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Management of a Patient with Neuroleptic Malignant Syndrome

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ABSTRACT

Neuroleptic Malignant Syndrome (NMS) is a rare but potentially fatal condition primarily induced by antipsychotic drugs, characterized by symptoms such as hyperthermia, muscle rigidity, altered mental status, and autonomic dysfunction. The complexity and limited understanding of its pathophysiology, combined with a high mortality rate of 20-30% if untreated, pose significant challenges for timely diagnosis and management. This study presents a case report of a 56-year-old male patient admitted with decreased consciousness, muscle rigidity, and high fever, who was diagnosed with NMS. The methodology involved detailed clinical observation, laboratory monitoring, and intensive care management. Treatment included the immediate cessation of offending antipsychotics, supportive care with fluid resuscitation and electrolyte correction, and administration of medications like dantrolene and bromocriptine to alleviate symptoms. The patient's gradual improvement highlights the effectiveness of early detection, multidisciplinary intervention, and individualized therapy. This case underscores the importance of clinical vigilance and education among healthcare professionals to recognize early warning signs and initiate prompt treatment, significantly reducing mortality and improving recovery outcomes. The study advocates for further research to develop standardized clinical guidelines to optimize diagnosis and therapeutic approaches for NMS.

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INTRODUCTION

Neuroleptic malignant syndrome (NMS) is a rare and life-threatening complication of antipsychotic therapy that may occur hours or weeks after drug administration (Guinart, Taipale, et al., 2021; Oruch et al., 2017; Wadoo et al., 2021). It has also accompanied the abrupt withdrawal of medication for Psychotic disorder (Larsen-Barr et al., 2018; Vinkers et al., 2024). Meperidine and metoclopramide can also precipitate the disorder. The mechanism is related to dopamine blockade in the basal ganglia and hypothalamus and impairment of thermoregulation.

In its most severe form, the presentation is similar to malignant hyperthermia (Mann et al., 2008). The neuroleptic malignant syndrome is a severe idiosyncratic reaction, commonly occurring in response to the use of potent psychotropic agents (Orsolini & Volpe, 2025). Less commonly, it occurs following the administration of low-potency psychotropic agents or the rapid withdrawal of dopaminergic medications. This is characterized by high fever, altered mental status (AMS), severe muscle rigidity, and signs of autonomic dysfunction. Leukocytosis and elevated serum creatine phosphokinase are common laboratory findings (Paul et al., 2022).

NMS is associated with drugs that influence dopamine-mediated synaptic transmission in the brain. A decrease in dopaminergic transmission in the basal ganglia and hypothalamic-pituitary axis may be responsible for many of the clinical manifestations of NMS. NMS can be the result of therapy with drugs that inhibit dopaminergic transmission or can be triggered by discontinuing drugs that facilitate dopaminergic transmission. The drugs most frequently implicated in NMS are *haloperidol* and *fluphenazine*. The incidence of NMS during therapy with neuroleptic agents is reported at 0.2– 1.9% (Marino, 2014).

There is no relationship between the intensity or duration of drug therapy and the risk of NMS, so NMS is an idiosyncratic drug reaction and not a manifestation of drug toxicity (Amal et al., 2022; Wu et al., 2023). There is some evidence of a familial tendency, but a genetic pattern of transmission has not been identified (Puspita et al., 2024). Due to its rarity and high mortality rate, it is important to understand the definition, causes, diagnosis, and management of NMS.

Neuroleptic Malignant Syndrome (NMS) is a rare and life-threatening condition often caused by the use of antipsychotic medications (Martin & Martin, 2016). NMS is characterized by symptoms such as hyperthermia, muscle rigidity, and altered mental status, which can be fatal if not addressed promptly (Strus et al., 2024). This issue becomes increasingly complex due to a lack of in-depth understanding regarding the mechanisms behind NMS and its management, potentially raising mortality rates among affected patients (Cooper et al., 2024; Yadav, 2024).

