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Neuroleptic malignant syndrome: literature review

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Abstract

Background. Neuroleptic malignant syndrome (NMS) is an adverse reaction to antipsychotic drugs as well as a rare and potentially lethal neurological condition. Because of its manifestation with non-specific signs and symptoms and possible severe complications or even lethal outcomes it is crucial to be informed about NMS.

Aim. To review the most recent scientific literature on neuroleptic malignant syndrome.

Materials and methods. PubMed and UpToDate were searched using terms "neuroleptic malignant syndrome" in combination with "diagnosis", "treatment" and "complications". Articles were included if they were in English, no more than 10 years old, and included adults. Articles were excluded if they did not meet the inclusion criteria and were not relevant.

Results. The risk for NMS increases for males, patients in their early to middle forties, patients using haloperidol or flupentixol and patients receiving polypharmacological treatment. NMS laboratory findings are nonspecific while SPECT may be a prospective diagnostic tool. Treatment of NMS is assigned individually and relies on the severity of the case. Patients can be treated with medications or electroconvulsive therapy, and receive intensive care unit monitoring. Acute respiratory failure can be the strongest independent mortality predictor.

Conclusions. Diagnosis of NMS can be complicated, once the condition is suspected patients should receive urgent care and treatment to avoid severe complications. Causative agents and other psychotropic drugs must be discontinued.

Keywords: neuroleptic malignant syndrome, adverse antipsychotic drug reaction, first-generation antipsychotics, second-generation antipsychotics

1. Introduction

Neuroleptic malignant syndrome (NMS) is a rare and potentially lethal neurological condition (1,2). It usually presents with fever (>38ºC), rigor, altered mental status and other neurological symptoms (3). NMS is a known adverse reaction to antipsychotic drugs, but it can also occur in patients taking drugs that inhibit or deplete dopamine such as antiemetics, benzodiazepines, antiepileptics and lithium (4). Even though the mortality of NMS has seemed to decrease over the years, it still reaches 5,6% (2). The goal of this literature review is to analyze the most recent data on diagnostics, treatment and complications of NMS.

2. Materials and methods

The search was conducted in the PubMed database and the UpToDate clinical database. The terms used for the search were "neuroleptic malignant syndrome" in combination with "diagnosis", "treatment", "complications". Articles were included in the review if they were written in English, if they were less than 10 years old and if they included adults aged 19 and older. Articles were excluded in the review if they did not fit the inclusion criteria and were not relevant. A total of 16 articles were analyzed.

3. Results

3.1 Diagnostics

3.1.1 Risk factor assessment

As NMS can be a fatal condition it is important to suspect and diagnose it as soon as possible. The incidence of NMS seems to be higher among male patients (3,5,6). The mean age of onset ranges from early to middle forties (5,6). Antipsychotic drugs are the main cause of NMS, however, a difference between the ability to trigger NMS of first-generation antipsychotics (FGAs) and second-generation antipsychotics (SGAs) has been observed. High-potency orally administered FGAs pose the highest risk of NMS (3,7,8). Long-acting injectable (LAI) anti-psychotics have significantly lower reporting rates of NMS, dystonia and extrapyramidal symptoms rather than oral antipsychotics (9). However, not all studies support this claim (10). Quetiapine has the lowest NMS incidence rate and does not seem to increase the risk of NMS, mostly haloperidol and flupentixol have been associated with an increased risk of NMS (3,7). Another important risk factor is polypharmacy, which includes polypharmacy across generation groups and other psychotropic medication (3,7,8,11).

3.1.2 Clinical manifestation

In some cases ICD-10, DSM-IV/DSM-IV TR criteria for NMS were not met, but the syndrome was recognized and diagnosed using the 2011 diagnostic criteria for NMS published by an international multispecialty consensus group (3,12). NMS can arise at any time during the course of an antipsychotic treatment. Usually, symptoms manifest during the first two weeks after initiation or modification of the antipsychotic treatment (3). As for LAI antipsychotics, NMS can occur within the first 4 months of treatment (the early stages of use) (11). The mandatory criterion for dopamine agonist-caused NMS is withdrawal within the last 72 hours (3). Main NMS clinical features include muscle rigidity, hyperthermia (>38ºC orally), autonomic instability and an altered mental status (2). Laboratory findings usually include elevated creatine kinase (as a result of rigidity) and serum aminotransferase levels, leukocytosis, electrolyte imbalance (hyperkalemia, hypokalemia, hypernatremia,

hypocalcemia), increased lactate dehydrogenase and metabolic acidosis all of which are common, but nonspecific findings during NMS (6,12,13). Serum creatine kinase can range from 572–220,000 IU/L (6). SPECT may be a prospective diagnostic tool for NMS as FP/CIT SPECT has shown either reduced or absent uptake in the putamen bilaterally and extremely reduced activity in the caudate nucleus (the feature of "burst striatum") with disappearance of the oval-shaped images corresponding to caudate (14).

3.2 Treatment

Treatment of patients with NMS is based on clinical symptoms (12). The most important step is the removal of the causing agent (3). Psychotropic drugs such as lithium, anticholinergic and serotonergic agents should also be removed. Specific medical treatment recommendations mostly rely on clinical experience. Medications are most commonly used in severe or moderate NMS. Patients receive dantrolene, bromocriptine and amantadine. If the case is severe, intensive care unit monitoring and treatment might also be required. Intensive care unit treatment could provide mechanical ventilation, antiarrhythmic medications and/or pacemakers, electrolyte balance correction through IV fluids, fever lowering with cool blankets, ice water and/or ice packs, blood pressure control (nitroprusside can be effective as it also causes cooling through vasodilation of the skin vessels), heparin or low molecular weight heparin to prevent deep venous thrombosis. Benzodiazepines may also be used for agitation control (12). Electro-convulsive therapy (ECT) might be another method to treat NMS, although randomized controlled trials are lacking (10). ECT is mostly used in treating NMS refractory to pharmacotherapy. Pre-procedure medications include glycopyrrolate to eliminate parasympathetic response, labetalol for hypertension, ketorolac for myalgia and flumazenil to dull antiepileptic effect of benzodiazepines. Patients can receive bitemporal or unilateral stimulation. This method is effective because of the treatment of underlying psychiatric illnesses which are refractory to medications (15).

3.3 Complications

Complications include rhabdomyolysis, kidney injury or failure, venous or pulmonary embolism, disseminated intravascular coagulation, acute cardiac and respiratory failure, aspiration pneumonia and sepsis (8,16). 56,9% of survivors continue their treatment in skilled nursing facilities, immediate care facilities (2). Population-based studies suggest that acute respiratory failure can be the strongest independent mortality predictor (13) . Patients with severe hyperthermia and older age also tend to have a higher mortality rate (2). NMS recurrence can be as high as 4,2 % (10).

4. Conclusion

NMS is a life-threatening condition that requires quick diagnostics. Usage of FGA is considered a high-risk factor for NMS along with polypharmacy. Diagnosing NMS can be complicated as diagnostic criteria of ICD and DSM are not always met, therefore the 2011 diagnostic criteria for NMS published by an international multispecialty consensus group is used to diagnose NMS. The most common NMS laboratory findings are nonspecific while SPECT may be a prospective diagnostic tool. Treatment mostly relies on clinical symptoms and can include pharmacological

approaches as well as electroconvulsive therapy. Acute respiratory failure is a complication that can be a strong mortality predictor.

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