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A retrospective analysis of cases with neuroleptic malignant syndrome and an evaluation of risk factors for mortality

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ABSTRACT

Objective: Neuroleptic malignant syndrome (NMS) is a neurological emergency rarely encountered in clinical practice but with a high mortality rate. Cases associated with atypical antipsychotic use or termination of dopamine agonists have been seen in recent years. The purpose of this study was to assess the presence of risk factors for mortality by investigating all clinical and laboratory characteristics of cases with NMS.

Material and methods: This descriptive, cross-sectional study retrospectively investigated all clinical and laboratory characteristics by scanning the ICD-10 codes of patients presenting to the XXXX Faculty of Medicine Emergency Department and diagnosed with NMS between 2006 and 2016. Patients were divided into surviving and non-surviving groups, and the data elicited were subjected to statistical comparisons.

Results: The mean age of the 18 patients diagnosed with NMS was 46.9 ± 4.8 years, and 50% were women. In addition to antipsychotics among the drugs leading to NMS, the syndrome also developed as a result of levodopa withdrawal in three patients and metoclopramide use in one patient. Statistically significant differences were determined between the surviving and non-surviving patients in terms of blood pressure, blood urea nitrogen (BUN), creatine kinase (CK) and mean platelet volume (MPV) values ($p \leq 0.05$).

Conclusion: In this study the most common agent that cause NMS was atypical antipsychotics. Also advanced age, increased blood pressure and serum CK, BUN and MPV values were identified as potential risk factors for mortality in NMS.

1. Introduction

Neuroleptic malignant syndrome (NMS) is a life-threatening neurological emergency that occurs following use of neuroleptic drugs and other dopamine antagonists or termination of a dopamine agonist and characterized by altered mental state, fever, rigidity and autonomic dysfunction. Although typical neuroleptics exhibiting an antagonist effect on dopamine receptors are frequently involved in the etiology, there are also reports in the literature of cases of NMS caused by drugs from various different groups.[1,2] Diagnostic criteria are used to overcome the diagnostic difficulty in NMS (Table 1).[3] There are no specific laboratory findings used in diagnosis, but in addition to increasing creatine kinase (CK) associated with muscle destruction, accompanying leukocytosis, increased serum aminotransferases (AST and ALT), electrolyte anomalies (hyperkalemia, hypo-hypernatremia or hypocalcemia), increased lactate dehydrogenase (LDH) and metabolic acidosis may be seen.[4]

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Table 1
Diagnostic criteria for NMS.

Criteria	Characteristics	At least
History of drug use	- Use of one antipsychotic - Use of one dopamine antagonist - Recent termination of treatment with one dopamine agonist	1
Major criteria	- Hyperthermia (37.5° or above) - Muscular rigidity, - Creatine kinase (CK) levels over 3 times above normal	2
Minor criteria	- Altered mental state, - Extrapyramidal findings, Autonomic instability, - Respiration problems, - Leukocytosis	4

The first stage in the treatment of NMS is to stop the agent responsible or to resume the discontinued dopamine agonist. In the second stage, intensive supportive therapy is applied. Dantrolene, a centrally acting muscle relaxant recommended for specific therapy but lacking sufficient levels of evidence for its efficacy, and the dopamine agonist bromocriptine and amantadine are pharmacological agents capable of use in addition to supportive therapy.[5,6] Mortality rates associated with complications of NMS, such as rhabdomyolysis, acute kidney failure, respiratory failure, cardiovascular collapse, aspiration pneumonia and disseminated intravascular coagulation, approach 50%, but this decreases to approximately 5% with adequate supportive therapy in cases without complications.[7] Early commencement of treatment through early diagnosis in emergency departments and the determination of prognostic factors affecting mortality are therefore important in terms of survival. Since the incidence of NMS in the community is low, evidence-based data concerning the epidemiology and clinical and pharmacological risk factors are limited. Our purpose was therefore to evaluate the epidemiological and clinical characteristics of patients diagnosed with NMS in our hospital and, in particular, to identify prognostic factors capable of affecting mortality by comparing the clinical and laboratory features of death and survived cases.

