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Age and Gender Specific Patterns of the Neuroleptic Malignant Syndrome

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Abstract

***Background:** Investigations of clinical correlates of the Neuroleptic Malignant Syndrome (NMS) may help to understand this phenomenon. This study examined age and gender related differences in NMS symptom patterns.*

***Method:** Archival data from medical journals and medical professionals were obtained on 233 patients with suspected NMS: 80 of these patients met the criteria for NMS according to DSM5. The sample contained more men (70.1%) than women (29.9%). The age ranged from 15 to 83 years, with the mean at 41.2 years (SD=16.9).*

The medication was known for 63 of the 80 patients: all were on the old antipsychotic medications, mostly on haloperidol (49.2%) and chlorpromazine (15.9 %). The frequent diagnoses were schizophrenia (30.3%), bipolar mood disorder (19.7%), and major depression (11.8%). The data file included frequencies of various clinical symptoms, vital signs, and results of laboratory tests.

***Results:** The following symptoms were recorded more often than in 12% of the 80 patients diagnosed with NMS by DSM5: decrease in level of consciousness (100% of patients), elevated creatine kinase (96.9%), tachycardia (94.0%), elevated WBC (93.8%), diastolic blood pressure above 89 (77.5%), systolic blood pressure above 139 (75.6%), autonomic dysregulation (77.5%), mutism (42.5%), tremor (33.8%), sialorrhea (21.2%), dysphagia (18.8%), stupor (17.5%), and urinary incontinence (16.2%). The patients' gender and age were not statistically related to any of these variables, except for a significant but weak correlation of gender with mutism (phi=.26, p=.025, 2-tailed): 60.9% of women, but only 33.3% of men displayed mutism.*

Numerous other symptoms and variables were evaluated, but were noted too infrequently, less often than in 12% in this sample, to be of relevance for the concept of NMS.

***Discussion and Conclusions:** Age and gender did not have a clinically important impact on the NMS symptom profiles. The high frequencies of lowered level of consciousness, elevated creatine kinase, tachycardia, elevated WBC, elevated blood pressure, autonomic dysregulation, mutism, tremor, sialorrhea, dysphagia, stupor, and incontinence are consistent with the existing clinical studies on the concept of NMS.*

Keywords: *neuroleptic malignant syndrome, antipsychotic medication, creatine kinase, sialorrhea, dysphagia, WBC, autonomic dysregulation*

Introduction

Neuroleptic malignant syndrome (NMS) is a rare but potentially fatal disorder characterized in the DSM5 manual [1] by three prominent symptoms: hyperthermia (temperature above 38° Celsius), muscular rigidity, and an intense diaphoresis. Various other symptoms are often, or at times, associated

with the NMS, including changes in mental status (e.g., delirium, altered consciousness), neurological symptoms (e.g., tremor, akinesia, sialorrhea, dystonia, dysphagia, dysarthria), changes in laboratory values (e.g., metabolic acidosis, hypoxia), and autonomic activation or instability (e.g., tachycardia, elevation or fluctuation of blood pressure, tachypnea, and pallor).

The NMS, if undiagnosed, can lead to fatal outcomes [2, 3]. Guidelines for the evaluation, management, and treatment of this syndrome were outlined by Velamoor in 2017 [2].

It is important to statistically investigate the various psychobiological correlates of the NMS [4]. To this date, almost all NMS studies have been carried out on extremely small samples or were published only in the form of case histories. Individual differences such as those based on gender or age in NMS symptom profiles may not be obvious from such case histories or small groups of patients, but need to be examined on larger samples in order to provide clinically relevant and reliable conclusions. Large data sets with measures potentially relevant in NMS research are not readily available because the incidence of NMS is rare: it is estimated at 0.02% to 2.23%, see a review by Velamoor [5].

The present study analyzed archival data extracted from available clinical scientific publications and also case data received from medical professionals: the goal was to statistically review NMS cases with respect to gender or age related differences in the NMS symptom profiles.

Materials and Method

Information on 233 suspected NMS cases was obtained from professionals across the USA and Canada and from medical journals. Only 80 of these patients showed temperatures over 38° Celsius, muscular rigidity, an intense diaphoresis, and also some of the associated conditions listed in the DSM5 manual [1]: they met the DSM5 criteria for NMS. All patients for whom medication information was available (63 of the 80) were on the old antipsychotic medications prior to developing the NMS, most frequently on haloperidol (49.2%) or chlorpromazine (15.9%), either alone or in combination with other older antipsychotics. None of these 63 patients were on newer antipsychotic medications.

The gender was accidentally left undocumented in the archival documentation on 3 of these 80 patients: the rest of the sample consisted of 54 males and 23 females. This reduced the number of patients in the data analysis on correlates of gender to 77 cases.

The age was adequately documented in 75 cases and ranged from 15 to 83 years, with the mean at 41.2 years (SD=16.9).

