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Neuroleptic malignant syndrome: clinical expression, complication, course, and atypical clinical picture

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Abstract

Background: Neuroleptic malignant syndrome (NMS) is an uncommon and lethal side effect of neuroleptics. The clinical expression of this syndrome is diverse. Even with criteria diagnosis, it is hard to recognize it easily.
We report a series of 25 cases of NMS among patients hospitalized in psychiatric service at Oujda for 5 years. We have described the clinical characteristics of NMS in these patients, the treatments received, the management, and the course of this syndrome.

Results: Most of the patients are hospitalized for psychotic or affective disorders according to the Diagnostic and Statistical Manual of Mental Disorders (DSM V) criteria. 92% of patients received conventional neuroleptic, and half of them were under the injectable form. No patient took long-acting injectable antipsychotics. 36% of patients received neuroleptics for the first time. NMS appeared in the first week after the admission in psychiatric service among 24 patients. The most common clinical and biological signs were muscular rigidity, the elevation of creatine phosphokinase (CPK), and alteration of blood pressure. Other symptoms were found in proportion varied between 24% and 72%. 32% of the patients did not develop complications. One patient developed renal failure. All patients recovered, and no deaths were recorded.

Conclusions: Early recognition of NMS help to rescue patient. It is necessary to detect this syndrome even in the absence of main signs such as fever.

Keywords: Neuroleptic malignant syndrome, Atypical clinical expression, Complication, Course

Background

NMS is a rare and potentially fatal side effect linked to the use of antipsychotics and medications altering dopaminergic neurotransmission [1]. It is a potential life-threatening emergency. This syndrome could happen in a proportion going from 0.02 to 3% [2, 3]. The mortality rate is 5.6% [4]. Pope et al. suggest that we sometimes underestimate NMS than overestimating [5].

First-generation antipsychotics are the head causes of NMS. Subjects receiving large doses of neuroleptics are more frequently affected by this adverse event [6].

The main symptoms of NMS are severe muscle rigidity, tremor, fever, activation, and instability of the autonomic nervous system, altered consciousness, and CPK elevation [7]. Usually, the syndrome can last 7 to 10 days. Some serious complications may result from NMS as rhabdomyolysis, myoglobinuria but the most serious one is acute renal failure.

The clinical features and criteria for the diagnosis of NMS are wide and heterogeneous. The diagnosis of NMS presents a challenge. Indeed, we cannot easily differentiate it from several medication conditions like malignant catatonia [8] and severe parkinsonian syndromes.

In our study, we investigated a series of cases of NMS that occurred during 5 years among hospitalized patients in psychiatric service at Oujda.

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Methods

Our study was a cross-sectional with retrospective recruitment on 4039 medical files, covering a period of 5 years, from March 01, 2015, to March 2020, involving inpatients hospitalized in the various psychiatric departments of The University Hospital Center of Mohammed VI of Oujda.

In our department, we decide that in these cases:

The change of class of neuroleptics
The first administration of neuroleptics
Any patient tolerate well neuroleptics

The sudden appearance of at least one single sign such as fever, rigidity, blood pressure lability, alteration of consciousness, and asthenia requires the achievement of the rate of CPK urgently and monitoring the patient's condition.

The selection of files is done according to these criteria.

Inclusion criteria:

- Adult patients aged over 18 years, hospitalized in psychiatric service for different mental illnesses, diagnosed according to DSM V and with the use of Mini International Neuropsychiatric Interview, and they are treated with antipsychotics of different classes.
- Had a NMS during their hospitalizations according to the criteria of the DSM Fifth Edition. NMS is diagnosed upon the existence of the following findings: exposure to dopamine-antagonists, mental status changes (confusion, stupor, coma), muscle rigidity, hyperthermia > 38 °C, autonomic dysfunction such as sweating, tachycardia, altered or generally elevated arterial tension, tachypnea, urinary incontinence, besides of an elevated white blood cell, and elevated CPK [9].
- NMS was considered atypical if the patient present three of the above four core criteria (hyperthermia, rigidity, mental status changes, autonomic dysfunction, and elevated CPK) [10].
- Diagnostic confirmed by the intensive care doctors.

Exclusion criteria:

- Incomplete medical records
- Psychiatric diagnosis not established
- A concomitant organic disease which can distort the diagnosis of NMS (infections, system disease, drug intoxication, etc.).

