Research Article

NEUROLEPTIC MALIGNANT SYNDROME IN HIV-POSITIVE PATIENT. A CASE REPORT AND LITERATURE REVIEW.

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ABSTRACT: HWe report a 30-year-old and HIV-positive female patient who was on antipsychotic medication at the base hospital (Clopixol 200mg intramuscularly monthly, Risperidone 2mg orally daily, and Haloperidol 2.5mg orally twice a day) for psychosis and presented a neuroleptic malignant syndrome (NMS). She also received Lorazepam and sodium valproate. She was then referred to us because she had developed the upper limbs' involuntary movements and focal simple permanent focal seizure on the lower part of the left hemiface. Clinically she had altered consciousness, autonomic dysfunction, rigidity. Her blood tests showed elevated CK (1467U/L but no leucocytosis. We did a thorough workup for other causes of such a presentation. A comprehensive history was taken from the family to exclude other medications used. Her CSF results were on average. Blood tests did not show evidence of infection or other abnormalities. The CT brain was normal. We observe this type of seizure in HIV-female patient that usually die a few days after the beginning of the attack. For our knowlege, it is the first report about this comorbidity reported in the medical literature.

KEYNOTES:

Neuroleptic Malignant Syndrome, HIV, permanent focal simple motor seizure, elevated creatine kinase, neuroleptic side effects.

INTRODUCTION

Most authors define neuroleptic malignant syndrome (NMS) is a rare, yet life-threatening, idiosyncratic reaction to medications, mostly but not limited to neuroleptic drugs (dopamine receptor antagonists) [1-3]. Though fatal, it is potentially a treatable condition [4].

Initially described by Delay and colleagues in 1960, where they noticed it in patients treated with high-potency antipsychotics [5,6]. Though rare, every clinician must bear in mind that this is a significant differential to consider and that it is also a diagnosis of exclusion. One study conducted in 1986 discovered about 500 patients who were on neuroleptic, and about 1.4% clinically had NMS and had one fatally since it was not found in time [1].

Here we inform about a case of a young HIV positive woman whose history was not evident to us initially and had permanent focal seizures on the lower part of the left hemiface and features meeting the Leveson's and DSM IV criteria for NMS. She then demised on the third day of admission. This cluster of presentation is for the first time published in the literature.

CASE

A 29-year old female with a past medical history of chronic psychosis and agitated behavior. For the past three months, she was admitted to the Level One regional hospital because she presented with a sudden onset of confusion, restless behavior: jumping fences and foul language, palpitations, delusions of persecution, and anxiety. She also complained of tachycardia, diaphoresis, and urinary disturbances. She received Clopixol 200 mg IM monthly, Risperidone 2 mg PO nocte, Lorazepam 2.5 mg PO nocte, Valproic acid 600 mg PO twice, and Haloperidol 2.5 mg twice a day during this hospitalization. Laboratory tests revealed Hb 11 g/dL, ESR: 42 mm/hr, creatine kinase 3049 U/L, creatinine 96 µmol/L, Alanine transaminase 47 U/L. CSF was normal.

On Jun 11, 2020, the patient came to the Neurology OPD of Nelson Mandela Academic Central Hospital in Mthatha, South Africa. She is admitted due to altered mental status, permanent partial simple myoclonic seizure on the left lower hemiface, and the upper limbs' involuntary movements. On examination, her blood pressure was labile (129/79–154/112 mm Hg-158/112 mm hg), she had tachycardia (119 beats/minute), and mild dehydration. She also was fully conscious but disorientated to place and time with generalized muscle rigidity characterized by bilateral cogwheel signs at the wrist level and lead pipe signs on both elbows and knee level. Bilateral resting tremors of the upper limbs with focal simple myoclonic seizures on the left lower face. Decreased muscle strength on four limbs, more remarkable on the lower limbs (3/5), normal deep tendon reflexes, and generalized myalgias on palpation. On the second day of admission, we were unaware of her previous treatments (especially the neuroleptics). The patient presented a temperature: 40.5oC; then, based on her clinical picture and follow up with the family by the social workers on her previous medications, the diagnosis of Neuroleptic Malignant Syndrome was made. She was started on Orphenadrine 50mg PO 8 hourly, L-dopa and Carbidopa 125 mg orally eight hourly, and Bromocriptine 5 mg loading dose then 2.5 mg three times daily.