Psychiatric diagnosis prior to NMS was available for 76 patients. The diagnostic labels were often from the DSM4 or from older psychiatric manuals. Most frequent diagnoses were schizophrenia (30.3%), bipolar mood disorder (19.7%), and major depression (11.8%). Diagnostic information on the remaining patients was only in the form of brief notes by emergency staff in general hospitals such as follows: paranoid psychosis (N=2), atypical psychosis (N=1), unspecified psychosis (N=6), schizoaffective disorder (N=5), postpartum psychosis (N=1), Alzheimer (N=2), unspecified dementia (N=2), mental retardation (N=4), withdrawal from addiction (N=2), etc.

As already mentioned, the temperature of all 80 patients was above 38° Celsius (as one of the prerequisites for the DSM5 diagnosis of NMS): the range of the elevated temperature was from 38.1° to 42.2° Celsius, with the average at 39.6° (SD=1.0°).

Our statistical analyses of potential correlates of gender and age included vital signs (blood pressure, pulse, and respiration rate), laboratory measures (CKUL, WBC, PH, P-0_2, P-$C0_2$), and the following symptoms: dysarthria, dysphagia, focal dystonia, waxy flexibility, myoclonus, seizures, masked facies, bradykinesia, akinesia, cogwheeling, stupor, coma, obtundation, unresponsiveness, decrease in the level of consciousness, disorientation, drowsiness, incoherence, delirium, withdrawal, catalepsy, mobility, alertness, agitation, confusion, autism, autonomic instability, diaphoresis, sialorrhea, incontinence, and tremor. The importance of these variables has been discussed in Velamoor [2, 5] and in Velamoor et al. [4].

Some of these clinical variables have a distribution in which the values at both extremes are unhealthy. For example, blood pressure values are pathological if below or above the normal range. For this reason, we have transformed each of such problematic measures into two new variables: the first of these two new variables only included measurements on patients with the normal range values plus the upper pathological extreme (e.g., systolic hypertension) and

the second new variable included only measurements on patients with the normal range values plus the lower pathological extreme (e.g., pathologically low systolic blood pressure). This facilitated the statistical tests of the relationship of such variables to gender and age.

Statistical trends involving age are easier to detect in similar data if the age dimension is subdivided into several groups. We have divided the sample into 5 age groups: age 15 to 24 years (N=14), 25 to 34 years (N=17), 35 to 44 years (N=15), 45 to 60 years (N=17), and 61 to 83 years (N=12). The division into these age groups was determined mainly by the available frequencies: each subgroup should consist of at least 10 persons as a prerequisite for meaningful statistical analyses (for example, in the present sample, there would be only 6 persons if a group were formed above the age of 65 years to study the NMS in the elderly).

All patients were also evaluated by Caroff's system for diagnosing NMS [6]. To satisfy Caroff's diagnostic system for NMS, the following criteria must be met. Besides hyperthermia and muscular rigidity, the patient must display 5 or more of the following: change in mental status, tachycardia, hypertension or hypotension, tachypnea or hypoxia, diaphoresis or sialorrhea, dysarthria or dysphagia, tremor, incontinence, CPK elevation or myoglobinuria, leucocytosis, and metabolic acidosis [6]. Diagnostic criteria for NMS as specified by Caroff's system were met by 48 patients (mean age=43.2 years, SD=18.6; 33 males, 12 females, and 3 with undocumented gender), i.e., by 60% of the sample of 80 patients diagnosed with NMS by DSM5. The temperature of Caroff's NMS patients ranged from 38.1° to 42.2° Celsius with the average of 39.3° (SD=0.9°).

Results

Frequencies of Symptoms.

The abnormal symptoms or pathological measures that were present in at least 12% or more in the sample are listed in Table 1.

Table 1. *Frequent pathological symptoms (>12% of patients)*

Symptom:	Frequency - %	Number of persons for whom the measures or data were available:	Criterion:
Decrease in level of consciousness	100%	80	
Elevated creatine kinase	96.9%	64	>198 units per liter
Tachycardia (pulse)	94.0%	50	>100 /minute
Elevated WBC	93.8%	48	>11,000 per microliter
High diastolic blood pressure	77.5%	40	>89 mmHg
High systolic blood pressure	75.6%	41	>139 mmHg
Autonomic dysregulation	77.5%	62	multiple indicators
Mutism	42.5%	80	
Tremor	33.8%	80	
Sialorrhea	21.2%	80	
Dysphagia	18.8%	80	
Stupor	17.5%	80	
Urinary incontinence	16.2%	80	

Of course, hyperthermia, muscular rigidity, and diaphoresis were all present in all 80 patients because these three symptoms are the necessary requirements for NMS diagnosis by DSM5.

Tachypnea (more than 20 breaths per minute) was recorded in 9 (11.3%) of the 80 patients, however, it is feasible that this symptom remained unnoticed in some cases. The recorded tachypnea ranged from 24 to 40 breaths per minute.

Coma was reported in 9 (11.3%) of the 80 patients.

Confusion was reported only in 7 of the 80 patients, dysarthria in only 6, catalepsy in 5, drowsiness in 5, "masked facies" in 4, akinesia in 3, delirium in 3, bradykinesia in 2, lack of alertness in 2, being withdrawn in 2, disoriented in 2, obtunded in 1, agitated in 1, and cogwheel symptom in 1 of the 80 patients. No seizures were observed in the 80 patients.

