



Contents lists available at ScienceDirect

Turkish Journal of Emergency Medicine

journal homepage: <http://www.elsevier.com/locate/TJEM>

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

Aynur Sahin ^{a,*}, Mustafa Cicek ^a, Ozgen Gonenc Cekic ^b, Mucahit Gunaydin ^c,
Demet Saglam Aykut ^d, Ozgur Tatli ^a, Yunus Karaca ^a, Mualla Aylin Arici ^e

^a Karadeniz Technical University, Faculty of Medicine, Department of Emergency Medicine, Trabzon, Turkey

^b Fatih Public Hospital, Department of Emergency Medicine, Trabzon, Turkey

^c Giresun University, Faculty of Medicine, Department of Emergency Medicine, Giresun, Turkey

^d Karadeniz Technical University, Faculty of Medicine, Department of Psychiatry, Trabzon, Turkey

^e Dokuz Eylül University, Faculty of Medicine, Department of Pharmacology, Izmir, Turkey

ARTICLE INFO

Article history:

Received 13 July 2017

Received in revised form

26 September 2017

Accepted 5 October 2017

Available online 27 November 2017

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.

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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-hyponatremia or hypocalcemia), increased lactate dehydrogenase (LDH) and metabolic acidosis may be seen.⁴

* Corresponding author. Karadeniz Technical University, Faculty of Medicine, Department of Emergency Medicine, 61080, Trabzon, Turkey.

E-mail address: dr-aynursahin@hotmail.com (A. Sahin).

Peer review under responsibility of The Emergency Medicine Association of Turkey.

Table 1
Diagnostic criteria for NMS.

Criteria	Characteristics	At least
History of drug use	- Use of one antipsychotic - Use of one dopamine antagonist	1
Major criteria	- Recent termination of treatment with one dopamine agonist - 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) ($p \leq 0.05$).

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

Table 2
Characteristics of NMS cases.

No.	Age, sex (M: Male, F: Female)	Disease	Drugs used	TA (mmHg)	Pulse (min)	Temperature (°C)	GCS	Clinical symptoms and findings	Outcome	Length of stay in hospital (Day)	Causes of death
1	47, F	Schizophrenia	Alprazolam, quetiapine, aripiprazole, paliperidone	164/123	113	38.6	8	Muscular rigidity, sweating, dysphagia, tremor, incontinence, altered consciousness, mutism	Death	10	Sepsis
2	75, M	Schizophrenia	Biperiden, mirtazapine, paroxetine, amisulpride, clozapine, risperidone	160/140	170	39.0	9	Muscular rigidity, sweating, dysphagia, tremor, incontinence, altered consciousness, mutism	Death	2	Respiratory failure
3	76, F	Parkinson	Levodopa (withdral), pramipexole, gabapentin, paroxetine, amitriptyline	180/100	140	39.3	10	Muscular rigidity, sweating, tremor, altered consciousness, mutism	Death	42	Sepsis
4	42, M	Mental retardation	Biperiden, olanzapine	170/100	117	38.4	12	Muscular rigidity, sweating, tremor, altered consciousness	Recovery	32	
5	43, F	Bipolar disorder	Biperiden, amitriptyline, lithium, phenothiazine, chlorpromazine, quetiapine	90/60	122	39.1	11	Muscular rigidity, sweating, tremor, altered consciousness, mutism	Recovery	19	
6	64, F	Bipolar disorder	Valproic acid, lorazepam, haloperidol, quetiapine, olanzapine	140/80	108	38.0	13	Muscular rigidity, tremor, altered consciousness,	Recovery	11	
7	20, F	Mental retardation	Risperidone, quetiapine	110/80	80	39.0	11	Muscular rigidity, dysphagia, tremor, incontinence altered consciousness, mutism	Recovery	47	
8	44, M	Schizophrenia +Substance dependence	Amisulpride	120/70	84	38.6	12	Muscular rigidity, sweating, tremor, altered consciousness, mutism	Recovery	31	
9	18, F	Schizophrenia +acute psychosis	Clonazepam, amisulpride, olanzapine	100/80	112	38.2	12	Muscular rigidity, sweating, tremor, altered consciousness, mutism	Recovery	22	
10	32, M	Substance dependence	Lorazepam, quetiapine	110/70	92	38	8	Muscular rigidity, sweating, altered consciousness, mutism	Recovery	54	
11	25, M	Mental retardation	Lorazepam, amisulpride	140/90	88	37.9	13	Muscular rigidity, sweating, dysphagia, altered consciousness, mutism	Recovery	19	
12	40, F	Schizophrenia	Biperiden, mirtazapine, olanzapine	100/60	130	38.5	13	Altered consciousness mutism	Recovery	92	
13	46, M	Delirium	Haloperidol, olanzapine	145/90	125	38.5	12	sweating, dysphagia, incontinence, altered consciousness, mutism	Recovery	8	
14	23, K	Acute psychosis	Lorazepam, quetiapine, risperidone	160/90	140	39.0	11	Muscular rigidity, tremor, altered consciousness, mutism	Recovery	33	
15	32, M	No characteristic	Metoclopramide	140/100	120	40.0	10	Muscular rigidity, sweating, dysphagia, tremor, incontinence, altered consciousness, mutism	Recovery	20	
16	79, M	Dementia +Parkinson +Alzheimer	Levodopa (withdral), pramipexole	150/100	112	38.2	12	Muscular rigidity, sweating, dysphagia, altered consciousness, mutism	Recovery	10	
17	74, F	Parkinson	Levodopa, paroxetine, quetiapine	150/100	81	37.7	10	Muscular rigidity, sweating, dysphagia, tremor, altered consciousness, mutism	Recovery	11	
18	65, M	Parkinson	Levodopa (withdral), paroxetine	90/50	144	40.0	7	Muscular rigidity, sweating, dysphagia, altered consciousness, mutism	Recovery	9	

