Ref: Ro J Neurol. 2022;21(1)
DOI: 10.37897/RJN.2022.1.8

Frequency of pattern of clinical and laboratory features in patients presenting with neuroleptic malignant syndrome

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ABSTRACT

Objectives. Neuroleptic malignant syndrome (NMS) is a life-threatening adverse reaction of antipsychotic drugs, especially of dopamine receptor antagonists (DRA's). Excitation, exuberant behavior, violent behavior and lack of insight predispose the patients to the use of depot preparations and high doses of the antipsychotics. These behaviors also make the patients suffer from dehydration leading to cognitive impairment, confusion and incontinence. In addition to clinical and pharmacological risk factors, legal and ethical risk factors may be contributory towards the incidence, diagnosis and prognosis of NMS in Pakistan.

Material and methods. This study was conducted as a descriptive, observational study to determine the frequency of deranged pattern of clinical and laboratory feature patients presenting with Neuroleptic Malignant Syndrome at Department of Neurology, Jinnah Postgraduate Medical Center (JPMC), Karachi. Data was prospectively collected from patients after taking a verbal consent. 55 patients who met the diagnostic criteria were included. Quantitative data was presented as simple descriptive statistics giving mean and standard deviation and qualitative variables was presented as frequency and percentages. Effect modifiers were controlled through stratification to see the effect of these on the outcome variable. Post stratification chi square test was applied taking p-value of ≤0.05 as significant.

Outcomes. A total of 55 patients who met the inclusion and exclusion criteria were included in this study. Mean age, duration of NMS symptoms, length of hospital stay, SBP and DBP in our study was 39.41±12.67 years, 10.56±7.29 hours, 9.74±3.21 days, 135.87±10.97 mmHg and 83.21±6.42 mmHg. 24 (43.6%) and 31 (56.4%) were male and female. Out of 55 patients, 81.8%, 38.2%, 69.1%, 56.4%, 47.3%, 74.5% and 25.5% had fever, autonomic dysfunction, EPS symptoms, altered GCS, elevated CPK, elevated WBC and abnormal LFT.

Conclusions. NMS is an important preventable clinical entity. Early diagnosis and judicious use of antipsychotics is warranted to prevent mortality and heightened morbidity.

Keywords: neuroleptic malignant syndrome, movement disorders, neurohospitalist, antipsychotics and predisposing factors

INTRODUCTION

Neuroleptic malignant syndrome (NMS) is a severe disorder caused by an adverse reaction to medications with dopamine receptor-antagonist properties or the rapid withdrawal of dopaminergic medications [1]. Although NMS is often regarded in the literature as an idiosyncratic and unpredictable reaction related to the administration of dopamine antagonists and other compounds, there are a number of risk factors that increase the likelihood of de-

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Article history:
Received: 23 February 2022
Accepted: 3 March 2022

veloping NMS [2]. These risk factors can be grouped into four categories, which include pharmacological risk factors (type of drug, pharmacokinetics, polypharmacy); environmental (high ambient temperature, restraint, dehydration); demographic (age, concurrent medical conditions or comorbidity); and genetic liability (history of previous NMS, family history of catatonic disorder, channelopathy) [3-4]. Although NMS occurs only rarely, it remains an unpredictable and potentially life-threatening neurologic condition that hospitalists must be able to recognize, as early identification and proper medical management are essential to ensure improved patient outcomes [5-6].

The diagnosis of NMS is based on history and the presence of certain physical examination and laboratory findings [7]. Patients typically develop NMS within hours or days after exposure to a causative drug, with most exhibiting symptoms within 2 weeks and nearly all within 30 days [8]. This receptor antagonism triggers a series of homeostatic responses that raise temperature, create muscular rigidity and impair mental status as a result of autonomic nervous system dysregulation [9]. Secondly, it has recently been postulated that NMS is the result of a toxic effect of the pharmacological compounds on musculoskeletal fibers, leading secondarily to the full syndrome [10-11]. NMS is characterized by hyperthermia, extra-pyramidal rigidity, autonomic dysfunction and altered consciousness [12]. Morbidity and mortality in NMS is most often secondary to cardiopulmonary and renal complications [13]. Berman et al found the prevalence of NMS to be 3.2% [14]. Khan et al evaluated patients presenting with Neuroleptic Malignant Syndrome and found the prevalence of clinical features {(Fever ≥ 37.8°C (95%), Autonomic dysfunction (hypertension (65%), labile BP (20%), tachycardia (70%), tachypnea (40%), diaphoresis (10%) and incontinence (25%), EPS symptoms (rigidity (85%), tremor (10%), dyskinesia (10%) and Flexor-extensor posturing (20%), diaphoresis (10%) and incontinence (25%) and altered GCS (95%)} and laboratory features {CPK ≥ 1000 IU/L (38%), WBC ≥ 10,000 cells/mm3 (73.7%) and abnormal LFT (28.6%)} [15].

