SAS Journal of Medicine
Abbreviated Key Title: SAS J Med
ISSN 2454-5112
Journal homepage: https://saspublishers.com

OPEN ACCESS

Psychiatric

Atypical Presentations of Neuroleptic Malignant Syndrome: Diagnostic Challenge

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DOI: 10.36347/sasjm.2022.v08i11.004 | **Received:** 21.07.2022 | **Accepted:** 30.08.2022 | **Published:** 09.11.2022

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Abstract **Original Research Article**

Introduction*:** Neuroleptic malignant syndrome (NMS) is a rare, idiosyncratic, potentially fatal disease that can present with an atypical clinical picture that refers to subthreshold presentations of NMS. The aim of our study is to shed light on the atypical presentations of neuroleptic malignant syndrome by highlighting the different clinical and biological features of this entity that may be underestimated or confused with a differential diagnosis. ***Materials and Methods: A descriptive study that retrospectively studied the clinical characteristics and laboratory results of patients with a diagnosis of neuroleptic malignant syndrome; the patients were divided into two groups: typical malignant syndrome and atypicalNMS. All data were transferred and analyzed using SPSS 13.0 software. ***Results:*** The Amisulpride was the most frequently implicated drug (n = 36.6%), most patients were male (21 males versus 9 females). The majority of patients had psychosis, there were no statistically significant differences in terms of age, clinical and laboratory characteristics, but inthe atypical NMS group both gender were affected with comparable rates, more than half of the patients in the atypical NMS group had no rigidity with no fever and no disturbance of consciousness and creatine kinase (CK)values lower than those observed in the typical NMS group. The evolution was favorable in the atypical NMS group compared to the typical NMS group in which one death was noted and 5 patients were transferred to intensive care. ***Conclusion*:** Neuroleptic malignant syndrome is a fatal complication. Clinicians must be vigilant while carefully assessing the features of NMS in a patient on antipsychotics even in the absence of cardinal signs such as rigidity and fever. Furthermore, the need to adopt a spectrum concept of NMS to challenge the underdiagnosis and misdiagnosis of this fatal entity is of paramount importance.

Keywords: Neuroleptic malignant syndrome- Atypical presentations-neuroleptic- antipsychotics –diagnostic.

INTRODUCTION

Neuroleptic malignant syndrome (NMS) was first described in the late 1960s. It is a potentially fatal idiosyncratic drug reaction. It usually develops within the first 2 weeks of treatment, and can occur with long-term drug therapy. The incidence of NMS in developed countries has been reported to be approximately 2% of patients exposed to antipsychotics [1, 2].

The Second generation of antipsychotics were initially assumed to be safe from the risk of inducing NMS, based on their different pharmacological properties. Hypothesis have concluded that the so-called atypical NMS has emerged, presenting with different clinical features than those of NMS induced by first generation of neuroleptics [3]. Several sets of criteria have been proposed over time with subtle differences, the latest being established by the DSM 5 [4]. Furthermore there is a less discussed but equally important entity is that of atypical NMS, due to lack of validated criteria, clinicians have been at risk of missing the diagnosis of NMS, often attributing atypical presentations of NMS to other pathologies.

Few case reports have defined atypical NMS, as having at least the presence of three of the above four basic criteria [5, 6].

- Hyperthermia: (> 100.4 ° F / 38 ° C)
- Generalized rigidity.
- Vegetative disorders: (tachycardia, diaphoresis, elevated or fluctuating blood pressure, urinary incontinence, pallor).
- Changes in mental status (delirium, altered consciousness, ranging from stupor to coma).
- Elevated creatine kinase (at least four times the

upper limit of normal).

Objective

The aim of our study is to shed light on the atypical presentation of NMS by highlighting the different clinical and biological features of this entity that may be underestimated.

MATERIALS AND METHODS

It is a retrospective study spread over a period of 3 years, from January 2017 to December 2020, at the psychiatric university hospital Ar-razi of Salé Morocco, All patients older than 18 years and diagnosed with NMS according to DSM 5 criteria as well as the above-mentioned atypical NMS criteria were included. Patients with incomplete registration data and with an age below 18 years were excluded. The ethics committee of the scientific research unit approved the study.