2. Materials and methods

In this cross-sectional, descriptive study, following receipt of ethical committee approval, patients aged 18 or over presenting to the Karadeniz Technical University Faculty of Medicine Emergency Department in 2006–2016 and diagnosed with NMS were identified by scanning their ICD-10 codes from the hospital computer software system, and patient files obtained from the archive were examined retrospectively. Cases with incorrect ICD-10 entries and patients with incomplete record data were excluded. Patients' ICD-10 diagnoses were confirmed on the bases of the NMS criteria shown in Table 1. The diagnosis of NMS was made in the presence of at least two of the major and four minor diagnostic criteria. Cases' demographic characteristics, existing diseases, clinical and laboratory findings, all drugs used, lengths of stay in hospital and survival were evaluated. Cases were divided into two groups on the bases of clinical outcomes *death* and *recovery*. All data were transferred to and analyzed on IBM Statistical Package for the Social Sciences 23.0 (IBM SPSS Inc., Chicago, IL, USA) software. The Mann Whitney *U* test was used to compare the two groups' non-parametric data, and p values ≤ 0.05 were regarded as statistically significant.

3. Results

Records were available for all 18 patients diagnosed with NMS among the 505,520 patients presenting to the emergency department in 2006–2016. According to our records, the rate of NMS among patients presenting to our hospital in the previous 10 years was 0.004%.

The distribution of patients' clinical characteristics is shown in Table 2 and 3. Half of the patients were women, and the general median age was 43.5 (IQR, 30.2–67.2). The most common existing chronic diseases among the patients were schizophrenia at 27.8% (n = 5), Parkinson's disease at 22.2% (n = 4), and mental retardation at 16.7% (n = 3), with lower incidences of substance dependence, dementia, bipolar disorder, acute psychosis and delirium. A history of use of two or more drugs was present in 88.9% (n = 16) of cases, and of antipsychotic drug use in 77.8% (n = 14). Drug use was at therapeutic doses in all NMS cases. The most common antipsychotic agents used by NMS patients were atypical antipsychotic agents (78.6%, n = 11).

In addition to antipsychotic drugs such as quetiapine, clozapine, risperidone, amisulpride, and haloperidol, the medications leading to the development of NMS also included drugs affecting the central nervous system, such as paroxetine, amitriptyline and lithium. NMS developed following discontinuation of levodopa in three cases and use of metoclopramide in one case (Table 2). Among the three fatal cases of NMS, two cases used more than one neuroleptic agents and a 76-year-old woman with Parkinson's disease used no neuroleptic medication, but NMS developed in association with withdrawal of levodopa and multi-drug use consisting of amitriptyline, pramipexole, gabapentin and paroxetine.

When the death (n = 3) and recovery (n = 15) groups were compared in terms of clinical and laboratory characteristics, statistically significant differences were observed in terms of age, systolic and diastolic blood pressure, blood urea nitrogen (BUN), serum creatine kinase (CK) and mean platelet volume (MPV) values (Table 4) ($\mathbf{p \leq 0.05}$).

4. Discussion

Our study is one of the largest cohort of NMS patients from Turkey. According to results of this study, both neuroleptic and non-neuroleptic drug use were the causes of NMS. Contrary to common belief, atypical antipsychotic drug use was most commonly observed as the cause of NMS in this study, and also we found that advanced age and high CK, BUN and MPV values can be potential risk factors for mortality.

Factors such as age and sex affect the incidence of NMS in addition to various clinical and pharmacological factors. The incidence of NMS among neuroleptic users therefore ranges between 0.024% and 3%.[8,9] There are several reasons for this, such as the population selected and the different diagnostic criteria used. Since ICD-10 coding of subjects using neuroleptics was not possible in our hospital's data recording system we determined the rate as a proportion among all populations. There is no consensus in the literature concerning gender as a potential risk factor for NMS, although the general opinion in the 1980s was that it is more common in