The rationale of this study is to determine the frequency of pattern of clinical and laboratory features in patients presenting with Neuroleptic Malignant Syndrome in order to establish the local perspective. Accurate diagnosis and effective treatment of Neuroleptic Malignant Syndrome is critical for successful management. Many international and local studies have been published concerning prevalence, etiology and outcome of Neuroleptic Malignant Syndrome but very few have evaluated the clinical and laboratory presentation. Data from this study would provide insight into presentation in our population in light of variable demographic, cultural, socioeconomic and co-morbid condition. Moreover, in light of the information obtained from this study an effective management plan will be developed.

METHODOLOGY

STUDY DESIGN: Descriptive study.

STUDY SETTING: Study was conducted at Department of Neurology, Jinnah Postgraduate Medical Center (JPMC), Karachi.

DURATION OF STUDY: Six months after approval of synopsis from 24-09-20 till 24-03-21.

SAMPLE SIZE: The required sample size came out to be 55 patients. By taking the prevalence of tremor 10% 15 at margin of error = 8% and confidence level 'C.I'=95%. This sample size was calculated using the WHO sample size calculator.

SAMPLING TECHNIQUE: Non-probability consecutive sampling.

SAMPLE SELECTION:

INCLUSION CRITERIA: The study included newly diagnosed patients with Neuroleptic Malignant Syndrome as per operational definition of either gender, and Age between 20-60 years.

EXCLUSION CRITERIA: The study excluded patients who were non-consenting, or had a history of taking any of concomitant drug use of anticholinergics, tricyclic antidepressants (TCA), selective serotonin receptor inhibitors (SSRI), and lithium. Patients with history of serotonin syndrome, hypothyroidism or hyperthyroidism, myasthenia gravis, Pregnant patients assessed by history and confirmed by dating scan, CNS disease (e.g, head trauma, multiple sclerosis), asthma, renal impairment, congestive heart failure, myocardial infarction, chronic obstructive pulmonary disease and chronic liver disease were also excluded.

DATA COLLECTION PROCEDURE:

This study was conducted after approval from College of Physicians and Surgeons Pakistan. Patients as defined in operational definition, meeting inclusion criteria were enrolled in the study from the Inpatient Department of Neurology, Jinnah Postgraduate Medical Center (JPMC), Karachi. Permission from the institutional ethical review committee was taken prior to conduction of study. Informed consent was obtained from all the patients for assigning them to sample and using their data in research and those unable to sign consent it was taken from their attendants. Brief history about demographic information was taken at the time of admission from the patient or the attendant in case of aphasia or low GCS. Patients were examined by the researcher under the guidance of supervisor with over ten years of experience to look for clinical fea-

ture of NMS as per operation definition. Blood sample was drawn by the researcher by using 5 cc disposable syringe and will draw 10 ml of blood from peripheral vein and collect in specific tube for the measurement of CPK, WBC and LFT at the time of admission and sample was transported to hospital standardized laboratory by proper labeling as well as the investigation requested and patients was labeled as having laboratory features as per operational definition. The findings was noted in the proforma for quantitative variables (age, SBP, DBP, length of hospital stay and duration of symptoms of NMS) and qualitative variables (gender, educational status, occupational status, family monthly income, diabetes mellitus type II, hypertension, pattern of clinical and laboratory features in Neuroleptic Malignant Syndrome).

DATA ANALYSIS PROCEDURE:

Data was analyzed on SPSS Version 25. Demographic data was presented as simple descriptive statistics giving mean and standard deviation for age, SBP, DBP, length of hospital stay and duration of symptoms of NMS. Frequencies and percentages was calculated for categorical variable like gender, place of residence, educational status, occupational status, family monthly income, diabetes mellitus type II, hypertension and clinical features {(Fever ≥ 37.8°C, Autonomic dysfunction (hypertension, labile BP, tachycardia, tachypnea, diaphoresis and incontinence, EPS symptoms (rigidity, tremor, dyskinesia and flexor-extensor posturing and altered GCS Yes/No} and laboratory features {CPK ≥ 1000 IU/L, WBC ≥ 10,000 cells/mm^3 and abnormal LFT Yes/No}. Effect modifiers were controlled through stratification of age, gender, educational status, occupational status, family monthly income, diabetes mellitus type II and hypertension to see the effect of these on the outcome variable (pattern of clinical and laboratory features in Neuroleptic Malignant Syndrome). Post stratification chi square was applied taking p-value of ≤ 0.05 as significant.

RESULTS

A total of 55 patients admitted at the Department of Neurology, Jinnah Postgraduate Medical Center (JPMC), Karachi who met the inclusion and exclusion criteria were included in this study. Out of 55 patients minimum age of the patient was 20 while maximum age of the patients was 60 years. Mean age, duration of NMS symptoms, length of hospital stay, SBP and DBP in our study was 39.41±12.67 years, 10.56±7.29 hours, 9.74±3.21 days, 135.87±10.97 mmHg and 83.21±6.42 mmHg respectively, as shown in Table 1. Out of 55 patients, 45 (81.8%) and 10 (18.2%) had and did not have fever respectively, as shown in Figure 1. 21 (38.2%) and 34 (61.8%) had and did not have autonomic dysfunction, 38 (69.1%) and 17 (43.6%) had and did not have EPS symptoms, 31 (56.4%) and 24 (43.6%) had and did not have altered GCS, respectively. Out of 55 patients, 26 (47.3%) and 29 (52.7%) had and did not have elevated CPK, 41 (74.5%) and 14 (25.5%) had and did not have elevated WBC, 14 (25.5%) and 41 (74.5%) had and did not have abnormal LFT respectively, as shown in Figure 2. Out of 55 patients, 24 (43.6%) and 31 (56.4%) were male and female, as shown in Figure 3.