Neuroleptic Malignant Syndrome (NMS) is a complex condition with multifactorial pathophysiology that is not yet fully understood (Caroff et al., 2021). Beyond dopamine blockade in the central nervous system, inflammatory processes and acute phase reactions are suspected to contribute to the clinical manifestations of NMS. Studies have shown that low iron levels are associated with increased risk of NMS, indicating that metabolic and immunological factors should also be considered in the management of this syndrome. Therefore, a comprehensive and multidisciplinary therapeutic approach is necessary to improve patient outcomes.

The primary management of NMS involves the immediate discontinuation of the offending agents and the initiation of intensive supportive care. Fluid resuscitation and electrolyte correction are essential to prevent complications such as acute kidney injury due to rhabdomyolysis. In addition, specific medications like dantrolene and bromocriptine can alleviate muscle rigidity and restore dopaminergic balance. However, optimal dosing and duration of therapy must be tailored to the individual patient's clinical condition.

Severe complications of NMS, including cardiac arrhythmias, respiratory failure, and renal impairment, are significant causes of mortality in affected patients. Hence, continuous monitoring of vital signs, organ functions, and laboratory parameters is crucial in intensive care.

A multidisciplinary team involving neurology, psychiatry, nephrology, and rehabilitation specialists is vital to deliver comprehensive care.

Prevention of NMS is equally important in managing patients receiving antipsychotic treatment. To mitigate risk, close supervision of drug dosages and regimen changes, and educating patients and families about early warning signs are necessary. Moreover, choosing safer antipsychotic agents and careful dose titration can significantly reduce the incidence of NMS.

Although NMS is a rare syndrome, it demands high clinical vigilance, especially during the initial phase of antipsychotic therapy. Early recognition and prompt intervention can reduce mortality rates and facilitate faster recovery. Further research is needed to develop more specific and effective clinical guidelines for diagnosing and managing NMS.

In conclusion, Neuroleptic Malignant Syndrome is a serious neurological emergency that requires rapid diagnosis and immediate treatment. Multidisciplinary collaboration and enhanced clinical awareness are essential to optimize patient care. Additionally, the ongoing collection of epidemiological data and case reports will improve the understanding and management of NMS in the future.

The high mortality rate associated with NMS, reaching 20-30% if left untreated, underscores the importance of early detection and appropriate treatment to improve patient outcomes. Given the increasing number of patients receiving antipsychotic therapy, there is an urgent need to enhance awareness among healthcare professionals regarding the early signs and effective management strategies for NMS. This urgency is amplified by the growing patient population at risk of developing NMS due to the widespread use of antipsychotic drugs.

Furthermore, as the utilization of antipsychotic medications rises among individuals with mental health disorders, research into the factors influencing NMS occurrence and its management strategies becomes imperative. This study aims to significantly contribute to developing better clinical guidelines for handling NMS, thereby reducing mortality rates and improving patient care.

Prior research has highlighted that NMS is frequently observed in patients treated with antipsychotic drugs, particularly haloperidol and fluphenazine. A study by Puspita et al. (2024) emphasizes the importance of early detection of NMS symptoms and suggests that healthcare providers must be more vigilant in identifying this condition. Additionally, research by Touzani et al. (2021) indicates that appropriate management can mitigate the severity and mortality of NMS, although many clinical practices have yet to adopt these guidelines.

Another study by Guinart et al. (2021) found that predisposing factors could increase the risk of NMS, including the use of combined antipsychotic medications and abrupt dosage changes. This research highlights the need for closer monitoring of at-risk patients, although the implementation of such practices remains suboptimal in many healthcare settings.

Moreover, there is a lack of research examining the differences in treatment outcomes for NMS with varied therapeutic approaches. This gap suggests that much remains to be learned about the effectiveness of existing interventions and how management strategies can be optimized to improve patient outcomes.

While there is existing research on NMS, there is a notable gap in studies that comprehensively link the various causative factors and treatment approaches. Many studies

focus on singular aspects, such as medication or causes, without considering the interactions among multiple factors that can holistically influence the occurrence and management of NMS.

This research offers a novel approach by analyzing the relationship between various risk factors, such as the type of antipsychotic medication, dosage, duration of use, and different therapeutic interventions to manage NMS. By focusing on clinical experiences and treatment outcomes, this study aims to provide deeper insights that can be applied to improve NMS management.