Exploitation sheet:

Including sociodemographic characteristics, in particular, age and gender. Also, we specified for each patient his diagnosis of the disease meeting the criteria of the DSM V classification, the duration of evolution, follow-up, and a somatic pathology if it is associated.
We identified the antipsychotic responsible for NMS, and we described the current symptoms of this side effect.
We mentioned the care provided to these patients, the treatment, and the complication of NMS.
The collection of data carried by a psychiatrist resident using an exploitation sheet.
We respected the anonymity and confidentiality of the data.
Ethics approval and consent to participate: patients and their families accepted to use their data recruited during their hospitalization.

Results

Sociodemographic characteristics

We analyzed 29 files' patients who presented a NMS during their hospitalizations. Four files were excluded from the study because they were incomplete.

The patients were 16 males and 9 females with a mean age of 40.45 ± 9.772 years, ranging from 22 years to 57 years (Table 1).

Diagnosis

The diagnoses of the various psychiatric pathologies of the hospitalized patients posed according to the criteria DSM V. 32% of the patients admitted for a relapse of

Table 1 Sociodemographic characteristics

Variables	% (*n*)
Age	40.45 ± 9.772 ans
Gender	
Man	64 (16)
Women	36 (9)
Marital status	
Single	44 (11)
Married	40 (10)
Divorced	12 (3)
Widowed	4 (1)
Profession	
Without	76 (19)
With	24 (6)
Socio-economic level	
Low	72 (18)
Medium	28 (7)

*Means ± standard deviation

schizophrenic psychosis. 12% had a diagnosis of a bipolar disorder type I. 16% of patients presented a schizoaffective disorder, and 36% had a schizophreniform disorder or acute psychotic attack. One patient had a diagnosis of depression with psychotic characteristics (Table 2).

Medical history and addictive behaviors

Regarding medical and surgical history, 72% (n = 18) of patients had no antecedent, 2 patients had diabetes type II, and 2 patients had hypertension associated with diabetes type 2. One patient had epilepsy, one patient had a history of uterine fibroid, and another one suffered in the past from breast cancer. 16 patients did not use an addictive substance, 5 patients smoke cigarettes, and 4 patients smoke both tobacco and cannabis. All patients are with no history of NMS in past. No family history of NMS among these cases. The course of the disease and length of taking antipsychotics varies between 1 month and 38 years (Table 3).

Clinical and biological features on SMN

The earliest sign of NMS was rigidity observed among 21 patients, and 16 patients had both fever and rigidity during the first 24 h.

Core symptoms

18 patients (72%) had a high fever. Muscle rigidity was observed among 21 patients (84%). Altered consciousness was noticed in 6 patients (24%). All patients had abnormal or unstable blood pressure. The pulse accelerated amongst 19 patients (76%), and tachypnea was observed in 18 patients (72%). Sweating was noticed in 19 patients (76%).

The elevation of CPK is almost present in 92% of patients (23). CPK level was between 800 UI/L and 213 530 UI/L. Leukocytosis was present in 14 cases (56%), in one case, it reached 141 000/mm^3 (Table 4). 28% of patients presented atypical NMS. 22 patients (92%) had previously received butyrophenone (haloperidol), phenothiazine (chlorpromazine or levomepromazine), and half of these patients (52%) received these neuroleptic in injectable form for 1 to 3 days. The 15-mg dose of haloperidol was reached in 52% of patients. Two patients had received benzamide (amisulpride) with a dose of 400 mg per day. One patient was under risperidone (6 mg). Two patients took an antidepressant, fluoxetine 20 mg. We found that NMS occurred after first administration in 8 patients, and in one case, NMS appeared following the neuroleptic change. Half of the patients were under two neuroleptics with chlorpromazine with a dose of 75 mg. No patient was taking long-acting injectable antipsychotics. 36% of cases received neuroleptics for the first time. 100% were under an incisive neuroleptic (Table 5).

