further treatment at his parent institution.

Discussion

The incidence of NMS varies between 0.02-3% of patients on neuroleptic the-

Table 1: Neuroleptic malignant syndrome diagnostic criteria.

Diagnostic criteria	Priority score
Exposure to dopamine antagonist or dopamine agonist withdrawal within past 72 h	20
Hyperthermia (>100.4 ° F or >38 ° C on at least 2 occasions, measured orally)	18
Rigidity	17
Mental status alteration (reduced of fluctuating level of consciousness)	13
Creatinine 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% above baseline) Blood pressure fluctuation (≥ 25 mm Hg systolic change within 24 h) Diaphoresis Urinary incontinence	10
Hypermetabolism defined as heart rate increase (≥ 25% above baseline) and respiratory rate increase (≥ 50% above baseline)	5
Negative work-up for infections, toxic, metabolic or neurologic causes	7
Total	100

Table 2: Generalized guidelines on restarting neuroleptic therapy

Wait at least 2 weeks before resuming therapy, longer if any clinical residua exist
Use lower rather than higher potency agents
Start with low doses and titrate upward slowly
Avoid concomitant lithium
Avoid dehydration and carefully monitor for symptoms of NMS

NMS, neuroleptic malignant syndrome

rapy. (1) Cases have been described in all age groups, but among the cases described men of younger age were predominant. Factors that increase the risk of developing NMS are high doses of neuroleptic drugs, parenteral administration, depot preparations, parallel treatment with lithium or other psychotropic drugs, alcohol abuse, addiction and other acute diseases. (2) Assumptions about a genetic predisposition for developing NMS are suggested. (3) The main clinical features make the tetrad of symptoms: change in mental status, muscle rigidity, hyperthermia and autonomic dysfunction in terms of tachycardia, blood pressure variability, tachypnea and diaphoresis. (4) In an analysis of 340 cases of NMS, 70% of patients followed a typical pattern of symptoms with the altered mental status change as the initial symptom, followed by muscle rigidity, then hyperthermia and dysfunction of the autonomic nervous system occurring last. (5) The most important laboratory parameter is high CPK (> 1000 IU/L). (6) Leukocytosis is a consistent finding, and there are mild elevations in LDH and transaminases, electrolyte imbalance and myoglobinemia with the possibility of myoglobinuric acute renal failure. Atypical NMS cases, without developing muscle rigidity, as well as afebrile cases, also exist. (7) In differential diagnosis, a physician should think of neurological diseases such as infections of the central nervous system, convulsions within epilepsy or acute intracranial process, acute intoxication, heat stroke and tetanus. Diagnosis is clinically made. In 2011, diagnostic criteria for NMS were published (table 1). (8) Treatment consists of neuroleptic therapy discontinuation and further supportive therapy. Of the specific measures, dantrolene, bromocriptine and amantadine can be used. Clinical studies on the use of these drugs have not been implemented, and recommendations are based on the cases described in the literature. In most cases applied therapy leads to a regression of the disease within 14 days of the onset of symptoms. (4) Overall mortality ranges from 5-20%. Developing complications are the strongest predictor of mortality. Re-initiation of neuroleptic therapy is not contraindicated in recovered patients, but great caution is necessary regarding recurrent cases described in the literature. (9)

Conclusion

In our case a positive clinical outcome resulted by using only supportive therapeutic measures thanks to a timely recognition of the disease. Given the relatively rare incidence of the disease and insufficient literature (lack of clinical studies and the lack of clear treatment guidelines) this life threatening condition is still represented by high values of mortality (20%). We emphasize the

necessity for early diagnosis to prevent further complications and the importance of placing timely doubt in high-risk patients, Regarding the possibility of regression and the need for further treatment of the underlying disease, to reduce the risk of relapse we emphasize the need to follow the general recommendations summarized in table 2.

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