This study aims to analyze the factors associated with the incidence of Neuroleptic Malignant Syndrome and evaluate the effectiveness of different treatment methods in improving patient care outcomes.

This research will provide valuable information for healthcare professionals to recognize, diagnose, and manage NMS more effectively. The findings are expected to serve as a reference for developing clinical guidelines and raising awareness about the importance of proper management of NMS, ultimately reducing mortality rates and enhancing the quality of patient care.

RESEARCH METHOD

Based on the document you provided, the research type used is a case report. This study details the management of a 56-year-old male patient diagnosed with Neuroleptic Malignant Syndrome (NMS). The approach involves a thorough clinical observation of the patient's condition, medication history, physical examination, laboratory findings, and medical treatment during hospitalization, especially in the intensive care unit (ICU). The report aims to illustrate the clinical presentation, therapeutic interventions applied, and patient outcomes.

The method employed includes longitudinal clinical observation, monitoring vital signs, laboratory parameters, and the patient's response to treatment. Key therapeutic strategies involved the immediate discontinuation of causative antipsychotic drugs, intravenous fluid resuscitation, electrolyte correction, and administration of medications such as dantrolene and bromocriptine to alleviate muscle rigidity and restore dopaminergic balance. Supportive care and management of complications like pneumonia and acute kidney injury were also part of the treatment protocol.

This patient management approach is multidisciplinary and tailored individually based on the patient's clinical status, with close monitoring in the ICU setting. The study emphasizes the critical importance of early detection, prompt withdrawal of triggering medications, and intensive supportive therapy to reduce the high mortality rate associated with NMS. Additionally, it highlights the need for heightened clinical awareness among healthcare professionals to recognize and appropriately manage this potentially fatal syndrome.

RESULT AND DISCUSSION

Case Report

Patient Identity

Patient Name	: Tn. S
Age	: 56 years old
Sex	: Male
Religion	: Islam

Address : Pekanbaru
Marriage status : Married
Medical Record : 08.46.066
Time admitted to hospital : 18/10/2022

The patient was admitted with decreased consciousness ±48 hours before being admitted to the Hospital. The patient came with an unconscious condition brought by the patient's family, with the condition of the eyes looking up, a stiff body, and a high fever. History of seizure (-), history of trauma (-). History of hypertension taking amlodipine 1x5 mg, controlled to Tampan Mental Hospital, history of taking routine antipsychotic drugs from the Mental Hospital; Trihexyphenidyl 2x1 mg, Lorazepam 1x3 mg, Haloperidol 2x5 mg. The patient lives with his brother, who has the same illness. History of drug use. The history of allergy and asthma was denied. The patient's brother is also taking antipsychotic medications. There was no family history of high blood pressure, diabetes, or heart disease. The patient is no longer working.

Physical Examination

General condition : appears severely ill
Awareness : GCS E3M5V2

Vital sign

BP : 163/93 mmHg
Heart Rate : 122/minute
Respiration Rate : 36 /minute
SpO_2 : 99% (Nonreabreathing Mask 10 LPM)
Temperature : 39.6 °C
Body weight : 70 kg
Height : 170 cm
IMT : 24.2 kg/m^2

Head Examination

Eyes : Anemic Conjunctiva (-), Icteric sclera (-), pupil isokor ϕ mm (2/2), Light reflect (+/+)
Neck : Stiffness neck (+), JVP normal

Thorax Examination

Inspection : Chest wall and chest wall movements are symmetrical, there appears to be retraction of the ribs and use of the auxiliary respiratory muscles
Palpation : Vocal fremitus is symmetrical, right and left
Percussion : Sonor throughout the lung field, heart border within normal value
Auscultation : Vesicular Breathing Sound (+/+), ronkhi (+/+), wheezing (-/-), Heart sound S1 and S2 normal and regular, murmur (-), gallop (-).