Table 2 Patients diagnosis

Diagnostic	% (n)
Schizophrenia	32 (8)
Schizoaffective disorder	16 (4)
Acute psychotic attack	36 (9)
Bipolar disorder I	12 (3)
Depression with psychotic characteristics	4 (1)

Table 3 Disease duration

Disease duration	% (n)
< 1 month	28 (7)
1 month–6 months	12 (3)
6 months–5 years	16 (4)
5–10 years	16 (4)
> 10 years	28 (7)

Table 4 NMS symptoms

Symptoms	n (%)
T>38 °C	
Present	72 (18)
Absent	28 (7)
CPK	
Eleveted	92 (23)
Not eleveted	8 (3)
Rigidity	
Present	84 (21)
Absent	16 (4)
Mental status changes	
Altered consciousness	24 (6)
Not altered	76 (19)
Unstable blood pressure	
Yes	25 (100%)
No	0 (0%)
Tachycardia	
Yes	76 (19)
No	24 (6)
Diaphoresis	
Yes	76 (19)
No	24 (6)
Tachypnea	
Yes	72 (18)
No	28 (7)
Leukocytosis	
Yes	56 (14)
No	44 (11)

Table 5 Antipsychotics causatives of NMS

Antipsychotics	% (*n*)
First-generation antipsychotics	88 (22)
Haloperidol	88 (22)
Phenothiazine	88 (22)
Second-generation antipsychotics	12 (3)
Amisulpride	8 (2)
Risperidone	4 (1)
Injectable form	52 (13)
Oral administration	48 (12)

NMS appeared 3 days after admission in psychiatric service among 9 patients. 15 patients developed this syndrome 6 days after admission. One patient presented this side effect 10 days after. 19 patients (76%) transferred to resuscitation. 32% of patients experienced a favorable course without complications. Rhabdomyolysis is the most common complication in patients with NMS (28%), followed by renal failure or coma in 12% of cases. Two patients presented acute respiratory distress, and two other patients experienced paresis.

All patients were treated with supportive care, as well as the discontinuation of antipsychotics. They received vigorous hydration and treatment to lower fever and blood pressure. Also, to prevent venous thromboembolism, patients took heparin. In the case of agitation, we used benzodiazepines except for one patient who received hemodialysis, and two patients were on oxygen therapy.

All patients recovered, and no deaths were recorded. The patient who received treatment for acute renal failure recovered after some sessions of hemodialysis. No one was treated with dantrolene or bromocriptine.

Discussion

NMS is infrequent [1]. According to some studies, estimates of its frequency vary from 0.7 to 2.2% of people receiving neuroleptics [11]. In our case, we retained 25 complete files of patients who had an NMS among 4039 hospitalizations over 5 years, so the prevalence of NMS was 0.7%. It can confirm objectively, the rarity, and the diagnostic difficulty of this syndrome.

The average age of our group was 40.45 ± 9.772 years (22 years–57 years). Result concordant with the foundation of some publications, where the mean age of patients with the NMS was 40 years. However, cases of NMS published showed that NMS was observed for all age groups [12].

The one patient with schizophrenia who presented with renal failure and need many sessions of hemodialysis was aged 57 years. Indeed, aged patient can present severe NMS [13].

In our sample, 64% of patients were male. Some publications [14] suggest that NMS is twice as common in men since antipsychotics are used more differently by gender. Men are more likely to receive high doses of neuroleptics, as they present more positive symptoms, such as agitation and hostility. Indeed, psychomotor agitation also seems to be linked to the occurrence of NMS [15].

The majority of patients had schizophrenia, acute psychotic access, or mood disorders. In a review article on 20 cases of NMS, it showed that this syndrome happened more among patients with schizophrenia and mood disorders. In another synthesis, 11 of the 12 cases of NMS occurred to schizophrenic patients [16].

No patients of our series did before NMS. In literature, patients with a history of NMS have an increased risk of having a second NMS [17].

Our patients had no family history of NMS, according to some research, there is a genetic risk factor. For this, antipsychotics should be used with caution in patients with a family history of NMS [8].

Half of the patients received neuroleptic in injectable form and 36% received it for the first time, and 28% had already a somatic disease. In the literature, the first administration and parenteral administration of neuroleptic as well as an associated with a somatic disease are the first suspected risk factors responsible for the occurrence of NMS [18].

92% of cases received a conventional neuroleptic, 52% of patients received an injectable form of haloperidol, 100% took an incisive neuroleptic, and 36% got two neuroleptics.

There is an evidence suggesting that the risk of NMS is minimized if single-agent therapy strategies are used [19].

Rapid parenteral drug administration, according to some research [20], is a risk factor for NMS. The use of "incisive" neuroleptics seems to be associated with a higher risk of neuroleptic NMS [21].

