REVIEW REPORT

DOI: 10.31736/2020v16i2/32-38

Neuroleptic Malignant Syndrome: A Review of diagnosis and treatment

Journal Homepage: www.jist.org.in; Email: article@jist.org.in

[1]Patria Yudha Putra, [2#]Yunias Setiawati

[1]General Practitioner, Faculty of Medicine, Universitas Airlangga / Dr. Soetomo General Academic Hospital, Surabaya, Indonesia.
[2]Consultant Psychiatrist, PhD, Department of Psychiatry, Faculty of Medicine, Universitas Airlangga/ Dr. Soetomo General Academic Hospital, Surabaya, Indonesia.

ARTICLE INFO

#Correspondence Author: Consultant Psychiatrist, PhD, Department of Psychiatry, Faculty of Medicine, Universitas Airlangga/ Dr. Soetomo General Academic Hospital, Surabaya, Indonesia. Email: yunias.setiawati@gmail.com

How to cite this article: Putra PY, Setiawati Y. Neuroleptic Malignant Syndrome: A Review of diagnosis and treatment. J Ind. Soc. Toxicolo 2020;16:2.32-38. DOI: jist.org in/10.31736/2020v16i2/32-38.

Keywords:
neuroleptic malignant syndrome; early detection; prevention; risk factor; schizophrenia, psychiatry emergencies; complication of anti-psychotic drugs

Conflicts of Interest and funding: Declared none

Received – **09 October 2020**
Accepted – **31 December 2020**
Published – **31 January 2021**

ABSTRACT

Background: Neuroleptic Malignant Syndrome is a life-threatening neuropsychiatric emergency because of the use of neuroleptic drugs characterized by specifically clinical syndrome, like changes in mental status, stiffness, fever, and dysautonomia. The current problem in managing of the Neuroleptic Malignant Syndrome is still not yet optimized causing the death rate is quite high with an incidence rate of the Neuroleptic Malignant Syndrome is ranging from 0.02 to 3 percent among patients taking antipsychotic agents occur throughout the world.

*Methods***:** From published articles conducted by the experts that concerning in neuroleptic malignant syndromes and its management have been considered and reviewed.

Comments: It is important for medical workers to understand steps in managing and treating Neuroleptic Malignant Syndrome from the initial management such as the immediate termination of Neuroleptic Malignant Syndrome drug agents, giving supportive management, early detection of clinical symptoms, prevention of risk factors until understanding the medical conditions associated with Neuroleptic Malignant Syndrome specifically.

BACKGROUND

Schizophrenia is a psychiatric disorder that consists of a complex heterogeneous group of cognitive and behavioral syndromes, which come from brain development disorder caused by genetic or environmental factors, mainly characterized by a loss of understanding of reality and a loss of insight.[1,2] Schizophrenia occurs worldwide with its prevalence around 1% globally. [3] Patients experiencing episodes of schizophrenia tend to have a higher likelihood of responding to pharmacological therapy by administering antipsychotic drugs using a first generation antipsychotic drugs has a more stronger effect on D2 dopamine antagonist effects than second generation antipsychotic.[4] This could lead to some side effects of the antipsychotic drugs such as extrapyramidal syndromes or even Neuroleptic Malignant Syndrome.[5] high-quality treatment guidelines should be available. In this article, we analyzed and compared different international therapy guidelines for the treatment of schizophrenia, in which NMS treatment recommendations might be contained. Methods We performed an Internet-based search for schizophrenia guidelines via the website of the respective medical society. Guidelines in English, French, Italian, and German

from countries whose medical care meets high standards were selected for further analysis and comparison of the NMS treatment recommendations (if present] Neuroleptic Malignant Syndrome is a life-threatening complication reaction of using the antipsychotic drugs and the incidence rate is reported between 0.06% to 1.4% from patients using antipsychotic, that mostly occurred in patient with schizophrenia, schizoaffective and other psychotic disorders.[6,7] few data on the risk and epidemiology of NMS are available. Objectives: The aim of this study was to ascertain the incidence risk and all-cause mortality of NMS associated with antipsychotic use, and to assess the association of recent antipsychotic exposure and NMS. Methods: We did a population-based study using data from the Hong Kong Hospital Authority's Clinical Data Analysis and Reporting System database. Cases had a first diagnosis of NMS between 1 January 2004 and 30 November 2017. A case-crossover analysis was used to compare antipsychotic exposure 30 days before the diagnosis of NMS (index date] Sudden discontinuation of dopamine-reducing agents also affects the molecular mechanisms in causing Neuroleptic Malignant Syndrome. [8] Neuroleptic Malignant Syndrome generally occurs within 4 weeks after administration of antipsychotic drugs, but several studies found that 2/3 cases usually occur within 1 week of initial administration of antipsychotic drugs.[9] So that, clinician must be aware of using antipsychotic drugs in order to prevent the fatal complication and recognize it as early as possible to avoid potential mortality. [10,11]