The exploitation of the files was carried out via an exploitation form, studying the demographic characteristics, the existing diseases, the clinical and biological results, all the drugs used, the time of appearance of the SMN, the therapeutic management and the evolution. The cases were divided into two groups: the first group includes patients with typical malignant syndrome and the second group dedicated to patients with atypical NMS. All data were transferred and analyzed via SPSS 13.0 software.

RESULTS

The number of patients who developed NMS hospitalized from January 2017 to December 2019 was 30 patients, with an incidence of 0 .026%. The average age was 27.23.

Most of the patients were male, 21 men versus 9 women, the majority of patients had psychosis; schizophrenia (70%), schizo-affective disorder (6.6%), acute psychotic access (10%), bipolar disorder type I to (6.6%), dementia type Alzheimer and intellectual disability (3.3%).

The significant majority of cases were attributable to second generation antipsychotics (61.1%). Amisulpride was the most frequently implicated drug (36.6%) followed by risperidone (23.3%), olanzapine (6.6%) and aripiprazole (3.3%). One patient developed NMS during the same hospitalization with both amisulpride and risperidone.

The duration of NMS development ranged from the same day to approximately 20 days after administration of the offending agent. NMS was diagnosed in 19 patients between the third and the fifth day of treatment initiation and in eight cases after 6 day (Figure 1).

Most of the patients had gathered all the criteria of typical NMS according to the DSM 5 versus seven patients who presented an atypical clinical picture, the average value of CK was 1309.5 IU/L with a maximum value of 10299 IU/L (Table 2).

There were no statistically significant differences in terms of age, clinical and biological characteristics between the two groups, but in the atypical NMS group both gender were affected with comparable levels, rigidity was absent in three cases, fever was also absent in five cases, with the absence of both rigidity and fever in three patients, and the CPK values were relatively high but lower than those observed in the typical NMS group (Table 3).

The evolution was favorable in the atypical NMS group compared to the typical NMS group in which there was one death and 5 patients transferred to intensive care.

Table 1: Demographic and clinical characteristics of patients

Variable	**N**	**%**
Age	27 .23 (average)	
Gender	21H/9F	70H /30F
Diagnosis		
Schizophrenia	21	70
Schizo-affective	2	6 ,6
Bipolar disorder type I	2	6,6
Acute psychotic disorder	3	10
Dementia	1	3,3
Intellectual disability	1	3,3
1st generation neuroleptic		
Haloperidol	7	23,3
Chlorpromazine	5	16,6
2nd generation neuroleptic:		
Amisulpride	11	36,6
Risperidone	7	23,3
Olanzapine	2	6,6

aripiprazole	1	3,3
Amisulpride+ risperidone	1	3,3
Anxiolytics	9	30
Antidepressants	2	6,6
Thymoregulators:		
Sodium valproate	4	13,3
Carbamazepine	1	3,3

Table 2: Clinical characteristics of NMS in patients

Symptoms	**N**	**%**	**Symptoms**	**N**	**%**
Fever	25	83.33	Diaphoresis	18	60
Stiffness	27	90	Pallor	13	43.3
Tachycardia	27	76.6	Tachypnea	14	46.6
Blood pressure abnormality	23	9	Consciousness disorder	7	23.3

Table 3: Clinical, biological and therapeutic characteristics of the two groups

Variable	**Typical NMS (23)** **N %**	**Atypical NMS (7)** **N %**
Age	35,05	37
Gender	17H/6F	4H/3F
Symptoms:		
Fever	23 100	2 28,5
Rigidity	23 100	4 57,1
Tachycardia	22 95	5 71,4
Blood pressure	18 78,2	5 71,4
Diaphoresis	15 65,2	3 42,8
Pallor	11 47,8	2 28,5
Tachypnea	11 47,8	3 42,8
Consciousness disorder	7 30,4	0 0
Creatine kinase IU/L(average)	1484	852
Duration of initiation (days)	6.5(days)	5.1(days)
1st generation neuroleptic	6 26,08	
2nd generation neuroleptic		
Amisulpride	7 34,7	1 14,2
Risperidone	6 26,08	3 42,8
Olanzapine	3 13,04	2 28,5
Aripiprazole	-- --	-- --
Amisulpride+ risperidone	1 3 ,70	1 14,2
Taking charge		
Symptomatic	17 73,91	7 100
Intensive care	5 21,73	-- --
Deaths	1 3,70	-- --