Frequency distribution of age showed that out of 55 patients, 18 (32.7%) and 37 (67.3%) patients were in age group 20-40 years and 41-60 years respectively, 45 (81.8%) and 10 (18.2%) had urban and rural residence, 23 (41.8%) and 32 (58.2%) had duration of symptoms < 12 hours and > 12 hours, 06 (10.9%) and 49 (89.1%) had and did not have diabetes mellitus type II, 08 (14.5%) and 47 (85.5%) had and did not have hypertension respectively, 05 (9.1%), 14 (25.5%), 26 (47.3%), 08 (14.5%) and 02 (3.6%) belonged to income group of lower, lower middle, middle, upper middle and upper respectively, 03 (5.5%), 08 (14.5%), 21 (38.2%) and 23 (41.8%) were in illiterate, primary, secondary and higher respectively, 31 (56.4%) and 24 (43.6%) were employed and unemployed respectively, as presented in Figure 4.

Stratification for age with respect to fever showed that 13 (58.9%) and 32 (71.1%) patients who were in age group 20-40 years and 41-60 years had fever respectively. Whereas 05 (50%) and 05 (50%) patients who were in age group 20-40 years and 41-60 years did not have fever respectively (P-value was 0.17), as presented in Table 2. Stratification for gender with respect to fever showed that 18 (40%) and 06 (60%) who were in male group had and did not have fever respectively. Whereas 27 (60%) and 04 (40%) who were in female group had and did not have fever respectively (P-value was 0.21). Stratification for residence status with respect to fever showed that 39 (86.7%) and 06 (60%) who had urban residence had and did not have fever respectively. Whereas 06 (13.3%) and 04 (40%) who had rural residence had and did not have fever respectively (P-value was 0.07). Stratification for duration of NMS symptoms with respect to fever showed that patients who had the symptoms for < 12 hours, 19 (42.2%) and 04 (40%) had and did not have fever respectively. Whereas patients who had symptoms for > 12 hours, 26 (57.8%) and 06 (60%) had and did not have fever respectively (P-value was 0.59). Stratification for diabetes mellitus type II with respect to fever showed that patients who had diabetes mellitus, 06 (13.3%) and 00 (00%) had and did not have fever respectively. Whereas patients who did not have diabetes mellitus, 39 (86.7%) and 10 (100%) had and did not have fever respectively (P-value was 0.28). Stratification for hypertension with re-

TABLE 1. Descriptive statistics (n=55)

Variable	Mean ± SD	Standard deviation	Min-max
Age (years)	39.41	±12.67	20-60
Duration of NMS symptoms (hours)	10.56	±7.29	02-24
Length of hospital stay (days)	9.74	±3.21	4-14
SBP (mmHg)	135.87	±10.97	120-160
DBP (mmHg)	83.21	±6.42	60-95