DISCUSSION

Neuroleptic Malignant Syndrome (NMS) is a life-threatening neuropsychiatric emergency associated with the use of antipsychotic (neuroleptic) drugs and characterized by a specific clinical syndrome including altered mental status, stiffness, fever, and dysautonomia. [12] This condition may results from acute depletion of central dopamine or functional dopamine deficiency caused by dopamine receptor blockade.[13] NMS affecting all ages group and both female and male but the incidence is higher in postpartum female patients. Elderly patients with comorbidities and other risk factors are more prone in developing Neuroleptic Malignant Syndrome.[9] The mortality rate is reported to be around 10-20% in unidentified Neuroleptic Malignant Syndrome and the mean recovery period of Neuroleptic Malignant Syndrome is 7-10 days after treatment discontinued. [14]

The pathogenesis theory of Neuroleptic Malignant Syndrome is the presence of dopamine blockade with ongoing disturbance of hypothalamus and corpus striatum, which leads to deregulation of temperature and muscle contraction.[15]assaultive behavior, persecutory delusion and auditory hallucination for three days. Past history of 3 similar episodes. 1st episode preceded by fever and associated with cerebral edema. Subsequent episodes not preceded by fever and patient was treated with Risperidone and Olanzapine. After admission patient was started on Risperidone along with THP when he had fever, tremors, altered sensorium and rigidity at 3 mg dose. After stopping Risperidone fever and rigidity improved with worsening of psychotic symptoms. Following this Olanzapine was started and very gradually uptitrated to 7.5 mg when patient had recurrence of fever and disorientation without tremors and minimal rigidity. Both the instances blood investigations including CPK levels were normal except for thrombocytopenia and leucopenia. Provisional impression of NMS was made in both instances. A er stopping Olanzapine fever subsided with improvement of blood counts. Following this patient had catatonic symptoms for which patient received 9 sessions of Electroconvulsive therapy (ECT The dopamine pathway plays an important role in regulating hypothalamic function and temperature, which can be disrupted by dopamine receptor antagonists such as Haloperidol and Risperidone.[16] Hypothalamic dysfunction can cause hyperthermia, arrhythmias, and irregular blood pressure as well as breathing. In addition, dopamine blockade in corpus striatum can lead to increased muscle rigidity and non-traumatic rhabdomyolysis.[17]

The clinical diagnostic criteria for Neuroleptic Malignant Syndrome based on a formal consensus procedure are as follows: Hyperthermia (>38.0°C on 2 measurements); Body stiffness; Altered mental status (level of consciousness decreases or fluctuates); Increased serum CPK (at least 4 times of upper normal limit); Sympathetic nervous system lability, defined as at least 2 of the following, increased blood pressure (systolic or diastolic ≥25% above baseline) and fluctuation in blood pressure (≥20mmHg diastolic change or ≥25 mmHg systolic change within 24 hours); Diaphoresis; Urinary incontinence; Hypermetabolism, defined as increased heart rate (≥25% above baseline), increased respiratory rate (≥50% above baseline) and no evidence for infectious, toxic, metabolic, or neurological causes.[9] Hyperthermia usually developed

DOI: 10.31736/2020v16i2/32-38

as late manifestation of early clinical symptoms of NMS. An increase in the body temperature exceeding 42°is induced by central dopaminergic thermoregulation mechanisms that mediate heat loss and increased heat production, resulting from neuroleptic effects on skeletal muscle tone. General body rigidity, described as a "***lead pipe***" in its most severe form, is reported in 97% of cases of NMS and is associated with myonecrosis.[18] Cogwheeling symptoms may or may not be present in patient with NMS. Other clinical symptom of Neuroleptic Malignant Syndrome is altered in mental status which occurs in almost 97% of cases. The consciousness may vary from stupor, coma, delirium and catatonic.[10,19] There is radiological findings that indicate the diagnosis of NMS. The Abdominal X-Ray showed some gas distension liquid-air levels in the large and small intestine of patient in the decubitus position, thus indicating the appearance of paralytic ileus in patients with NMS that received benzodiazepines for several days experienced abdominal distention symptoms without defense or tenderness or increased bowel sounds. Paralytic ileus is a sign of autonomic dysfunction in NMS and might be caused by hypodopaminergic status in the hypothalamus.[20]

