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CLINICAL CHARACTERISTICS, MANAGEMENT, AND OUTCOMES OF NEUROLEPTIC MALIGNANT SYNDROME: A HOSPITAL-BASED SERIES OF 47 PATIENTS

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ABSTRACT

Background: Neuroleptic malignant syndrome (NMS) is a rare but potentially life-threatening adverse reaction to dopamine-antagonist treatment. Its heterogeneous presentation, particularly with second-generation antipsychotics, may delay recognition. **Objective:** To describe the epidemiological, clinical, therapeutic, and outcome characteristics of patients with NMS and to explore factors associated with intensive care use. **Methods:** We conducted a hospital-based observational study of 47 patients with a clinical picture compatible with NMS and documented exposure to at least one antipsychotic. Cases were identified at Ar-Razi Hospital across participating inpatient services between June 2025 and June 2026. Data were collected using a standardized form and analyzed in Jamovi. Intensive care admission was used as a pragmatic proxy for severity. Exploratory comparisons used the Mann-Whitney U test and chi-square test. **Results:** Mean age was 28.45 years (SD 9.27; range 17-58), and 33 of 44 patients with known sex were male (75.0%). Schizophrenia was the most common recorded diagnosis (29/35, 82.9%). Exposure involved conventional antipsychotics in 18 patients (38.3%), atypical agents in 15 (31.9%), and combined conventional-atypical treatment in 11 (23.4%). Rigidity was present in 40 patients (85.1%), altered consciousness in 19 (40.4%), autonomic signs in 19 (40.4%), and hyperthermia in 16 (34.0%). Maximum creatine phosphokinase (CPK) was available for 45 patients (median 800 IU/L; range 157-42,231); 16/45 (35.6%) had CPK >1,000 IU/L. Sixteen patients (34.0%) required intensive care. Median CPK was higher among patients requiring intensive care than among those who did not (1,595 vs 634 IU/L; p=0.002). Forty-five of 46 patients with documented outcomes recovered without reported sequelae; no death was explicitly recorded. **Conclusions:** In this young, predominantly male hospital series, rigidity was the most

frequent clinical feature, whereas hyperthermia was documented in only one-third of cases. Higher CPK values were associated with intensive care use in exploratory analysis. Prompt recognition, immediate withdrawal of the suspected agent, supportive care, and close multidisciplinary monitoring remain central to management. Prospective multicenter studies using standardized diagnostic and severity criteria are needed.

KEYWORDS: Neuroleptic Malignant Syndrome; Antipsychotics; Creatine Phosphokinase; Intensive Care; Rigidity; Retrospective Study.

1. INTRODUCTION

Neuroleptic malignant syndrome (NMS) is an uncommon, potentially fatal reaction most often associated with dopamine D2 receptor blockade. The classic syndrome comprises hyperthermia, severe muscle rigidity, altered mental status, autonomic instability, and biochemical evidence of muscle injury. Although historically linked to high-potency first-generation antipsychotics, NMS has been reported with virtually all antipsychotic classes, including second-generation agents [1,6-8].

Diagnosis remains clinical and can be challenging because individual manifestations may be absent or emerge at different times. Incomplete or atypical presentations may be encountered, especially with newer antipsychotics. Rapid dose escalation, a recent switch in therapy, parenteral administration, polypharmacy, agitation, dehydration, and previous NMS are commonly cited risk contexts [1,7,8]. Early recognition is essential because delayed withdrawal of the causative drug and delayed supportive treatment may increase the risk of rhabdomyolysis, acute kidney injury, cardiorespiratory complications, thromboembolism, and death.

Data describing NMS in North African hospital settings remain limited. Local patterns of antipsychotic prescribing, access to intensive care, documentation practices, and patient profiles may influence both presentation and management. This study therefore aimed to characterize patients diagnosed with NMS at a Moroccan psychiatric hospital and to explore whether age, antipsychotic class, and maximum creatine phosphokinase (CPK) were associated with the need for intensive care.