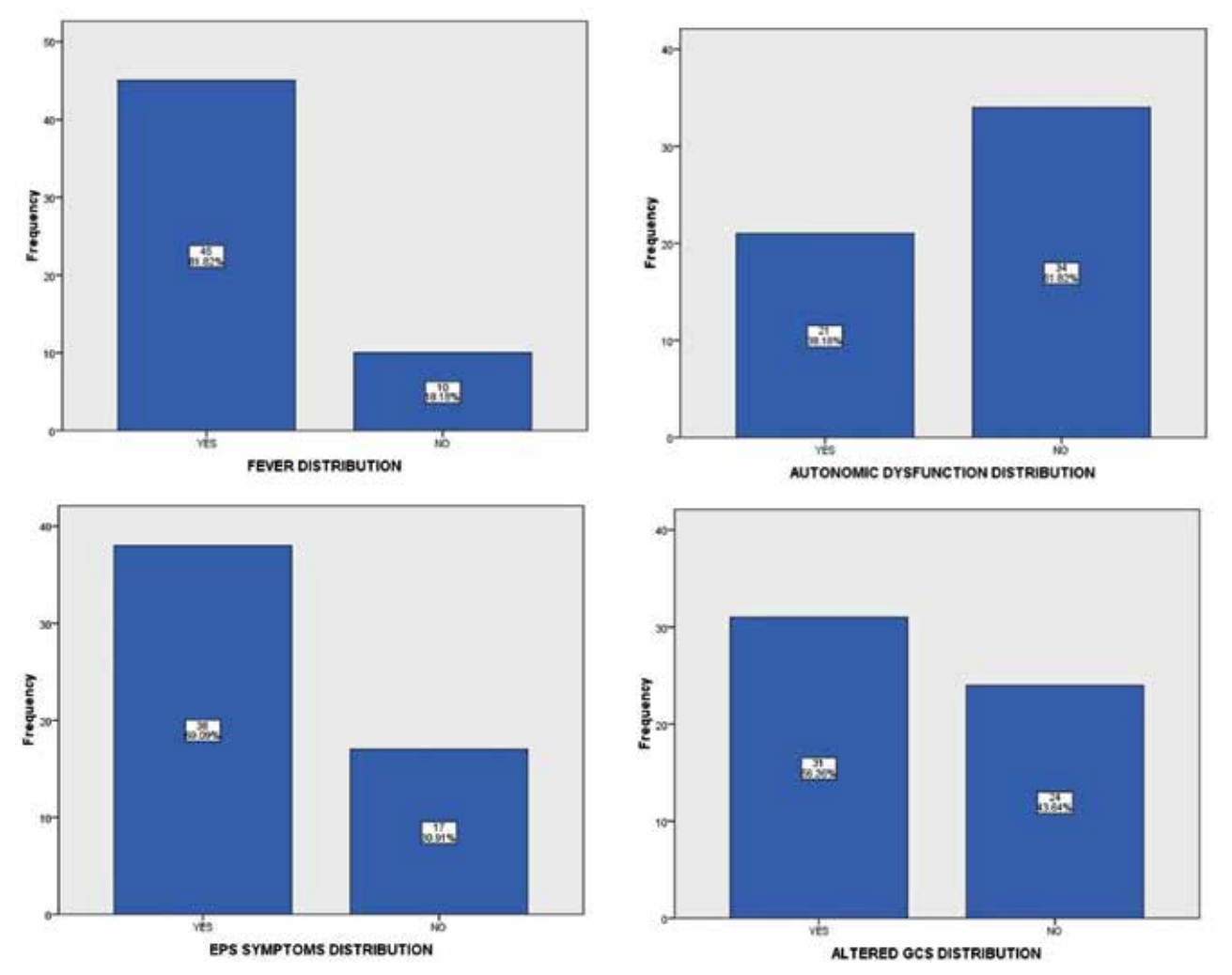

FIGURE 1. Distribution of fever, autonomic dysfunction, EPS symptoms and altered GCS

spect to fever showed that patients who had hypertension, 07 (15.6%) and 01 (10%) had and did not have fever respectively. Whereas patients who did not have hypertension, 38 (84.4%) and 09 (90%) had and did not have fever respectively (P-value was 0.55).

Stratification for family monthly income status with respect to fever showed 03 (6.7%), 14 (31.1%), 20 (44.4%), 07 (15.6%) and 01 (2.2%) had fever in patients who belonged to lower, lower middle, middle, upper middle and upper income group respectively. Whereas, 02 (20%), 00 (00%), 00 (60%), 01 (10%) and 01 (10%) did not have fever in patients who belonged to lower, lower middle, middle, upper middle and upper income group respectively (P-value was 0.15), as presented in Table 3. Stratification for educational status with respect to fever showed 02 (4.4%), 06 (13.3%), 18 (40%) and 19 (42.2%) had fever in patients who belonged to illiterate, primary, secondary and higher educational group respectively. Whereas, 01 (10%), 02 (20%), 03 (30%) and 04 (40%) did not have fever in patients who belonged to illiterate, primary, secondary and higher educational group respectively (P-value was 0.81). Stratification

TABLE 2. Stratification of fever according to age, gender, residence, occupation, diabetes, hypertension and duration of NMS symptoms (n=55)

Age (years)	Fever		Total	P-value
	Yes	No		
20-40	13 (28.9%)	05 (50%)	18 (32.7%)	**0.17**
41-60	32 (71.1%)	05 (50%)	37 (67.3%)	
Total	45 (100%)	10 (100%)	55 (100%)	
Gender				
Male	18 (40%)	06 (60%)	24 (43.6%)	**0.21**
Female	27 (60%)	04 (40%)	31 (56.4%)	
Total	45 (100%)	10 (100%)	55 (100%)	
Residence				
Urban	39 (86.7%)	06 (60%)	45 (81.8%)	**0.07**
Rural	06 (13.3%)	04 (40%)	10 (18.2%)	
Total	45 (100%)	10 (100%)	55 (100%)	
Occupation				
Employed	27 (60%)	04 (40%)	31 (56.4%)	**0.21**
Unemployed	18 (40%)	06 (60%)	24 (43.6%)	
Total	45 (100%)	10 (100%)	55 (100%)	
Type 2 Diabetes Mellitus				
Yes	06 (13.3%)	00 (00%)	06 (10.9%)	**0.28**
No	39 (86.7%)	10 (100%)	49 (89.1%)	
Total	45 (100%)	10 (100%)	55 (100%)	
Hypertension				
Yes	07 (15.6%)	01 (10%)	08 (14.5%)	**0.55**
No	38 (84.4%)	09 (90%)	47 (85.5%)	
Total	45 (100%)	10 (100%)	55 (100%)	
Duration of NMS symptoms				
<12 hours	19 (42.2%)	04 (40%)	23 (41.8%)	**0.59**
>12 hours	26 (57.8%)	06 (60%)	32 (58.2%)	
Total	45 (100%)	10 (100%)	55 (100%)	

for occupational status with respect to fever showed that patients who were employed, 27 (60%) and 04 (40%) had and did not have fever respectively. Whereas patients who were unemployed, 18 (40%) and 06 (60%) had and did not have fever respectively (P-value was 0.21).