Management of Neuroleptic Malignant Syndrome

Initial Management

Clinical symptoms and signs that appear at the beginning of Neuroleptic Malignant Syndrome can be used as outcomes predictor. Hence, it is important for clinicians to be able to understand the early symptoms that arise. However, the clinical manifestations of each NMS appeared may vary and require the expertise of medical personnel in managing this syndrome.[9] Once the suggestive diagnosis has been established, the most important initial strategy in the management of NMS is to discontinue any pharmacological treatment suspected to trigger the onset of Neuroleptic Malignant Syndrome. It is important to keep in mind that there is no need to wait for laboratory results, for example in findings elevated serum CPK in these patients who have symptoms of Neuroleptic Malignant Syndrome.[7]

Non-Pharmacological Management

The target of the initial non-pharmacological treatment is to stabilize the patient, which may predispose or worsen the patient's condition. Specifically, patients with Neuroleptic Malignant Syndrome should be made in a comfortable environment with room temperature range between 21-23°C.[7] Patients should be immediately transferred and treated in ICU that is well equipped with circulatory and ventilator support and cooled down using a cooling blanket and applying ice packs to patient's groin and axilla.[21] In case of immobilization due to rigidity in patients with Neuroleptic Syndrome Malignant, then prophylaxis can be added to prevent venous thrombosis [22]Patients with Neuroleptic Malignant Syndrome in coma should be administered fluids via intravenous lines and if necessary addition of pharmacotherapy treatment. The aim of administering fluids intravenously is to avoid dehydration due to hyperpyrexia and to avoid acute renal failure due to extremely high myoglobin serum level which can cause kidney damage. This can be avoided by aggressive intravenous hydration with cooled IV fluids to induce urinary alkalization and diuresis. These steps can prevent the occurrence of kidney failure and increase the excretion of products from muscle breakdown. With these supportive techniques, it is expected that the symptoms of Neuroleptic Malignant Syndrome will disappear within a few weeks or more, or longer (> 4 weeks) if the syndrome is initially caused by overuse of antipsychotics.[21]

Pharmacological Management

Management of Neuroleptic Malignant Syndrome is considered an emergency case management since the morbidity and mortality is extremely high. The most important first step in managing Neuroleptic Malignant Syndrome is to discontinue the neuroleptic agent that is suspected as the causes. After discontinuing the medication, the patient should be transferred to ICU ward where supportive therapy is started. If the blood pressure rises sharply, administration of antihypertensive drugs can be started. Then, the first-line pharmacological therapy that can be given to patients with Neuroleptic Malignant Syndrome is the administration of anticholinergic drugs such as Dantrolene, Bromocriptine and Biperiden.[23]

Dantrolene

Dantrolene is a hydantoin derivative that causes muscle relaxation by inhibiting the release of calcium by the endoplasmic reticulum resulting in decreased intracellular calcium availability. This drug has a good therapeutic effect in cases of musculoskeletal toxicity and malignant hyperthermia. Dantrolene is given intravenously at a dose of 1-10 mg per kg/BW or orally 50-600mg once daily.[4] Dantrolene administration can be started at a dose of 1 to 2.5 mg per kg/BW, then 1 mg per kg/BW every 6 hours

if there is a response following the initial dose. Typically, the administration of Dantrolene to patients with Neuroleptic Malignant Syndrome will be slowly reduced or transitioned to oral therapy for several days before complete drug withdrawal.[23] Although some literature contradicts each other, until now Dantrolene is still used as the first line because of the lack of other treatment options even though Dantrolene itself has the potential effect to cause hepatotoxicity, so that liver function tests should be carried out at the beginning before Dantrolene administration and repeated during the therapy.[23]