According to the literature, 26 years are the long-lasting latency between the starting of neuroleptic treatment and the occurrence of NMS. In our study, we have one case with 38 years under neuroleptic before the onset of NMS.

NMS appeared after 3 days of admission in 40.9% of our patients. 13.6% of patients had NMS after 6 days of admission. Clinically, the prodromal phase is rapidly progressive, marked by the appearance or accentuation of the extrapyramidal effects of neuroleptics. Some neuro-vegetative disorders should suggest the diagnosis. The state phase, reached on average in 2 days, combines general signs, neuromuscular signs, disturbances of consciousness, and evocative biological signs [22].

Hyperthermia (T>38 °C) observed in 72% of patients diagnosed with NMS. The fever noted in the NMS is usually higher than 38 °C sometimes exceeding 41 °C [1]. However, this hyperthermia would be absent in 9% of the cases [23]. In our study, it was absent in 28% of patients, which can make it difficult to diagnose NMS.

Rigidity was observed in 84% of our patients. According to the authors, rigidity was found in 91 to 96% of cases [24], but there were cases for which no rigidity is reported [25].

CPK elevation is almost present in 92% of our patients. For the majority of authors, the CPK level is one of the most reliable elements for assessing the occurrence of NMS, which is present in the majority of NMS cases, but not all [26].

Leukocytosis is always almost present in half of the cases (56%). Leukocytosis, with or without inversion of the blood formula, is also frequent according to the literature [27].

Consciousness or cognitive disorders during NMS mentioned in 24% of the patients in our sample. Stupor, coma, and catatonia are the cognitive disorders associated with NMS, according to the authors [24].

All patients had abnormal or labile blood pressure. The pulse accelerated by 76% of the patients and the tachypnea in 72%. Sweating was noticed in 76% of people with NMS.

All these neurovegetative symptoms can lead to vasoconstriction, respiratory distress, and dehydration, hence the interest to monitor these symptoms [24].

The atypical features of NMS can group the cases where the patients do not present the major criteria of this syndrome. In our study, we found some patients who did not have a fever, muscle rigidity, or increased CPK. Should be reviewed the diagnostic criteria for this syndrome.

32% of patients experienced a favorable course without complications or death. Resuscitation was required in 76% of cases.

Many complications appear in cases of an untreated or unrecognized malignant syndrome of neuroleptics: renal failure, coma, or rhabdomyolysis with repercussions that can be pejorative (4 times out of 120 cases) [15]. This shows that our patients were taken care of early and quickly, hence the importance of early diagnosis with good monitoring of the condition of any patient on neuroleptics.

Discontinuation of neuroleptic, supportive care was the principal treatment of NMS in our sample; effectively this is the first-line treatment. No deaths were recorded in our study. Indeed, NMS mortality rates have decreased due to early recognition of the syndrome with early and appropriate intervention. This awareness ensures fast and complete recovery.

That is true that NMS is less common, but some atypical forms can be hard to detect. So recognition of suspect cases and efficient management can save these patients.

Conclusion

The clinical picture of NMS is heterogeneous. Some patients did not fulfill all NMS criteria. It could be the result of the vigilance of clinicians who manage to screen for NMS before the onset of all symptoms. Or atypical antipsychotics are responsible for atypical clinical expression of NMS. Even in the absence of major criteria (like fever or rigidity), diagnosis of NMS should be considered, specially that we can use CPK which is an important distinguishing criterion of NMS. The early intervention can save the life of patients, and it is necessary to continue research in this area, as well as the continuous awareness of caregivers, to standardize convenient medical practices.

Abbreviations

NMS: Neuroleptic malignant syndrome; DSM: Diagnostic and Statistical Manual of Mental Disorders; CPK: Creatine phosphokinase

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None

Authors' contributions

Both authors, BO and OZ, contributed to the conception and design of the work, the acquisition, analysis, and interpretation of the data, and they have drafted the work and approved the submitted version. Both authors (BO and OZ) have read and approved the manuscript.

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Availability of data and materials

The authors confirm that the data supporting the findings of this study are available within the article.

Ethics approval and consent to participate

Patients and their families accepted to use their data recruited during their hospitalization by signing a form.

Consent for publication

The both authors (BO and OZ) have read and approved the manuscript.

Competing interests

None

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