Table 3
Distribution of clinical symptoms and findings in NMS cases.

	n	%		n	%
Hyperthermia	18	100.0	Tremor	11	61.1
Muscular rigidity	17	94.4	Dysphagia	10	55.6
Altered consciousness	15	83.3	Hypertension	9	50.0
Sweating	15	83.3	Incontinence	5	27.8
Mutism	15	83.3	Hypotension	3	16.7
Tachycardia	13	72.2	Tremor	11	61.1

males, the reason being the denser muscle mass in men and the clinical manifestation (muscular rigidity and fever secondary to hypermetabolism) being more visible than in women. In contrast, a meta-analysis by Gurrera et al. from 2017 concluded that NMS appeared equally in males and females, but more commonly in young adults.¹⁰ Women represented 50% of the cases in our study,

and patients' mean age was also compatible with the previous literature.⁸

Sudden interruption of dopamine reduction is an important agent in the molecular mechanism of the development of NMS. This may result from termination of dopaminergic agent use with dopamine receptor antagonism mediated by neuroleptic or other pharmacological agents.⁴ Although typical neuroleptics are the most commonly implicated pharmacological agents in the literature, examination of the cases in our study revealed metoclopramide use in one and multiple pharmacological agent use in others, and the level of atypical antipsychotics use was higher compared to other drugs.^{11–13} The reason atypical antipsychotics are preferred by psychiatrists that they are superior to typical antipsychotics at side effects.

NMS may be difficult to diagnose since it begins with non-specific symptoms in the early period, such as unexplained

Table 4
Clinical and laboratory findings of groups in NMS.

	Groups		p
	Death (n = 3)	Recovery (n = 15)	
Clinical characteristics (MD, Min-max)			
Age	75 (47–76)	42 (18–79)	0.05
GCS	9 (8–10)	12 (7–13)	0.054
Hearth rate (bpm)	140 (113–170)	112 (80–144)	0.097
SBP (mmHg)	164 (160–180)	140 (90–170)	0.01
DBP (mmHg)	123 (100–140)	80 (50–100)	0.01
Temperature (C°)	39 (38.6–39.3)	38.5 (38–40)	0.191
Length of hospital stay (Day)	10 (2–42)	20 (8–92)	0.34
Laboratory findings (MD, Min-max)			
Glucose	139 (108–155)	117 (73–349)	0.514
NR:74–110 mg/dL			
BUN	42 (27–71)	18 (7–35)	0.024
NR:6–20 mg/dL			
Cre	1.36 (0.91–2.2)	0.7 (0.39–1.70)	0.137
NR:0.5–0.9 mg/dL			
CK	5543 (2702–10343)	1720 (700–3496)	0.021
NR:38–176 U/L			
AST	75 (56–94)	74 (70–118)	0.374
NR:0–35 U/L			
ALT	54 (3–106)	54 (29–94)	0.373
NR: 0–45 U/L			
Troponin	88.7 (47–538)	40 (4.2–321)	0.930
NR: < 14 ng/mL			
Myoglobin	983 (870–3000)	511 (32–3147)	0.311
NR: 0–85 ng/mL			
CK-MB	16.1 (5.5–25.8)	8.7 (2.2–181)	0.638
NR: 0 - 4.8 U/L			
Lactate	15.5 (11–20)	7.78 (7–10.24)	0.064
NR: 4.5–19.8 mg/dL			
LDH	620 (384–669)	403 (165–620)	0.097
NR:122–222 U/L			
WBC	15,900 (14,027–22,270)	10,000 (1000–26,200)	0.260
NR:4800–10800 per μ L			
Hemoglobin	13.5 (10.1–16)	12.6 (9–15.7)	0.406
NR:12–17 g/dL			
Platelet	162 (154–327)	230 (51–474)	0.767
NR:130–400 $\times 10^3/\mu$ L			
MPV	13 (10.3–13.8)	8.7 (6.2–11.5)	0.021
NR: 7.4–11 fl			
RDW	14.3 (13.3–16.1)	14.2 (12.3–21.5)	0.767
NR: 11.6–16.5(%)			
NLR	11.2 (3–27.9)	7.5 (1–32.3)	0.514

According to Mann Whitney U test.