Bromocriptine

Bromocriptine has been proven in clinical trials as one of pharmacology therapy to treat Neuroleptic Malignant Syndrome. Bromocriptine acts based on the dopamine blockade hypothesis which is one of the etiopathogenesis pathways of Neuroleptic Malignant Syndrome. The recommended dosage for Bromocriptine starts with 2.5 mg 3 times daily and can be increased to 2.5-7.5mg per day to a maximum of 45 mg once daily. The side effects including nausea, vomiting, or deteriorating mental status. Bromocriptine can also be used to increase dopaminergic neurotransmission with minimal side effects of muscle stiffness or hyperthermia.[7] In some cases, Bromocriptine has a therapeutic effect of 94% when used as monotherapy and has a therapeutic effect of 88% when used as a combination therapy. It is proven that the mortality rate of patients with this syndrome can decrease by up to 50% in patients who are given only bromocriptine alone. [10]

Amantadine

At first, Amantadine was created for treatment of the Influenza A virus but later these drugs found effectively in treating rigidity, tremors and akathisia.[24] Parkinsonism is caused by blockade of Dopamine D2 receptor in the pre- and post- synaptic of the antipsychotics drugs and this made symptoms like movement disorders. Amantadine was also chosen to be one of the most effective dopamine agonists in treating this syndrome and as research stated that Amantadine could be used as monotherapy in 63% of Neuroleptic Malignant Syndrome cases.[24] However, amantadine can also act as N-methyl-D-aspartate (NMDA) as a receptor antagonist in supporting the release of endogenous dopamine, which can exacerbate psychotic symptoms but can still be tolerated. Amantadine works as an anticholinergic more than dopaminergic. Thus, its mechanism of action works more in stimulating NMDA receptor of cholinergic neurons rather than inducing dopamine release.[25] which was originally developed as an antiviral medication, functions as a dopamine agonist in the central nervous system and consequently is utilized in the treatment of Parkinson disease, drug-induced extrapyramidal reactions, and neuroleptic malignant syndrome. For reasons that are not entirely understood, abrupt changes in amantadine dosage can produce a severe withdrawal syndrome. Existing medical literature describes case reports of amantadine withdrawal leading to delirium, which at times has progressed to neuroleptic malignant syndrome. Amantadine withdrawal may be under-recognized by mental health clinicians, which has the potential to lead to protracted hospital courses and suboptimal outcomes. The goal of this case series is to highlight the role of amantadine withdrawal in the cases of 3medically complex patients with altered mental status. In the first case, the cognitive side effects of electroconvulsive therapy masked acute amantadine withdrawal in a 64-year-old man with Parkinson disease. In the second case, a 75-yearold depressed patient developed a catatonic delirium when amantadine was discontinued. Finally, a refractory case of neuroleptic malignant syndrome in a 57-year-old patient with schizoaffective disorder rapidly resolved with the reintroduction of outpatient amantadine. These cases highlight several learning objectives regarding amantadine withdrawal syndrome: First, it may be concealed by co-occurring causes of delirium in medically complex patients. Second, its symptoms are likely to be related to a cortical and limbic dopamine shortage, which may be reversed with electroconvulsive therapy or reintroduction of amantadine. Third, its clinical presentation may occur on a spectrum and may include features suggestive of delirium, catatonia, or neuroleptic malignant syndrome. (Journal of Psychiatric Practice 2017;23;191-199 Amantadine dosage is usually given between 200-400 mg per day orally, divided into several times a day. From the studies, the clinicians must be aware of the side effects of amantadine. There are several side effects nausea, dizziness, insomnia after receiving treatments on 5% patients. Besides, there are also another side effect found such as agitation, irritability, insomnia, delusions, anxiety, hallucinations, apathy, sedation, confusion, headache, seizures and dizziness.[26]

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Benzodiazepines

Benzodiazepines are thought to reduce and minimize the typical symptoms of Neuroleptic Malignant Syndrome. It has been reported that in some cases of Neuroleptic Malignant Syndrome that unresponsive to other types of medication were successful with benzodiazepines. For cases with rigidity and fever, benzodiazepines administration may help the symptoms to subside within 24-48 hours, while the secondary symptoms of NMS can subside within 64 hours without any side effects. [10] Types of Benzodiazepines that can be used in cases of Neuroleptic Malignant Syndrome are Lorazepam, Diazepam and Clonazepam. The mechanism of action of Benzodiazepines is to restore the hypofunction of the GABAergic system which causes symptoms of Neuroleptic Malignant Syndrome. However, because benzodiazepines have a significant risk factor for delayed consciousness in patient, they cannot be used as first-line pharmacotherapy in the case of Neuroleptic Malignant Syndrome.[22] Lorazepam 0.5-1mg intramuscularly every 4 to 6 hours was found to be effective as initial therapy. However, it should be noted that it may cause respiratory depression which harm the use of benzodiazepines, especially in elderly patients.[9]