2. METHODS

2.1 Study design and setting

This was a hospital-based observational, descriptive study with an exploratory analytical component. It included a series of 47 patients managed at Ar-Razi Hospital in collaboration with participating inpatient services between June 2025 and June 2026.

2.2 Participants

Eligible patients had a clinical picture considered compatible with NMS, documented exposure to one or more antipsychotics before syndrome onset, and sufficient clinical information for case-level analysis. Records were excluded when NMS was not retained as the diagnosis or when the minimum clinical information required for analysis was unavailable. For variable-specific analyses, denominators were restricted to patients with available data.

2.3 Data collection

Information was abstracted using a standardized data-collection form and consolidated in an Excel database. The 23 variables covered data source, age, sex, geographic origin, marital status, educational level, psychiatric diagnosis, substance-use disorder, antipsychotic exposure, antipsychotic class, route of administration, duration of exposure, recent therapeutic changes, rigidity, altered consciousness, hyperthermia, autonomic signs, maximum CPK, care setting, NMS treatment, intensive care use, clinical outcome, and antipsychotic reintroduction.

2.4 Outcomes and operational definitions

The primary descriptive outcomes were the frequency of cardinal clinical manifestations, maximum CPK values, management modalities, and documented clinical outcome. Because a validated severity score and detailed complication data were unavailable, admission or transfer to intensive care was used as a pragmatic proxy for a more severe episode. This operational definition should not be interpreted as a direct measure of physiological severity.

2.5 Statistical analysis

Analyses were performed in Jamovi. Continuous variables were summarized using means and standard deviations or medians and interquartile ranges, as appropriate. Categorical variables were reported as counts and percentages, with available-case denominators stated when data were missing. Exploratory associations with intensive care use were assessed using the Mann-Whitney U test for age and CPK and the chi-square test for recoded antipsychotic class. Statistical tests were interpreted cautiously because of the small sample and incomplete data.

2.6 Ethics

The source dissertation did not report the research ethics committee reference, consent procedure, or waiver. These details must be confirmed and inserted before submission to a journal.

3. RESULTS

3.1 Participant characteristics

The study included 47 patients. Mean age was 28.45 years (SD 9.27), median age was 26 years, and the range was 17-58 years. Patients aged 20-29 years accounted for 46.8% of the sample. Sex was recorded for 44 patients: 33 were male (75.0%) and 11 female (25.0%). Most patients were single (38/47, 80.9%). Geographic origin was documented for 34 patients, of whom 32 (94.1%) were from urban areas.

Psychiatric diagnosis was available for 35 patients. Schizophrenia predominated (29/35, 82.9%); acute psychotic disorder and schizophreniform disorder were each reported in two patients, while bipolar disorder and schizoaffective disorder were each reported in one. Substance-use disorder status was available for 34 patients and was positive in 19 (55.9%).

3.2 Antipsychotic exposure and timing

Conventional antipsychotics were implicated in 18 patients (38.3%), atypical antipsychotics in 15 (31.9%), and a combination of conventional and atypical agents in 11 (23.4%); exposure class was unspecified in one and missing in two. Frequently documented conventional agents included haloperidol and chlorpromazine, with levomepromazine and injectable fluphenazine also represented. Atypical agents included risperidone, amisulpride, olanzapine, and clozapine.

A change in antipsychotic type was the most frequently recorded precipitating context, followed by a change in route and rapid dose escalation. Time from exposure or therapeutic modification to syndrome onset was available for 44 patients after recoding: six (12.8% of the full sample) developed NMS within one day, four (8.5%) at two days, five (10.6%) within two to five days, 14 (29.8%) within five to ten days, and 15 (31.9%) after more than ten days.