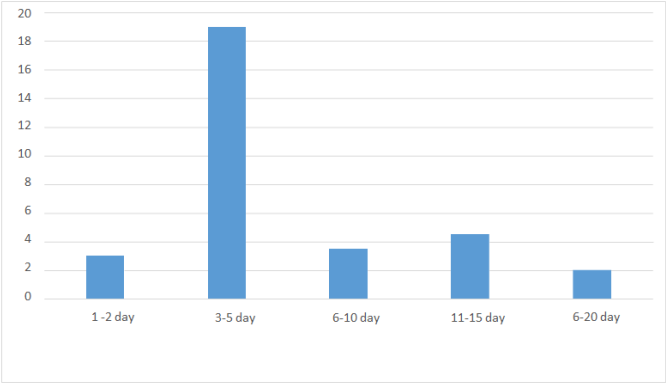

Figure 1: Number of patients versus duration of NMS initiation

DISCUSSION

The incidence of NMS in our study was 0.026%, which agrees with the results suggested in the literature with a value that varies between 0.024% and 3% [7]. In the past years, more than 12 sets of criteria have been proposed to determine NMS, each characterized by a type, a number of symptoms and by the differences in weight given to them to establish the diagnosis [8, 9], which affects the incidence of NMS reported in the literature.

In our sample, there was a male predominance of 70%, a high incidence in young people with a mean age of 27.23. This is consistent with the results of a meta-analysis, investigating sex and age as a risk factor for NMS, which concluded that males predominated in most estimates (75%) with an overall median sex ratio of 1.47 (95% CI, 1.20-1.80) and an incidence of NMS that peaks in the age range of 20-25 years [10]. However, there is no consensus in the literature regarding gender as a potential risk factor for NMS, although the general opinionopted for the idea that NMS is more common in men due to their denser muscle mass compared to women.

In our study, the characteristics of patients with atypical NMS were similar to those of patients with typical NMS in some aspects, however, rigidity was absent in three cases, fever was also absent in five patients with absence of both rigidity and fever in three patients, the majority of patients who presented with atypical NMS were on 2nd generation antipsychotics, mainly amisulpride and risperidone. The results of the literature suggest that in atypical presentationsof NMS, hyperthermia and muscle rigidity may be absent or develop slowly with less intensity [11]. In addition, several cases of NMS have been reported in the literature in which fever andrigidity were absent [12]. A German pharmacovigilance project found four cases of atypical NMS on amisulpride, without fever and rigidity with a CK elevation that ranged from 1, 498 IU/L to 21,018 IU/L. All four patients reported myalgia. In each case, CK returned to normal after cessation of amisulpride [13]. This could be explained by the particular pharmacodynamic profiles of amisulpride that may be associated with different presentations of NMS [14, 15].

A study published in 2000 which evaluated 164 cases of NMS found an absence of hyperthermia in 24% of cases with second-generation neuroleptics compared with 8% with first-generation neuroleptics. In addition, muscle rigidity was found in only 76% of cases with clozapine compared to 89% with olanzapine, 95% with risperidone and 91% with first generation neuroleptics [16]. These frustrated forms, which are mostly found with atypical neuroleptics, may lead to delays in diagnosis which may be life-threatening.

In addition, a study of 21 cases of risperidone-induced NMS in which temperature was recorded found, two patients did not develop fever throughout the syndrome [17]. In one case report, a patient reportedly presented with fever without any other signs associated with each administration of long-acting risperidone, the fever that did not regress was attributed to another pathology, CK measurement objectified high values [18]. Lack of muscle rigidity hasbeen described in case reports of NMS associated with clozapine, olanzapine, risperidone andaripiprazole [19, 20].

In the less discussed but equally important entity of atypical NMS, which refers to subthreshold presentations of NMS, due to the lack of well-defined validated criteria for atypical NMS, clinicians have been at risk of missing the diagnosis of NMS, often attributing atypical presentations of NMS to other pathologies [21].