Abdomen Examination

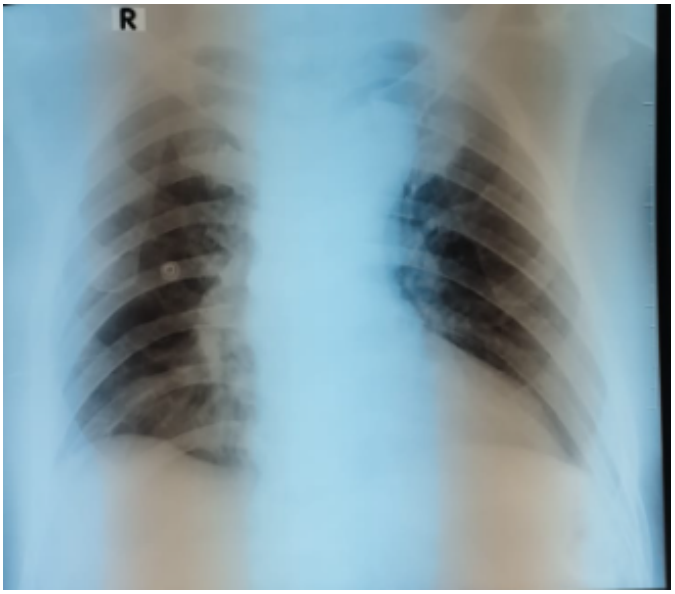
Inspection : flat abdomen, no visible enlargement or scar.
Auscultation : Bowel sound (+) 6 times/minute

Percussion : Timpani, no shifting dullness
Palpation : Abdomen normal

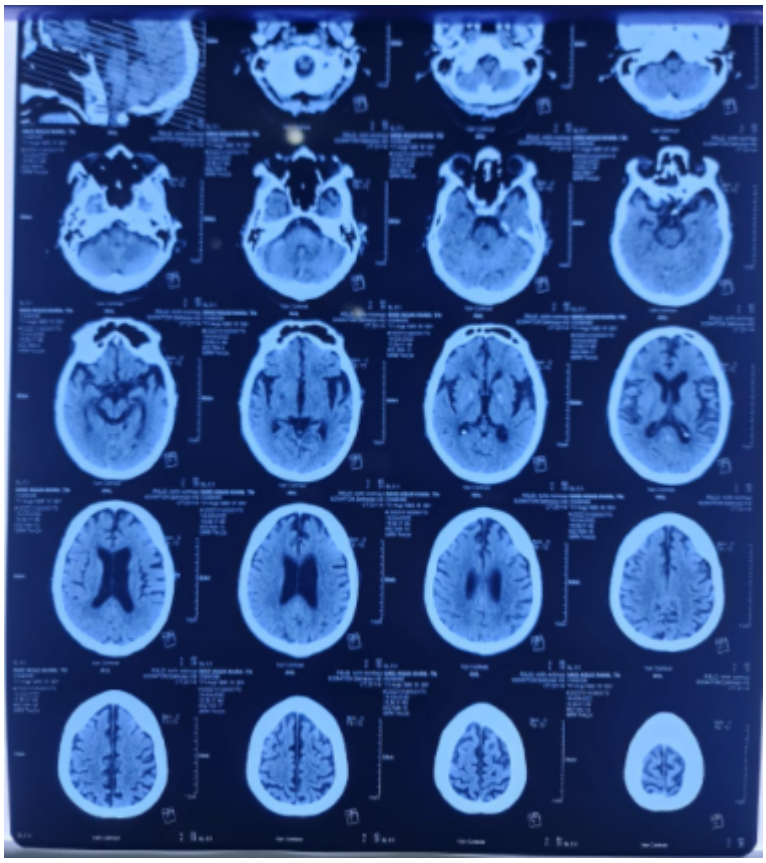
Extremity Examination
CRT < 2 seconds, warm acral, no oedema, rigidity in upper and lower extremities.
Pathologic Reflexes negative

Laboratory Findings
Blood Routine (18-10-2022)
Hb : 17.2 g/dL
Ht : 52%
Leukosit : 19.8x 10^3/ul
Trombosit : 309 x 10^3/ul
PT : 16.3 sec
INR : 1,16
APTT : 28 sec
Laktat : 4.30
Ureum : 182 mg/dl
Creatinin : 5.56 mg/dl
AST/ALT : 149/158 mg/dl
Blood Sugar : 86 mg/dl
Albumin : 4.6
Na/K/Ca : 154/1.8/0.96
pH/pCO2/pO2/HCO3/TCO2/Be/SaO2 : 7.55/25/71/22/23/-1/96%