On hematological investigations: white cell count: 7.59 x 109/L, ELISA test for HIV: positive, she also has creatine phosphokinase (CPK): 1,467 U/L, Vitamin B12:579 pmol/L, Toxoplasmosis ELISA: negative, VDRL non-reactive, Ferritin: 2136 ng/dL, Iron: 2.2 µmol/L, transferrin: 1.32 g/L, % saturation 10%, blood sugar was regular, hepatitis B surface ag: negative, urea: 8.6 µmol/L, creatinine 112 µmol/L, alkaline COVID-19 test by PCR was negative, average CSF results. Other blood test results (including CD4 and viral load) did not arrive during admission time. CT scan of the head is complete normal, and on the third day of hospitalization, the patient died. Her family rejected the post-mortem examination.

COMMENTS

Here we comment on a 30-year-old female, HIV positive, initiated on antipsychotic medication at the base hospital (Clopixol 200mg intramuscularly monthly, Risperidone 2mg orally daily, and Haloperidol 2.5mg orally twice a day) for psychotic symptomatology. She was also started on Lorazepam and Valproic acid and developed NMS clinical manifestations, as can be seen below.

Epidemiology of NMS

Our literature review showed three different studies collecting

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epidemiological data on NMS. One study showed an incidence of 1.4% in 500 patients [7]; this study also reported one fatality, and a delay is often reaching the diagnosis. Another 1.4/1000 over three years [4], the mortality rate was 14.28%, with 28% developing NMS after antipsychotic medication. The third study was in Turkey from 1985 to 2005 and had 36 patients; in this study, 22% developed NMS after the antipsychotic drugs [8].

Risk factors

- Age and sex do not have much of a role.
- No specific neuropsychiatric conditions can predispose one to NMS; however, more catatonia cases have shown a propensity to progress to NMS.
- Other systemic factors include agitation, restraint, and exhaustion.
- Metabolic factors such as dehydration and low serum iron have shown to predispose
- Drugs like dopamine antagonists and high potency antipsychotics more than low potency and atypical antipsychotics [9,10].

Causative agents

The primary trigger is dopamine receptor blockade, and that the causative agent is an antipsychotic. The sudden cessation/ reduction in the dosage of dopaminergic medications also precipitates NMS. Other drugs that are not neuroleptic but have antidopaminergic activity have also been implicated in NMS's causality. Please see (Appendix A) below.

Clinical presentation

The clinical presentation is usually with the four so-called cardinal features described by the earlier authors viz, hyperthermia, muscular rigidity, autonomic instability, and altered consciousness level. However, many authors have reported atypical presentations to this syndrome.

Hyperthermia of > 38oC associated with profound diaphoresis is present in almost all the cases reported and seemed to be one of the most unifying factors in the different diagnostic criteria to be discussed below [12]. Fever can be of late-onset and eventually increase fatality, as the diagnosis is missing due to the lack of fever.

The rigidity is commonly present as lead pipe/cogwheel signs [13]. It is also often associated with other neurological symptoms like tremors, sialorrhea, akinesia, dystonia, and dysphagia.

The laboratory findings can help rule out other causes such as substance abuse and other systemic neurological or psychiatric conditions. Despite the list below being the most expected findings listed in the literature, none are specific to NMS [11,13]:

- FBC will show elevated white cell count, leucocytosis
- ABG and U/E will show Metabolic acidosis
- Elevated CK
- Elevated Serum Muscle Enzymes – lactic acid dehydrogenase, transaminases
- Elevated Serum Catecholamines - aldolase
- Decreased Serum Iron levels

The above could lead to myoglobinuria and subsequent renal failure. CSF analysis is usually standard, approximately 95% of the time [1]. Imaging studies like CT brain and MRI show unremarkable findings [1]. The EEG recording shows features akin to those of metabolic encephalopathy [1].