In one case of olanzapine-induced NMS, the patient's body temperature fluctuated all the time, including the 10-day period during which the patient was febrile [22]. High-dose aripiprazole has also been reported to cause NMS without hyperthermia or with only moderate temperature elevations. NMS on aripiprazole was reported in another case report to present with diaphoresis, tremors, and elevated CK without fever or rigidity [23]. Perhaps the atypicality of the clinical presentation of NMS stems from the evolution of the syndrome with the advent of second generation antipsychotics. These observations have led to the hypothesis that "atypical" antipsychotics may determine "atypical" forms of NMS on the basis of different pharmacological properties [24]. This "atypical" presentations sometimes without cardinal signs could be explained by an earlier detection of NMS at the beginning of the prodromal phase, or before a syndromic presentation can occur, which generates the need to adopt a concept of NMS spectrum to challenge the underdiagnosis of this entity of fatal evolution [25].

The management of NMS is based on the cessation of the causative agent with hydration and sometimes intubation-ventilation, the prevention of thromboembolic events and the administration of specific agents such as dantrolene sodium, bromocriptine, and benzodiazepines that have been proven to be effective in the treatment of NMS [26, 27]. Mostof our patients who were managed in a psychiatric setting were treated with benzodiazepines, mainly diazepam. The literature supports the use of lorazepam, diazepam and clonazepam as treatments for NMS [22]. A stepwise approach based on NMS severity has been adapted by Strawn *et al*., [28] and Woodbury [29] to guide treatment with the most studied agents.

The evolution in the atypical NMS group in our study was favorable compared with the typical N²MS

group, which can be attributed to the early management of the syndrome and the vigilance of the clinician.

CONCLUSION

Neuroleptic malignant syndrome is a fatal complication. Clinician must be vigilant while carefully assessing the features of NMS in a patient on antipsychotics even in the absence ofcardinal signs such as rigidity and fever. Furthermore, the need to adopt a spectrum concept of NMS to challenge the underdiagnosis and misdiagnosis of this fatal entity is of paramount importance.

Study limitation:
Sample size.
Outpatients are not included.
Incomplete information in medical records

Links of interest: The author declares that he has no links of interest.