Chest X-ray
Cor : Cardiomegaly
Pulmo : Pneumonia



Picture 1. Rontgen Thorax



Picture 2. CT-Scan without contrast

CT-SCAN: - Infark lakunar ganglia basalis dextra, atrofi serebri

Working Diagnosis:

- Decreased consciousness, electrolyte imbalance, dd Neuroleptic Malignant Syndrome
- Pneumonia
- Hipernatremia
- Hipokalemia
- Acute Kidney Injury dd acute on CKD
- Hepar Insufisiensi
- Hipertensi
- Skizofrenia

Planning:

- Intubation
- Electrolite Correction
- Creatine Kinase labwork

Patient Management

While in the ICU, patients are monitored for vital signs, serial laboratory tests, and serial x-rays. Therapy:

F : IVFD D5 1/4NS 80cc/hour

KCL 50 Meq in NS 100 cc /4 hour

A :

S :
T : -
Head up 30o
U : Omeprazole 2x40mg IV
G : -
O : Ceftriaxone 2x1gr IV (H1)
Resfar 1x2,5 gr IV
Hepabalance 3x1 tab PO
Citicolin 2x250mg IV
Amlodipin 1x10mg PO
Candesartan 1x16mg PO

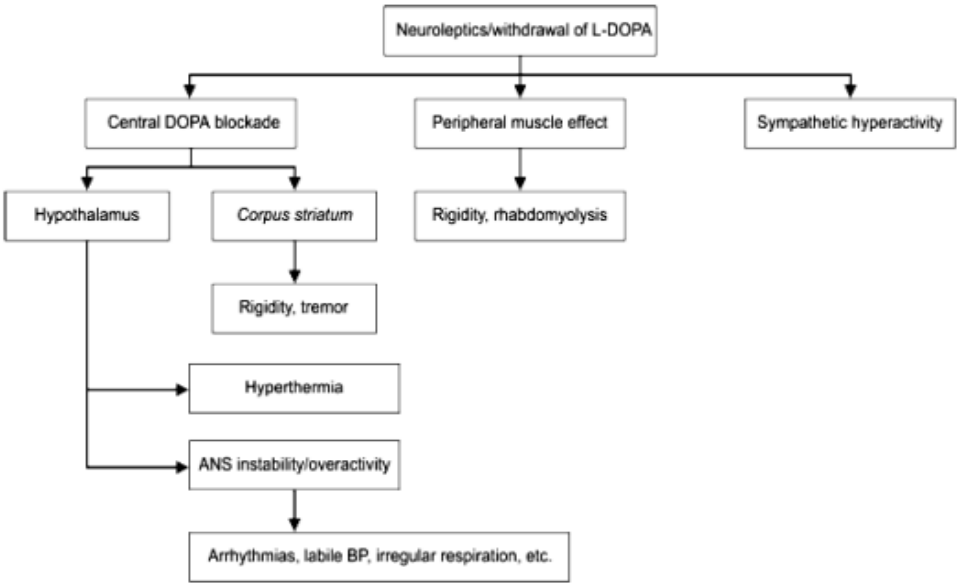
The patient in the ICU underwent close monitoring for vital signs, laboratory tests, and x-rays. Initial therapy included IV fluid (D5 1/4NS 80cc/hour), potassium chloride (KCL 50 Meq in NS 100cc/4 hours), and various medications, including ceftriaxone, resfar, omeprazole, and others. Throughout the hospitalization, the patient showed fluctuating levels of consciousness, monitored via the Glasgow Coma Scale (GCS), and was treated for various conditions, including neuroleptic malignant syndrome, pneumonia, and acute kidney injury, among others (Macedo et al., 2024). On Day 2, the patient's blood pressure was elevated (201/72 mmHg), and therapy adjustments were made, including adding fentanyl for pain control and midazolam for sedation. Over the following days, the patient was gradually weaned from the ventilator, and therapy was modified accordingly, with ongoing medication for infections and electrolyte imbalances. By Day 5, the patient's GCS improved, and the oxygenation status remained stable, though still requiring ventilatory support. Further improvements were seen in GCS by Day 12, and by Day 13, the patient was transferred from the ICU to the ward. Throughout the hospitalization, careful management of fluid balance, electrolyte levels, and medications was maintained, with continuous adjustments to the treatment plan based on the patient’s clinical status.