Diagnosis

Reaching NMS diagnosis is not easy, as much of the disease mimics many other conditions. However, the psychiatric and neurology society has come up with different means viz the APA DSM-4/5, the WHO ICD-10, and the Caroff-Mann criteria from 1993. One widely accepted is the Levenson's criteria, proposed in 1985, which has major and minor criteria for the diagnosis. Major Criteria: involve fever, rigidity and elevated CK, and Minor Criteria: labile BP, tachypnea, altered consciousness, leucocytosis. According to the author, all 3 of the major, or two major and four minor criteria met to diagnose NMS to be made [14].

According to the ICD-10, it is a fatal disease associated mainly with neuroleptic agents accompannied by dopaminergic receptor blockade in the lentiform nucleus, thalamus, head of caudate nucleus and hypothalamus with autonomic dysregulation.

Caroff and Mann postulated the following list [15].

1. Hyperthermia
2. Muscle rigidity
3. Use of neuroleptics within the last seven days.
4. Any 5 of the following:

a. Altered mental status

b. Tachypnea

c. Hypertension

d. tachycardia

e. hypotension

f. incontinence

g. diaphoresis

h. sialorrhea

i. elevated CK

j. myoglobinuria

k. leucocytosis

5. Absence of any other drug-induced, systemic, or neuropsychiatric disorder.

DSM IV is shown in Table 2 (APPENDIX A) below [13].

Though many authors and clinicians have often not found common ground in the diagnostic criteria, [16] showed agreement was best between IEC criteria with a cut-off score of 74 and modified DSM-IV-TR criteria (sensitivity 69.6%, specificity 90.7%); this cut-off score demonstrated the highest agreement in all comparisons.

The sequelae of the condition usually happen after the initiation of neuroleptic drugs (or dopaminergic drugs). In about 16% of patients, the NMS symptoms showed within 24 hours; in another two thirds, it showed up within one week, and almost all cases were showing at one month. Beyond a month, it is unlikely for the symptoms to start showing unless there has been an increase in the drugs' current dose [1].

Differential diagnosis

The differential diagnosis can broadly be divided into systemic causes: Environmental, Endocrine or infections, Toxic/Pharmaceutical agents, Psychiatric/Neurological causes [1,11]. We discuss examples and distinguishing features in (Appendix A).

Pathophysiology

The actual pathophysiology of NMS is still unproven, but there are some hypotheses like

1. The antipsychotic-induced dopamine blockade does play a key role in triggering NMS [17].

It can be evidenced by the presentation of symptoms when initiating antipsychotics or stopping the dopaminergic medications. Also, all the other reported drugs that have precipitated NMS have been dopamine receptor blocker medications. The decreased levels of homovanillic acid (HVA), a CSF metabolite of dopamine, also support this theory [18].

1. Sympathoadrenal dysfunction has a contributory role in NMS [19].

2. A low serum iron concentration can be a contributory factor in that it decreases the no of dopaminergic receptors and thereby leaving patients susceptible to developing NMS. It has been evidenced by finding low serum iron in patients with NMS [20].

3. Multiple neuroendocrine and neurochemical dysregulation cascade can lead to this hypermetabolic syndrome [1].

Figure 1 (Appendix B) shows an excellent composite aggregation of the many postulated theories.

Management

NMS should be considered an emergency by all managing physicians, and attending doctors should apply an urgent treatment, even if the diagnosis is in doubt [11].

There have been no systemic trials or studies conducted towards the best management protocol for the condition, mostly due to its rarity. Still, based on the many case reports, the following seem to be the most effective guidelines postulated.

As always, and as with any medical condition, the treatment is a priority tailored to the clinical setting and the patient, but the consensus is still the first step.

1. Cessation of the causative neuroleptic medication or if the NMS is because of withdrawal of a particular dopaminergic drug, then restart it as soon as possible.