3.3 Clinical and biological findings

Muscle rigidity was the most frequently documented manifestation, occurring in 40 patients (85.1%). Altered consciousness and autonomic signs were each reported in 19 (40.4%), while hyperthermia was documented in 16 (34.0%). The relatively low recorded frequency of hyperthermia may reflect incomplete or atypical presentations, timing of assessment, or limitations of retrospective documentation.

Characteristic	Available N	Finding
Age	47	Mean 28.45 years (SD 9.27); median 26; range 17-58
Male sex	44	33 (75.0%)
Schizophrenia	35	29 (82.9%)
Substance-use disorder	34	19 (55.9%)
Muscle rigidity	47	40 (85.1%)
Altered consciousness	47	19 (40.4%)
Autonomic signs	47	19 (40.4%)
Hyperthermia	47	16 (34.0%)
Intensive care use	47	16 (34.0%)

Maximum CPK was available for 45 patients. Values ranged from 157 to 42,231 IU/L; the mean was 2,346.6 IU/L, median 800 IU/L, and interquartile range 450-1,541 IU/L. Sixteen patients (35.6% of those tested) had a maximum CPK greater than 1,000 IU/L, including four with values of at least 5,000 IU/L.

Maximum CPK category	n	% of available values
<500 IU/L	13	28.9
500-999 IU/L	14	31.1
1,000-4,999 IU/L	14	31.1
5,000-9,999 IU/L	2	4.4
>=10,000 IU/L	2	4.4

3.4 Management and outcomes

Intensive care was required for 16 patients (34.0%). Among the 35 patients with a recorded care-setting category, 23 (65.7%) remained in psychiatry, 11 (31.4%) were referred to emergency or intensive care, and one (2.9%) received an intensive care opinion while remaining in psychiatry. Treatments documented in the database included oral or unspecified-route benzodiazepines (27 mentions), oral rehydration (20), intravenous benzodiazepines (8), intravenous fluids (4), and an oral antiparkinsonian agent (1). Immediate antipsychotic withdrawal, dantrolene, bromocriptine, and electroconvulsive therapy were not captured as separate variables and could not be quantified.

Outcome was documented for 46 patients. Thirty-three (71.7%) were recorded as cured without sequelae, 12 (26.1%) as having complete recovery, and one (2.2%) as cured with sequelae. Combining the first two categories, 45/46 patients (97.8%) had a favorable outcome without reported sequelae. No death was explicitly recorded in the outcome variable.

3.5 Exploratory analyses

Median age was 28 years among patients requiring intensive care and 25 years among those who did not; the difference did not reach statistical significance (Mann-Whitney p=0.060). Intensive care use occurred in 7/18 patients (38.9%) exposed to conventional agents, 5/15 (33.3%) exposed to atypical agents, and 2/11 (18.2%) exposed to combined conventional-atypical treatment. The association between recoded antipsychotic class and intensive care use was not statistically significant (chi-square p=0.503).

Maximum CPK was higher in patients requiring intensive care (n=15; median 1,595 IU/L, Q1 870, Q3 4,732) than in those not requiring intensive care (n=30; median 634 IU/L, Q1 371, Q3 982). This exploratory difference was statistically significant (Mann-Whitney p=0.002).

Exploratory comparison	Intensive care	No intensive care	p value
Age, median	28 years	25 years	0.060
Maximum CPK, median (Q1-Q3)	1,595 (870-4,732)	634 (371-982)	0.002
Antipsychotic class	See text	See text	0.503

4. DISCUSSION

This hospital-based series describes NMS in a predominantly young, male population with a high proportion of schizophrenia. Both conventional and atypical antipsychotics were represented, and recent therapeutic modification was commonly documented. Rigidity was the dominant clinical sign, while altered consciousness, autonomic features, and hyperthermia were less frequently recorded. One-third of patients required intensive care, and higher maximum CPK was associated with intensive care use in exploratory analysis.