DISCUSSION

Neuroleptic malignant syndrome (NMS) is a life-threatening idiosyncratic reaction to antipsychotic drugs characterized by fever, altered mental status, muscle rigidity and autonomic dysfunction. It has been associated with virtually all neuroleptics, including newer atypical antipsychotics, as well as a variety of other medications that affect central dopaminergic neurotransmission. Although uncommon, NMS remains a critical consideration in the differential diagnosis of patients presenting with fever and mental status changes because it requires prompt recognition to prevent significant morbidity and death. Treatment includes immediately stopping the offending agent and implementing supportive measures, as well as pharmacological interventions in more severe cases. Maintaining vigilant awareness of the clinical features of NMS to diagnose and treat the disorder early, however, remains the most important strategy by which physicians can keep mortality rates low and improve patient outcomes. Our study included a total of 55 patients who a had mean age, duration of NMS symptoms, length of hospital stay, SBP and DBP of 39.41±12.67 years, 10.56±7.29 hours, 9.74±3.21 days, 135.87±10.97 mmHg and 83.21±6.42 mmHg respectively. 24 (43.6%) and 31 (56.4%) were male and female. Out of 55 patients, 81.8%, 38.2%, 69.1%, 56.4%, 47.3%, 74.5% and 25.5% had fever, autonomic dysfunction, EPS symptoms, altered GCS, elevated CPK, elevated WBC and abnormal LFT.

A local study included 11 male and 9 female patients of NMS in a study with a mean age of 46.6±15.9 years (range: 17 to 73 years). There were 5 patients over 60 years of age and 3 were less than 25 years old. Table 1 summarizes the clinical features of all 20 patients. Affective disorder was the primary psychiatric diagnosis in 12 of our patients, 9 of whom