With respect to laboratory measures, hypoxia (blood O^2<75mmHg) was recorded only in 3 patients and acidosis was reported in 2 of the 80 patients.

From a statistical perspective, meaningful statistical analyses of gender or age related differences can be carried out only on symptoms occurring in at least 10 patients and they cannot be carried out on symptoms absent only in less than 10 patients. This left only the following 8 variables for an investigation of the gender and age related trends: systolic blood pressure, autonomic dysregulation, sialorrhea, dysphagia, stupor, urinary incontinence, tremor, and mutism.

Relationships Involving Gender

As already mentioned, the gender was recorded for only 77 patients: 70.1% of these were men and 29.9% were women. Men seem overrepresented in this sample of patients diagnosed with NMS by DSM5.

It is noteworthy that the gender difference was less evident and not statistically significant in patients meeting Caroff criteria for NMS: 61.1% were men and 52.2% were women in Caroff's group (phi=.08, p=.614).

Further analysis explored the relationships of gender to the following 7 variables: autonomic dysregulation, sialorrhea, dysphagia, stupor, urinary incontinence, tremor, and mutism. No significant phi correlations between gender and these 7 variables were found, except for mutism (phi=.26, p=.025, 2-tailed): mutism was recorded somewhat less often men than in women.

The point biserial correlation of gender to systolic blood pressure was nonsignificant (r=.06, p=.589): in the calculation of this linear correlation, the data on persons with systolic blood pressure below 90 (N=3) was removed from the data set to leave only measures on patients with normal or with pathologically elevated values.

Relationships Involving Age Groups.

As already explained, the patients were divided into 5 age groups: age 15 to 24 years (N=14), 25 to 34 years (N=17), 35 to 44 years (N=15), 45 to 60 years (N=17), and 61 to 83 years (N=12). The following variables showed adequate frequencies for x^2 tests procedures across these five age groups: autonomic dysregulation, sialorrhea, dysphagia, stupor, urinary incontinence, tremor, and mutism. However, no significant differences among the 5 age groups on these variables were found (x^2 tests, p<.05).

The differences among the 5 age groups with respect to systolic blood pressure were nonsignificant in ANOVA (F(4,70)=0.750, p=.561); to calculate this ANOVA, the data on persons with systolic blood pressure below 90 (N=3) were removed from the data set to leave only data on patients with normal or with pathologically elevated values.

Discussion

The sample of patients with NMS diagnosis by DSM5 cases consisted of more men than women (70.1% of men versus 29.9% of women). The reasons for this trend are unclear. Male patients are generally treated with a higher dose of neuroleptics and thus may be more prone to NMS. The information on the dose of antipsychotic medication might be important in future NMS studies.

No significant gender or age related differences in NMS symptom profiles were found except with respect to mutism (men showed mutism less often than women), but while statistically significant, the underlying correlation was too weak to be useful for clinical predictions. In the summary, the age and gender do not seem to have any noteworthy impact on the NMS symptom profiles.

An important finding of this study is that the statistically recorded frequencies of the following symptoms were very low (< 12%) in this sample of 80 NMS patients: delirium, seizures, catalepsy, akinesia, dysarthria, "masked facies," drowsiness, confusion, bradykinesia, cogwheel, lack of alertness, and being withdrawn, disoriented, obtunded, or agitated. These too infrequent symptoms are presumably, at most, of only secondary importance in future NMS research. Similarly, abnormal laboratory measures other than those of creatine kinase were rare: hypoxia (blood O^2<75mmHg) was recorded only in 3 patients and acidosis was reported in 2 patients.

The main contribution of this exploratory study lies in statistically documenting that gender and age do not appear to have an important impact on symptom profiles of NMS.

References

[1] American Psychiatric Association. *Diagnostic and statistical manual of mental disorders, 5th edition*. Arlington, VA: American Psychiatric Association, 2013.

[2] Velamoor VR. Neuroleptic malignant syndrome: A neuro-psychiatric emergency: Recognition, prevention, and management. *Asian Journal of Psychiatry*. 2017; 29: 106-109. doi: 10.1016/j.ajp.2017.05.004.

[3] Zarrouf FA, Bhanot V. neuroleptic malignant syndrome: Don't let your guard down yet. *Current Psychiatry*. 2007; 6 (8): 89-95.

[4] Velamoor VR, Norman RMG, Caroff SN, Mann SC, Sullivan KA, and Antelo RE. Progression of symptoms in Neuroleptic malignant syndrome. *Journal of Nervous and Mental Disease*. 1994; 182 (3): 168-73

[5] Velamoor VR. Neuroleptic malignant syndrome: Recognition, prevention, and management. *Drug Safety*. 1998; 19 (1): 73-82.

[6] Caroff SN, Mann SC, Lazarus A, Sullivan K, MacFaden W. Neuroleptic malignant syndrome: Diagnostic issues. *Psychiatric Annals*. 1991; 21: 130-147.

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