Levodopa and other types of drugs

Levodopa can also be used, although in some studies there are still few cases that show an effectiveness level comparable to Amantadine and Bromocriptine. Drugs used for Parkinson's disease such as Tolcapone, Pramipexole, Ropinirole, and Pergolide is an alternative option in treating NMS but are still under further research because they potentially have withdrawal effect with the increasing symptoms of NMS.[7] A series of studies have shown that the fastest cure rate for NMS can be achieved first by using Bromocriptine and then followed by Dantrolene. These two drugs can result in a much faster remission in patient with Neuroleptic Malignant Syndrome when compared to patients receiving only supportive treatment. Some researchers stated that the use of Bromocriptine and Dantrolene together will be more able to produce more significant healing results, but this is still needs further research.[7]

Electro-convulsive therapy

This therapy is controversial and is often stigmatized by the public due to inaccurate education about how this therapy works and performs to patients.[27] Pharmacotherapy effects are thought to appear usually within the first few days after administration of treatment, and if not, the drug may not be effective or there is an overlapping between NMS and catatonia.[28]we sought to describe all NMS cases requiring ECT from a large academic institution over a nearly 2-decade period. Methods We retrospectively identified all patients with NMS who were treated with ECT over a 17-year period. Patients were included in the study based on chart review using the International Consensus Diagnostic Criteria for NMS. Data were collected related to clinical findings, treatment course, and response to ECT. Results We identified 15 patients meeting the inclusion criteria. Most patients had neurocognitive or schizophrenia spectrum disorders and developed NMS after exposure to multiple antipsychotic drugs. All patients received bitemporal ECT after failed pharmacotherapy for NMS. Electroconvulsive therapy was well tolerated and resulted in a remission rate of 73.3% (n = 11 At this point, ECT therapy can be used as an alternative option because it is considered effective in decreasing mortality while increasing dopamine activity in the central nervous system effectively.[29] Despite the refusal of patient or their families to use ECT, there are sufficient data to make ECT therapy as a second-line treatment in the management of NMS.[20] The use of electro-convulsion therapy in patients with NMS is also not without harm. The complication that may arise are cardiovascular complications like ventricular fibrillation and cardiac arrest with permanent anoxic brain injury due to ECT therapy, malignant hyperthermia due to the anesthetic process and hyperkalemia.[30] The response to ECT therapy is usually seen after 6 sessions of therapy. In general, the recommended ECT therapy sessions for patients with NMS are 6 to 10 therapy sessions daily with a minimum of 6 sessions with the aim of minimizing the risk of recurrence.[31]

Giving anti-psychotic drugs after the occurrence of neuroleptic malignant syndrome

If antipsychotic drugs are needed again in patients who have recovered from Neuroleptic Malignant Syndrome, then the following things can be taken into consideration when starting to give antipsychotic drugs: wait at least 2 weeks before restarting antipsychotic drug therapy or wait for the sequelae to completely disappear from the patient; Always use an antipsychotic that has a lower potency than the antipsychotic medication the patient has used priorly; Always start treatment at the lowest dose and increase the dose slowly.[12] The success in

NMS treatment will largely depend on early diagnosis and active intervention without delay in transferring the patient to ICU. Although most cases can be managed successfully, it should still be noted that about 10% of cases can be fatal, regardless of early diagnosis and treatment. Hyperpyrexia, rhabdomyolysis, and nerve damage can cause amnesia (memory impairment), which can be temporary or persistent in certain cases. Elderly patients with a history of acute respiratory failure, acute renal failure, infection (septic shock), and congestive heart failure are significant predictors of mortality in this syndrome.[21]

CONCLUSION

Neuroleptic Malignant Syndrome is a neuropsychiatric emergency caused using neuroleptic drugs. Signs and symptoms including hyperthermia, muscle rigidity, decreased consciousness and an unstable autonomic system. Although this case is relatively rare, it has the potential to cause death. The importance of understanding the early symptoms and the steps of Neuroleptic Malignant Syndrome management is the key to the success of therapy.

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