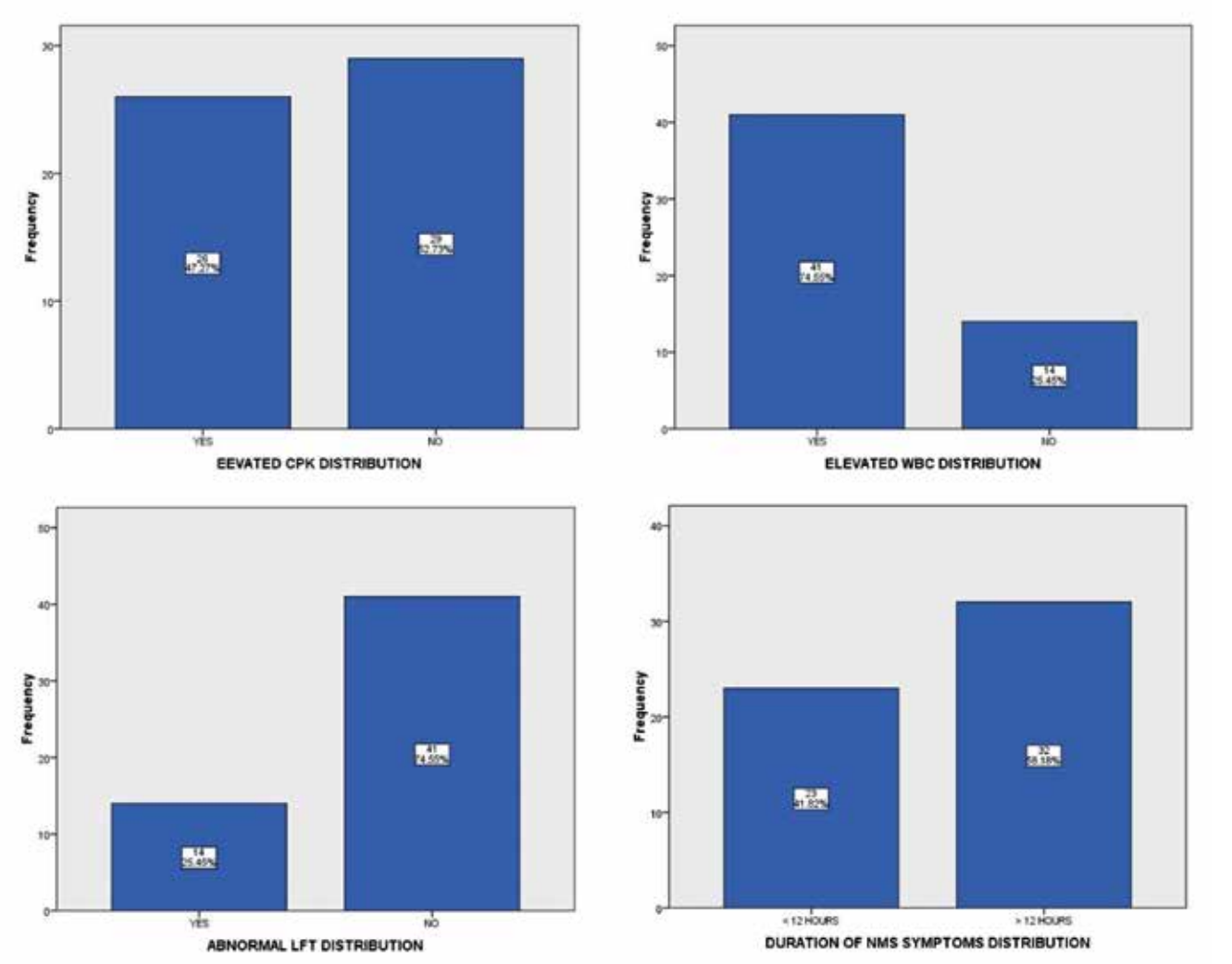

FIGURE 2. Distribution of elevated CPK, WBC, LFT and duration of NMS symptoms

TABLE 3. Stratification of fever according to family monthly income and educational status (n=55)

Family monthly income status	Fever		Total	P-value
	Yes	No		
Lower	03 (6.7%)	02 (20%)	05 (9.1%)	**0.15**
Lower middle	14 (31.1%)	00 (00%)	14 (25.5%)	
Middle	20 (44.4%)	06 (60%)	26 (47.3%)	
Upper Middle	07 (15.6%)	01 (10%)	08 (14.5%)	
Higher	01 (2.2%)	01 (10%)	02 (3.6%)	
Total	45 (100%)	10 (100%)	55 (100%)	
Educational status				
Illiterate	02 (4.4%)	01 (10%)	03 (5.5%)	**0.81**
Primary	06 (13.3%)	02 (20%)	08 (14.5%)	
Secondary	18 (40%)	03 (30%)	21 (38.2%)	
Higher	19 (42.2%)	04 (40%)	23 (41.8%)	
Total	45 (100%)	10 (100%)	55 (100%)	

were documented to have psychotic features. The other major psychiatric diagnosis was schizophrenia (n=4), including catatonic and undifferentiated types, while 1 patient had schizoaffective disorder Most patients developed symptoms slowly, while 8 patients (40%) developed full-blown NMS over a period of 3 days only. Six of the patients who had developed symptoms rapidly (≤3 days) were diagnosed NMS within 24 hours of presentation. In their case CPK was >1000 IU/l at admission, while in the other 2 cases, CPK was normal or only slightly elevated. In 2 cases, diagnosis was established in >1 week: one was an elderly patient with mild symptoms and no documented fever; the other had Parkinson's disease and had presented in septic shock following sudden withdrawal of anti-Parkinsonian medications [16].

Velamoor et al. found that of all order implications, 70.5% were consistent with the sequence of mental-status changes followed by rigidity, hyperthermia, and autonomic dysfunction. Changes in ei-