REFERENCE

1. Nielsen, R. E., Jensen, S. O. W., & Nielsen, J. (2012). Neuroleptic malignant syndrome—an 11-year longitudinal case-control study. *The Canadian Journal of Psychiatry*, *57*(8), 512-518.
2. Tural, Ü., & Önder, E. (2010). Clinical and pharmacologic risk factors for neuroleptic malignant syndrome and their association with death. *Psychiatry and clinical neurosciences*, *64*(1), 79-87.
3. Belvederi Murri, M., Bugliani, M., Calcagno, P., Respino, M., Serafini, G., Innamorati, M., ... & Amore, M. (2015). Second-generation antipsychotics and neuroleptic malignant syndrome: systematic review and case report analysis. *Drugs in R&D*, *15*(1), 45-62.
4. American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders (DSM-5®). *American Psychiatric Pub*, p. 22.
5. Caroff, S. N. (2003). Neuroleptic malignant syndrome: still a risk, but which patients may be in danger. *Curr Psychiatry*, *2*(12), 36-42.
6. Carroll, B. T., & Surber, S. A. (2009). The problem of atypical neuroleptic malignant syndrome: a case report. *Psychiatry (Edgmont)*, *6*(7), 45.
7. Morgan, C. N., & Rowe, R. (2003). The prevalence of neuroleptic malignant syndrome in learning disability. *Irish journal of psychological medicine*, *20*(3), 102-104.
8. Gurrera, R. J., Caroff, S. N., Cohen, A., Carroll, B. T., DeRoos, F., Francis, A., ... & Wilkinson, J. R. (2011). An international consensus study of neuroleptic malignant syndrome diagnostic criteria using the Delphi method. *The Journal of clinical psychiatry*, *72*(9), 9288.
9. Gründer, G., Hippius, H., & Carlsson, A. (2009). The'atypicality'of antipsychotics: a concept re-examined and re-defined. *Nature Reviews Drug Discovery*, *8*(3), 197-202.
10. Gurrera, R. J. (2017). A systematic review of sex and age factors in neuroleptic malignant syndrome diagnosis frequency. *Acta Psychiatrica Scandinavica*, *135*(5), 398-408.
11. Picard, L. S., Lindsay, S., Strawn, J. R., Kaneria, R. M., Patel, N. C., & Keck Jr, P. E. (2008). Atypical neuroleptic malignant syndrome: diagnostic controversies and considerations. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*, *28*(4), 530-535.
12. Strawn, J. R., Keck Jr, MD, P. E., & Caroff, S. N. (2007). Neuroleptic malignant syndrome. *American Journal of Psychiatry*, *164*(6), 870-876.
13. Tu, M. C., & Hsiao, C. C. (2011). Amisulpride and neuroleptic malignant syndrome. *Chang Gung Med J*, *34*(5), 536-540.
14. Gründer, G., Hippius, H., & Carlsson, A. (2009). The'atypicality'of antipsychotics: a concept re-examined and re-defined. *Nature Reviews Drug Discovery*, *8*(3), 197-202.
15. Horacek, J., Bubenikova-Valesova, V., Kopecek, M., Palenicek, T., Dockery, C., Mohr, P., & Höschl, C. (2006). Mechanism of action of atypical antipsychotic drugs and the neurobiology of schizophrenia. *CNS drugs*, *20*(5), 389-409.
16. Caroff, S. N., Mann, S. C., & Campbell, E. C. (2000). Atypical antipsychotics and neuroleptic malignant syndrome. *Psychiatric Annals*, *30*(5), 314-321.
17. Farver, D. K. (2003). Neuroleptic malignant syndrome induced by atypical antipsychotics. *Expert Opinion on Drug Safety*, *2*(1), 21-35.
18. Khouri, C., Planès, S., Logerot, S., Villier, C., & Mallaret, M. (2016). Case report: Neuroleptic malignant syndrome and diagnostic difficulties. *L'encephale*, *42*(3), 277-280.
19. Amore, M., Zazzeri, N., & Berardi, D. (1997). Atypical neuroleptic malignant syndrome associated with clozapine treatment. *Neuropsychobiology*, *35*(4), 197-199.
20. Spalding, S., Alessi, N. E., & Radwan, K. (2004). Aripiprazole and atypical neuroleptic malignant syndrome. *J Am Acad Child Adolesc Psychiatry*, 43, 1457-1458.
21. Singhai, K., Kuppili, P. P., & Nebhinani, N. (2019). Atypical neuroleptic malignant syndrome: a systematic review of case reports. *General hospital psychiatry*, *60*, 12-19.
22. Tibrewal, P., Bastiampillai, T., Kannampuzha,

C., Hancox, J., & Dhillon, R. (2017). Aripiprazole-induced neuroleptic malignant syndrome. *Asian Journal of Psychiatry*, *27*, 5-6.

23. Trollor, J. N., Chen, X., & Sachdev, P. S. (2009). Neuroleptic malignant syndrome associated with atypical antipsychotic drugs. *CNS drugs*, *23*(6), 477-492.
24. Abay, E., & Kose, R. (2007). Amisulpride-induced neuroleptic malignant syndrome. *The Journal of neuropsychiatry and clinical neurosciences*, *19*(4), 488-489.
25. Odagaki, Y. (2009). Atypical neuroleptic malignant syndrome or serotonin toxicity associated with atypical antipsychotics?. *Current Drug Safety*, *4*(1), 84-93.
26. Beaulne, C. (2006). Atypical neuroleptic malignant syndrome: clinical case. *Pharmactuel*, 39(1).
27. Pileggi, D. J., & Cook, A. M. (2016). Neuroleptic malignant syndrome: focus on treatment and rechallenge. *Annals of Pharmacotherapy*, *50*(11), 973-981.
28. Strawn, J. R., Keck Jr, MD, P. E., & Caroff, S. N. (2007). Neuroleptic malignant syndrome. *American Journal of Psychiatry*, *164*(6), 870-876.
29. Woodbury, M. M., & Woodbury, M. A. (1992). Case study: neuroleptic-induced catatonia as a stage in the progression toward neuroleptic malignant syndrome. *Journal of the American Academy of Child & Adolescent Psychiatry*, *31*(6), 1161-1164.