DISCUSSION

Malignant Neuroleptic Syndrome is a rare, life-threatening complication of antipsychotic therapy that can present within hours or weeks of medication use. It is also associated with drug discontinuation. The mechanism is associated with dopamine blockade of the basal ganglia and hypothalamus and impairment of thermoregulation. Muscle rigidity, hyperthermia, rhabdomyolysis, autonomic instability, and altered consciousness are common. Creatine kinase levels are high (Macedo et al., 2024). The mortality rate is high, at around 20-30%, with deaths occurring due to renal failure or arrhythmias. Management starts with stopping the drug and starting supportive care (Guinart, Misawa, et al., 2021).

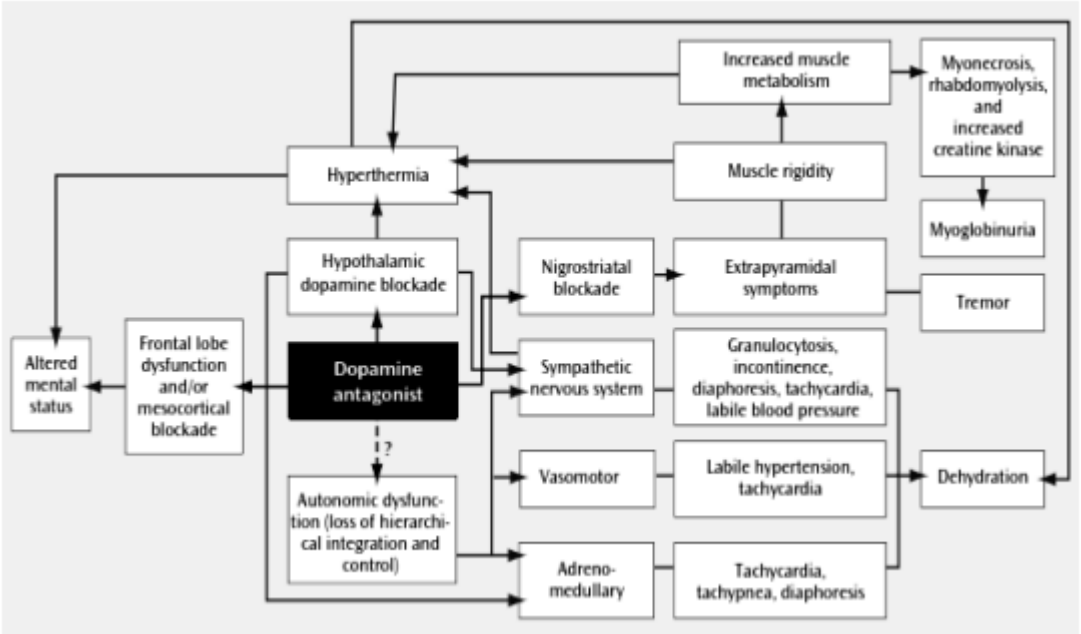
Two hypotheses were deduced, the first being that NMS is thought to result from the antagonistic action of D2 dopaminergic receptors on the central nervous system. Due to autonomic nervous system dysregulation, receptor antagonists trigger various homeostatic responses that increase temperature, create rigidity, and alter mental status. Secondly, it has been suggested that NMS is the result of the toxic effects of combined pharmacology on musculoskeletal fibres, causing the syndrome to appear secondarily. In addition to these two

theories on the etiopathogenesis of NMS, there is a trend towards the role of acute-phase reactants and inflammatory responses in NMS. It is unclear which is the causative factor or consequence, but low iron levels have been correlated with NMS and the degree of inflammatory response (Guinart, Misawa, et al., 2021).



Picture 3. Pathophysiology of the occurrence of Neuroleptic Malignant Syndrome.