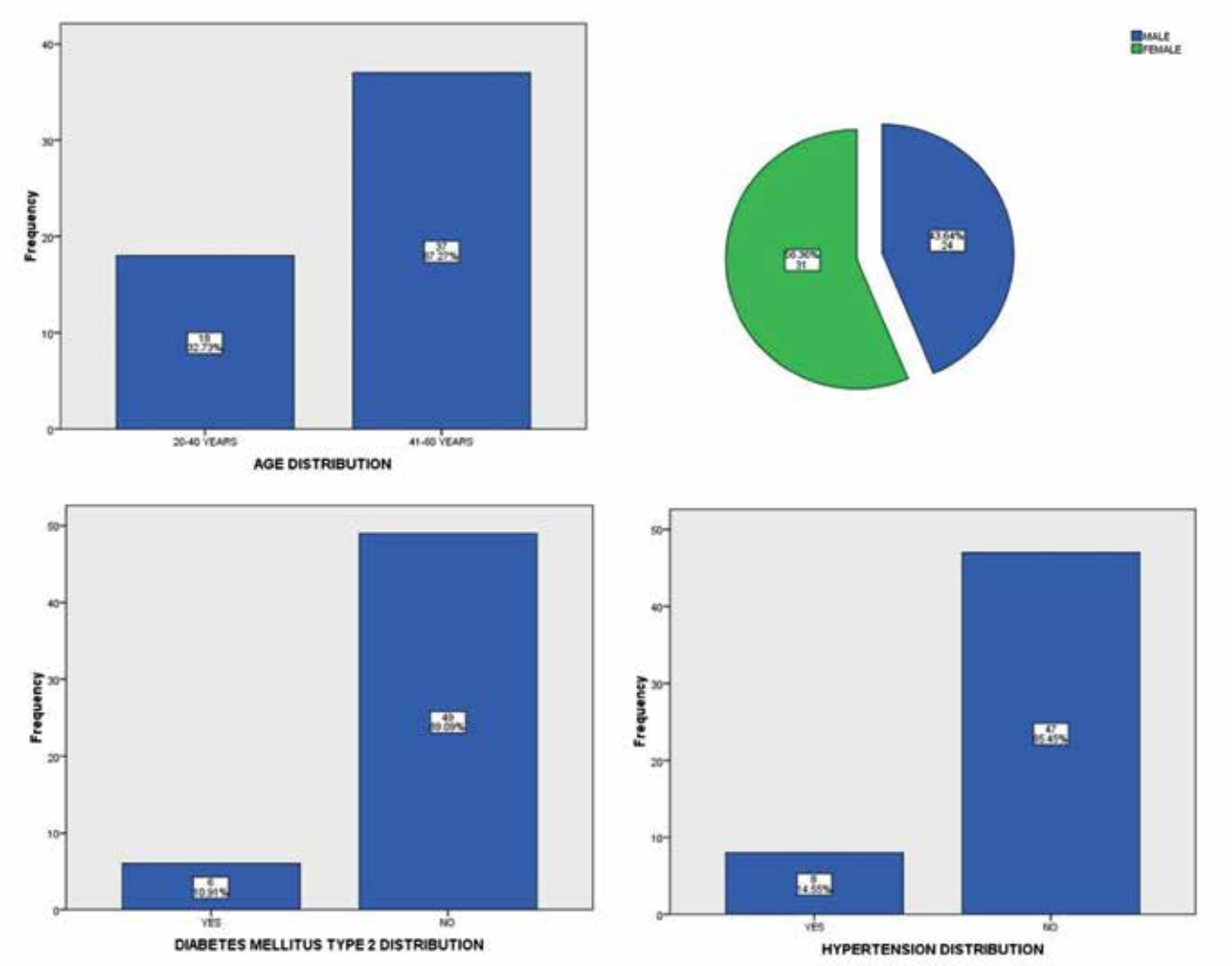

FIGURE 3. Distribution of age, gender, DM-II and hypertension

ther mental status or rigidity were the initial manifestations of NMS in 82.3% of cases with a single presenting sign and were significantly more likely to be observed before hyperthermia and autonomic dysfunction. One of our patients did not develop fever at any time throughout the episode of NMS. Extrapyramidal features and autonomic instability, however, were present in this patient. Several authors have reported such variants of NMS which suggests that NMS is a spectrum disorder and a number of cases of NMS with no rise in temperature or negligible temperature elevations have been described. This underlines the importance of looking at the complete clinical picture rather than relying on individual signs and symptoms meeting arbitrarily fixed thresholds for disease [17].

Most frequently considered differentials in our patients were Central Nervous System (CNS) infections (30%) and neuroleptic-induced dystonia or Parkinsonism (20%). CNS infection which can present with fever and altered consciousness can pose a special problem. An LP can be particularly helpful in such cases. Other infections can often co-exist with NMS and clinicians should not hesitate to make a diagnosis of NMS and a concomitant infection. Infection may predispose patients to NMS by causing dehydration and agitation. Conversely, NMS may create a setting for infection as a result of respiratory compromise, immobility and urinary catheterization. It is important that clinicians are able to make a diagnosis of NMS in the presence of a non-CNS infection as the two may often co-exist. Attributing the patients' symptoms to sepsis in this setting could be a costly mistake as delays in instituting appropriate therapy may result [18-20]. In the management of NMS, the most effective measures include prompt recognition, withdrawal of neuroleptic medication, and transfer to an intensive/special care unit, with attention to hydration, fever reduction, sedation with benzodiazepines, if indicated and control of rigidity with bromocriptine or dantrolene [21].

Given the absence of fever and of predisposing factors, except the psychiatric diagnosis and the recent introduction of an antipsychotic medication, the suspicion of NMS was delayed and confounded with the possibility of isolated extrapyramidal effects induced by chlorpromazine. Nevertheless,