2. The next step is supportive therapy:

a. Aggressive rehydration

b. Management of hyperthermia

c. Management of any complications

i. Cardiopulmonary failure

ii. Seizures

iii. Arrhythmias

3. As the severity of the condition worsens, empirical medication has to be used [1,11].

. Bromocriptine Mesylate- a Dopamine Agonist, is used to reverse the hypodopaminergic. The starting dose of 2.5mg per os is eight to 12 hours and increases the quantities by 2.5mg every 24hours. The maximum amount of 45mg/day. It should be for at least ten days when the NMS has been caused by oral neuroleptics and about 2-3 weeks where depot preparations denote the cause.

a. Dantrolene Sodium – muscle relaxant that inhibits calcium release from the sarcoplasmic reticulum. Starting dosage is 1- 2.5mg/kg iv bolus, then followed by 1mg/kg every 6 hours. Maximum dose of 10mg/kg/day. Oral dantrolene can be used in other less severe cases or when tapering down from the IV form. Dosages of 50 -200mg/day. The dantrolene s discontinue as soon as symptoms start to improve, as it is associated with a high risk of hepatic toxicity.

b. Other dopaminergic agents have been reported in studies and are worth mentioning here: amantadine hydrochloride [21], levodopa [22], and apomorphine [23].

c. Additionally, many clinicians have to use benzodiazepines for controlling agitation [24].

d. In patients no responding to the above empirical management, as second-line treatment, many have reported the use of electro convulsant therapy (ECT) [25].

There is always a challenge when restarting the neuroleptic medications for the patients that need continuous treatment, especially regarding the recurrence of the NMS. The literature consensus is that the drug should reinitiate in the lowest possible dose, with reasonable precaution been taken and close monitoring after about two weeks of recovery from an NMS episode in oral neuroleptics and about six weeks for depot preparations. However, many authors opine the use of different neuroleptic medication; we must bear in mind that this is an idiosyncratic disease [11].

An algorithm adapted from Woodbury and Woodbury, which appeared to be an invaluable tool in NMS management [1,26], is shown in (Appendix A).

Complications

There have been other medical reports of cases where NMS has had atypical presentations and unexpected comorbidities [12].

In one large study comprising of 1346 patients from 2002 to 2011, the authors report the commonest complication to be Rhabdomyolysis (30.1%), Acute Kidney Injury (17.7%), Acute Respiratory Failure (16.1%), and Sepsis (6.2%). Mortality rate was at 5.6% [27]. Hypoxemia and hemoconcentration that follow NMS predispose patients to cerebral infarction [28]. The use of neuroleptics in trauma centers for burn victims has precipitated NMS [29]. The complications can include dehydration, electrolyte imbalances, cardiac arrhythmias, aspiration pneumonia, myocardial infarction, deep venous thrombosis, and disseminated intravascular coagulation. So, it is especially important to have close monitoring of patients.

A morphometric study of cardiac patients conducted by other authors spoke about neuroleptic cardiomyopathy (NCMP) and patients who died from NMS. They described the damage in those patients' myocardium due to an acute process that involved disturbances in microcirculation, interstitial edema, and dystrophic degenerative changes of cardiomyocytes (CMC) [30]. The severity of the myocardium damage in NMS is directly dependent on the NCMP, NMS, and HIV.

The incidence of NMS is high in HIV patients; the consensus is that it is so because of the changes that occur to the brain structure either from opportunistic infections secondary to HIV or to the HIV itself. These have increased the possibility of patients developing NMS [31]. However, it has not been easy to get a thorough picture of the epidemiology since many NMS symptoms also fall under symptomatology caused by other opportunistic infections [32]. Nausea, vomiting, psychotic symptoms, agitation are all commonly seen in patients with HIV, and usually, many clinicians use neuroleptics to treat these symptoms(33).

Haloperidol is the most frequently associated medication with NMS. The main clinical signs were hyperthermia, rigidity, altered consciousness level, and autonomic disturbances. Below, Figure 2 (Appendix B) shows a self-explanatory diagram about the extrapyramidal reactions found in some patients and an algorithm adapted to the management of patients with NMS and HIV [33].

NMS and COVID-19

There are scanty publications about the presence of NMS and the COVID-19 disease, in whichever stage. However, some authors reported that two of their patients on the ventilator due to the severe acute respiratory distress syndrome (ARDS) had developed delirium when they received benzodiazepine and neuroleptics. They subsequently developed NMS, which was managed and

resolved [34].