Almost all cases of NMS begin to appear 24-72 hours after the onset of drug therapy, and almost all cases appear in the first 2 weeks of therapeutic use of the drug. The onset is usually slow and takes days to fully appear. In 80% of cases, the initial manifestation is muscle stiffness or altered mental status. Muscle rigidity is described as lead-pipe rigidity to differentiate from the rigidity associated with shaking, cogwheel rigidity. Mental status changes can range from agitation to coma. Hyperthermia, i.e., a body temperature of up to 41 ºC, is required to confirm the diagnosis of NMS, but an increase in body temperature may occur after 8-10 hours of muscle rigidity. Autonomic system instability may lead to cardiac arrhythmia, labile blood pressure, or persistent hypotension (Guinart, Misawa, et al., 2021).



Picture 4. Clinical symptom picture in NMS.

Dystonic reactions to neuroleptic agents can be difficult to distinguish from the muscle stiffness in NMS. It is particularly relevant in the early phase of NMS when muscle stiffness is the only clinical manifestation. Serum Creatinine Kinase (CK) examination can help to differentiate, as serum CK levels in dystonic reactions are only slightly elevated, compared to up to 1000 units/L in NMS. The number of leucocytes in the blood can increase up to 40,000/uL with a leftward shift in NMS, so the clinical symptoms that appear in SNM, such as fever, leucocytosis, and mental status changes, can be mistaken for sepsis. Serum CK levels can help differentiate NMS from sepsis (Guinart, Misawa, et al., 2021).

An important measure in the management of NMS is to discontinue the drugs that cause NMS as soon as possible. If the discontinuation of a dopaminergic drug causes SNM, the drug should be restarted as soon as possible, by slowly reducing the dose of the drug at the end. Common measures in NMS include fluid resuscitation for rhabdomyolysis or hypotension (Touzani et al., 2021).

Dantrolene sodium, a muscle paralyser used in Malignant Hyperthermia therapy, can be given intravenously in severe cases of muscle rigidity. The optimal dose has not been clearly defined, but the recommended regimen is 2-3mg/kg intravenous bolus and repeated every few hours if needed up to a total dose of 10mg/kg. May be supplemented with oral dantrolene at a dose of 50-200mg per day in divided doses every 6-8 hours (Touzani et al., 2021).

Bromocriptine mesilate is a dopamine agonist that has been successful in treating NMS when given orally at a dose of 2.5-10mg three times a day. Muscle stiffness changes can be seen within a few hours of therapy, but a full response sometimes takes a few days. Hypotension is an annoying side effect. There is no advantage of using bromocriptine over dantrolene, except in patients with advanced liver disease, where dantrolene is not recommended (Touzani et al., 2021).

Therapy in NMS should be continued up to 10 days after resolution of clinical symptoms due to delayed clearance of neuroleptic drugs, when drug availability is an issue, therapy should be continued up to 2-3 weeks after resolution of clinical symptoms. There is an increased risk

of venous thromboembolism when NMS occurs, so heparin prophylaxis is recommended. The mortality rate in NMS is about 20%, and it is unclear if dantrolene or bromocriptine has a favourable effect on mortality (Touzani et al., 2021).

CONCLUSION

Neuroleptic malignant syndrome is a potentially life-threatening neurological emergency syndrome associated with the use of neuroleptic drugs. This syndrome can be fatal, and mortality rates range from 5-20% if left untreated. Death is usually caused by complications of arrhythmias, DIC, heart failure, respiratory failure, and renal failure. Early detection of NMS clinical symptoms and prompt treatment may improve outcomes. The syndrome is usually non-fatal, and most patients will fully recover within 2-14 days. Although there are no standardised guidelines, the management of this syndrome involves discontinuation of neuroleptic drugs that are thought to trigger the onset of the syndrome, supportive therapy, and correction of metabolic factors if abnormalities are found.

Although NMS is a rare condition, it takes time and accurate diagnosis and management due to its life-threatening implications. Better recognition and monitoring of symptoms by the clinician is needed, especially at the beginning of antipsychotic therapy and when changing from one antipsychotic therapy to another. Alternative forms of pharmacological and non-pharmacological therapies for psychosis and NMS disorders should be considered when patients present with NMS symptoms.

Finally, to better understand serious conditions and improve patient care, clinicians should push to update national publication data so that medical practitioners can benefit from this experience.

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