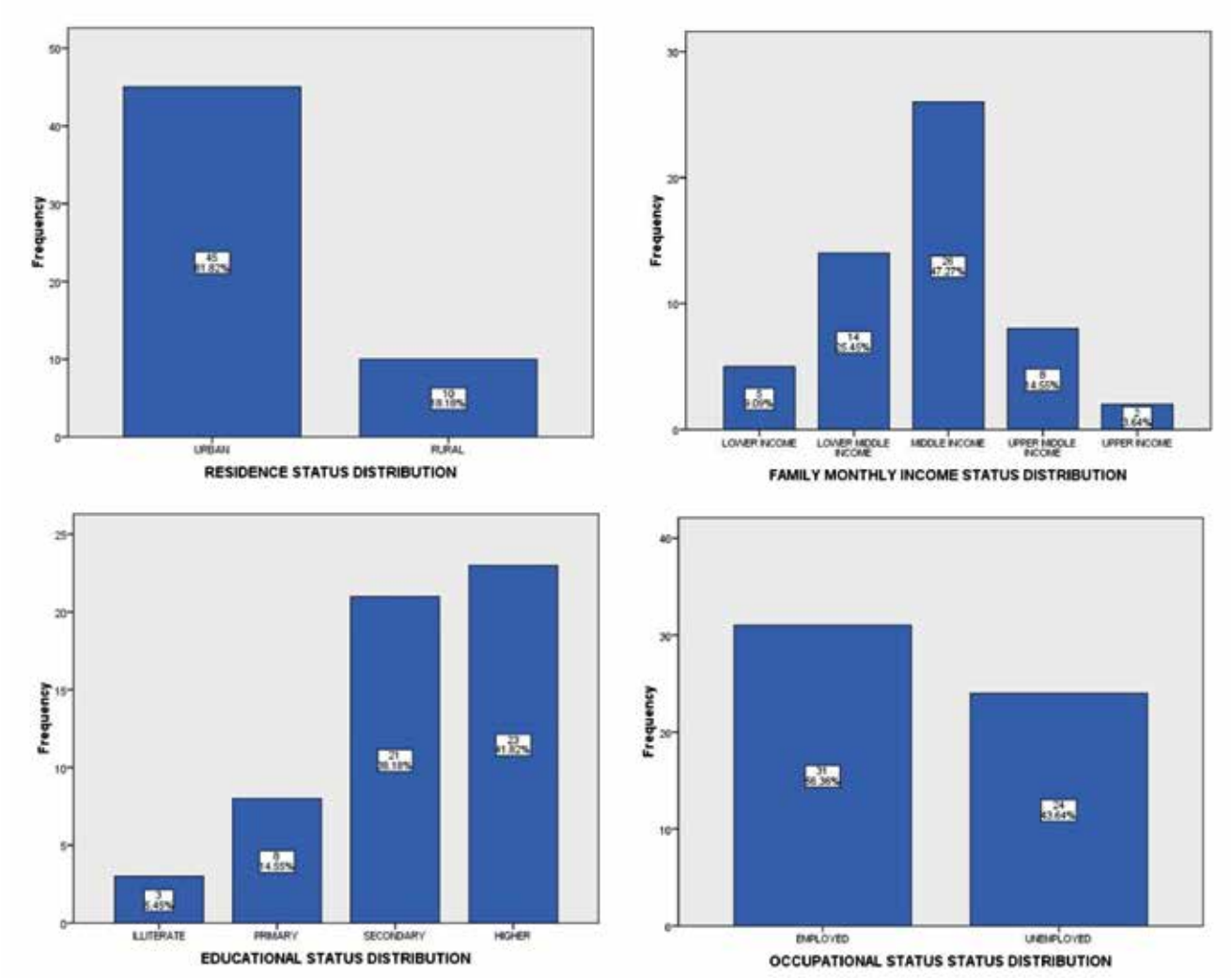

FIGURE 4. Distribution of residence, family income, educational and occupational status

chlorpromazine was started without titration, at a relatively high dose [22]. The administration of an anticholinergic agent for the treatment of extrapyramidal symptoms would be contraindicated if NMS had been considered, as anticholinergics may cause symptoms resembling NMS and may also be associated with the occurrence of delirium. Indeed, the patient developed delirium. This might have been a complication of the NMS itself, possibly precipitated or aggravated by the anticholinergic activity of biperiden [23].

The identification of early signs of NMS reflects on therapeutic actions, beginning by the suspension of the drug with antidopaminergic activity. The differential diagnosis can be difficult, mainly when presentations are not typical, and an evaluation of other clinical conditions, such as infections, inflammatory states, trauma, other neurological diseases etc., is mandatory. Acute extrapyramidal symptoms may be associated with secondary parkinsonism, serotonin syndrome, lethal catatonia, heart stroke, among other conditions, but they may also be associated with NMS, even without fever. We consider of most importance to expand the suspicion level of professionals, psychiatrists or not. The diagnosis of NMS in its classic presentation is not simple, and it becomes even more difficult in atypical situations. Considering the severity of the condition and its low incidence, we believe it is important to share experiences in order to raise awareness for the importance of early diagnostic suspicion of NMS. Its diagnosis shall be considered for every patient in use of antipsychotics who develop its clinical features, even if none of them are present at a same time.

CONCLUSION

Neuroleptic malignant syndrome (NMS) is a rare but potentially life-threatening side effect that can occur in response to treatment with antipsychotic drugs. Symptoms commonly include hyperpyrexia, muscle rigidity, autonomic dysfunction and altered mental status. Although NMS is a relatively infrequent condition, it requires timely and accurate diagnosis and treatment because of its life-threatening implications. Judicious use of antipsychotics

including cessation of rapid neuroleptization, better hydration of patients during titration of medication, avoiding use of multiple anti-psychotics simultaneously, and use of non-depot neuroleptics whenever possible, is warranted. Use of the newer atypical agents may also be considered.

Better recognition and monitoring of its symptoms by clinicians is needed, especially early on in the course of antipsychotic treatment and when switching from one antipsychotic medication to another, and alternative forms of pharmacological and non-pharmacological treatment for both the underlying psychosis disorder and NMS should be considered when patients present with NMS. Finally, in order to develop a better understanding of this serious condition and to improve care and service to patients and clients, clinicians should be encouraged to update public national databases so that all mental health practitioners may benefit from these experiences.

Conflict of interest: none declared
Financial support: none declared

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