The demographic profile is compatible with the clinical populations most frequently exposed to sustained or high-intensity antipsychotic treatment. The predominance of schizophrenia should be interpreted in the context of the hospital setting and the available-case denominator rather than as evidence that schizophrenia independently increases NMS risk. Likewise, the distribution of implicated drugs cannot establish comparative drug risk because the study did not include exposure denominators or an antipsychotic-treated control group.

The occurrence of NMS with both conventional and atypical antipsychotics reinforces the need for syndrome awareness across drug classes [6-8]. High-potency conventional agents have historically been prominent in case series, but atypical drugs are not risk-free. Clinicians should be particularly vigilant after initiation, rapid titration, switching, combination treatment, or parenteral administration. In this series, therapeutic changes were common antecedents, although their independent contribution could not be quantified.

Rigidity was recorded in more than four-fifths of patients, supporting its central diagnostic value. In contrast, hyperthermia was documented in only 34.0%. This finding should not be interpreted as demonstrating that fever is usually absent in NMS. It may instead reflect atypical or evolving presentations, early intervention, incomplete documentation, or heterogeneity in case ascertainment. A syndrome-level assessment remains essential when an antipsychotic-exposed patient develops rigidity, altered mental status, autonomic instability, and muscle-enzyme elevation, even when the full tetrad is not simultaneously present [1,7,8].

The CPK distribution was markedly right-skewed, with a maximum of 42,231 IU/L. Patients who required intensive care had substantially higher median CPK than those who did not. This association is clinically plausible because greater muscle injury may accompany more severe rigidity, hyperthermia, and rhabdomyolysis. However, CPK should not be used as a stand-alone diagnostic or severity marker. The analysis was exploratory, intensive care use was an imperfect proxy for severity, and decisions to transfer may also reflect local resources and clinician judgment.

Management documentation primarily reflected supportive measures, including hydration and benzodiazepines. Standard management begins with immediate discontinuation of the suspected dopamine antagonist, close cardiorespiratory and renal monitoring, temperature control, fluid and electrolyte management, and prevention or treatment of rhabdomyolysis-related complications [1-5,7,8]. Bromocriptine, dantrolene, amantadine, and electroconvulsive therapy may be considered in selected severe or refractory cases, but high-quality comparative evidence remains limited.

Documented outcomes were favorable, with 45 of 46 patients recovering without reported sequelae and no death explicitly recorded. These data are reassuring but require caution. Retrospective outcome coding may miss complications or post-discharge sequelae, and absence of an explicitly recorded death is not equivalent to independently verified zero mortality. Similarly, detailed duration of hospitalization and organ complications were not available.

4.1 Strengths and limitations

The study provides a clinically relevant description of NMS in a Moroccan hospital context and includes detailed antipsychotic exposure, cardinal clinical manifestations, CPK values, care setting, and outcomes. Nevertheless, several limitations constrain inference. The design was retrospective and apparently single-center, the sample was small, diagnostic criteria were not standardized in the available source, several variables had substantial missingness, and

there was no control group. Detailed organ complications, hospitalization duration, precise drug doses, chronology of all exposures, and standardized antipsychotic withdrawal or reintroduction data were unavailable. Intensive care use was only a proxy for severity. Multiple exploratory tests were performed without adjustment, and sparse cells limited the reliability of the chi-square analysis. The findings should therefore be considered descriptive and hypothesis-generating.

5. CONCLUSION

NMS remains a medical-psychiatric emergency across antipsychotic classes. In this series of 47 patients, rigidity was the most common feature, one-third required intensive care, and higher maximum CPK was associated with intensive care use. The incomplete documentation of fever in many cases highlights the importance of recognizing evolving or atypical presentations rather than waiting for the full classic tetrad. Safer antipsychotic prescribing, careful monitoring after treatment changes, rapid discontinuation of the suspected drug, and multidisciplinary supportive care are central to improving outcomes. Future prospective multicenter research should apply standardized diagnostic and severity criteria and systematically capture treatment timing, organ complications, antipsychotic reintroduction, recurrence, and long-term outcomes.

Declarations

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