Abbreviations (MD: Median, Min: Minimum, Max: Maximum, NR: Normal Range, GCS: Glasgow Coma Scale, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, BUN: Blood Urea Nitrogen, Cre: Creatinine AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase WBC: White Blood Cell, CK: Creatine Kinase, LDH: Lactate Dehydrogenase, MPV: Mean Platelet Volume, RDW: Red Cell Distribution Width, NLR: Neutrophil Lymphocyte Ratio).

tremor, muscular cramps, anxiety, confusion, agitation or catatonia, rather than the principal symptoms and findings such as fever, rigidity, mental state alterations and autonomic instability.⁴ In one case-controlled study, Berardi et al. particularly described psychomotor agitation, confusion, disorganized behavioral findings, and extrapyramidal findings as potential clinical risk factors for the development of NMS.¹⁴ Although there is evidence that the anti-dopaminergic effect of pharmacological agents is the mechanism underlying clinical and laboratory findings emerging in NMS, there are question marks concerning the mechanism by which agents with no effect on dopamine receptors give rise to the clinical manifestation.^{15,16} Analysis of the clinical characteristics of the cases in our study revealed no atypical findings other than mutism, dysphagia and incontinence, in addition to the classic findings. Hyperthermia and altered consciousness were determined in all patients and muscular rigidity was observed at a high level.

There are no 100% specific laboratory findings in NMS, although serum CK elevation increasing in association with muscular rigidity accompanies clinical findings. Serum CK levels exceeding 1000 IU/L and rising are generally correlated with severity of disease and

prognosis.^{17,18} Other non-specific findings seen in NMS include metabolic acidosis, leukocytosis, increased lactate dehydrogenase and aminotransferases and electrolyte anomalies (hypocalcemia, hypomagnesemia, hypo-hyponatremia and hyperkalemia).¹⁹ The findings of this study correlated with literature.

Prognosis varies depending on the presence of complications such as rhabdomyolysis, renal failure, aspiration pneumonia, sepsis and pulmonary embolism. The mortality rate in NMS irrespective of early diagnosis and treatment is 5–20%, but this rises to 70% in the presence of complications.^{20–22} In this study, the mortality rate in patients diagnosed with NMS was approximately 17%. Shalev et al. evaluated 202 cases of NMS-associated mortality and identified rhabdomyolysis, myoglobinuria and renal failure as powerful predictors of mortality.⁷ Additionally, septic shock and respiratory and cardiac failure associated with infections developing secondary to hospitalization have also been reported as important risk factors for mortality.⁴ When we compared cases of death and recovery groups in terms of outcomes, age and blood pressure were statistically significantly higher in the death group. Advanced age and high blood pressure may therefore be interpreted as factors potentially

affecting mortality. When death and recovery groups were compared in terms of laboratory values, CK, BUN and MPV values were statistically significantly higher in the death group. These findings support the idea that rhabdomyolysis and renal function impairment are important risk factors in terms of poor outcome. MPV values are involved in many studies as a current prognostic marker recently. Previous studies have linked MPV elevation with both poor prognosis and infarction area, particularly in patients with ischemic and hemorrhagic stroke, coronary artery disease and acute coronary syndrome.²³ There is no study performed relationship between NMS and MPV values. The mechanism involved in this significant elevation observed in fatal cases of NMS is unclear, and further clinical studies involving larger case numbers regarding its potential predictive value for prognosis are needed.

5. Limitations

There are limitations in this study. Due to the clinical rarity of NMS and the hospital's computerized database going back only 10 years, we were only able to access data for patients with entered ICD-10 diagnoses. The retrospective nature of the study also limited our access to all the information in the patient files.

6. Conclusion

In conclusion, despite being a rare disease, NMS is a life-threatening condition in terms of clinical course and outcome that develops in association with neuroleptic and non-neuroleptic drug use. Atypical antipsychotic drug use was most commonly observed in the NMS cases assessed in this study, and advanced age and high CK, BUN and MPV values may be potential risk factors for mortality.

Grant

No.

Conflict of interests statement

The authors declare that they have no significant competing financial, professional or personal interests that might have influenced the performance or presentation of the work described in this manuscript.

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