Other authors also reported a case with developed NMS, but the only causative agent they found was haloperidol given three weeks before the onset. An autopsy done showed a hyperemic and edematous brain. So unclear if COVID-19 itself can bring about changes that would lead to NMS due to changes it causes to the brain [35].

OTHER COMMENTS

Our patient meets the criteria by Levenson and the DSM IV criteria for NMS [36]. She developed NMS most likely due to the administration of antipsychotic medication and secondary to an idiosyncratic reaction. It occurs a few weeks after initiation, but it can occur even if the patient has been taking the drug for months to years [37]. In our patient's case, she had been on oral risperidone and haloperidol and the depot preparation of Clopixol for about eight weeks.

Her risk factors for developing NMS were the fact that she was on three different antipsychotic medications; she was HIV positive (new diagnosis, previously unknown), including low serum iron levels in the blood: also reported by other authors [38]. We want to highlight that she presented typical signs and symptoms for NMS and had elevated CK.

It would be prudent to know that this case presented to us as we were dealing with the COVID-19 pandemic. We weren't privy to psychiatric history at the time of admission, so NMS's diagnosis was made one day after entry. We had the social workers track the family members for a thorough history and medication details. The Delay was not intentional, but she had what seemed like an atypical presentation. It was not evident by the presence of a plethora of symptoms suggestive of pathology involving COVID-19 and the CNS.

The recommendations for treatment of NMS currently are based on case reports and clinical experience. There is no published clinical trial up to date. NMS treatment recommendations are as discussed earlier: 1. stop causative agents, 2. aggressive supportive care (rehydration, treat hyperthermia, and other complications) and 3. specific medical therapy.

Our patient had a mild pre-renal injury, but blood results did not show the development of the other mentioned complications.

In our medical practice, we have treated a small group of HIV-female (N=5) with low CD4 count levels presenting with permanent focal simple motor seizures affecting the lower part of the face with a few days duration without other comorbidities followed by an unexpected death. We do not know the cause of death of this mentioned non-reported patients, but we are sure that it is the first time that NMS and this type of seizures in HIV patients occur in our region.

FINAL REMARKS

This young HIV-positive female patient died because of NMS preceded by the intake of typical/atypical neuroleptics. Apart from her altered consciousness, autonomic disturbances, extrapyramidal signs, and high fever, she also presented permanent focal simple motor seizures on the lower hemiface. After reviewing our available medical literature, we found no similar case reported in the medical literature.

ABBREVIATIONS

ABG – Arterial Blood Gas

APA DSM– American Psychiatric Association Diagnostic and Statistics Manual of mental disorders

ARDS – Acute Respiratory Distress Syndrome

BP – Blood Pressure

CK – Creatinine Kinase

CPK – Creatinine Phosphokinase

CMC – Cardiomyocytes

CSF – Cerebrospinal Fluid

CT- Computed Tomography Scan

EEG – Electroencephalogram

ELISA – Enzyme-Linked Immunosorbent Assay

ESR – Erythrocyte Sedimentation Rate

FBC – Full Blood Count

HIV – Human Immunodeficiency Virus

HVA – Homovanillic Acid

IEC – International Expert Consensus

IV – Intravenous

Kg – Kilogram

mg – Milligrams

MRI – Magnetic Resonance Imaging

NCMP – Neuroleptic Cardiomyopathy

NMS – Neuroleptic Malignant Syndrome

OPD – Outpatient Department

U/E – Urea and Electrolytes

WHO ICD 10- World Health Organisation International Classification of Diseases 10th revision

Declaration

Patient Perspective: unfortunately, our patient passed away.

Consent: We obtained written permission from the family of our patient.

Potential conflicts of interest: All authors reported no conflicts of interest.

Source of Support: None.

Authors Contributions: All authors contributed equally to the elaboration of this manuscript.

Declaration of anonymity: All authors certify that they did not reveal names, initials, and other identity issues of this patient in this publication, and complete anonymity is guaranteed.

Statement of Ethics: Walter Sisulu University Ethical Committed considered that ethics approval is not necessary for this case.

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