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Review Article

Neuroleptic malignant syndrome: A neuro-psychiatric emergency: Recognition, prevention, and management

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ABSTRACT

Neuroleptic Malignant Syndrome (NMS) is a life threatening complication of antipsychotic therapy. It is often assumed to be rare. Observations suggest that rather than overestimating its frequency, we are more likely to underestimate it (Pope et al., 1986). It is a rare but potentially fatal disorder characterized by four principal symptoms. These are mental status changes, muscle rigidity, hyperthermia, and autonomic dysfunction. The diagnosis of NMS often presents a challenge because several medical conditions generate similar symptoms.

Although less common now than in the past, thanks to greater awareness, it remains a risk in susceptible patients receiving conventional or atypical neuroleptics. Reducing the risk factors, early recognition of suspected cases, and prompt management can significantly reduce morbidity and mortality of this dangerous condition. Collaboration between psychiatry and other medical specialities may be the key to a successful outcome.

1. Introduction

'*The person who takes medicine must recover twice, once from the disease and once from the medicine*'—William Osler

Neuroleptic Malignant Syndrome(NMS) is a rare but potentially lethal form of drug induced hyperthermia. It was largely unrecognised in the English language scientific literature until the 1980s when it was included in the DSM3 manual. This belated recognition is reminiscent of the tardive dyskinesia story. First described by Delay and Deniker (1968), the first English translation appeared in 1968. The overall incidence of NMS ranges between 0.02% and 3.23% (Velamoor et al., 1998). NMS affects patients of all ages. Men have a higher reported incidence than women, perhaps because young adult males may be receiving higher doses of neuroleptics. The four principal symptoms of NMS are hyperthermia, rigidity, mental status changes, and autonomic dysfunction. This is usually characterized by rigidity unresponsive to anticholinergic medications, hyperthermia of unknown cause, diaphoresis, and dysphagia, changes in level of consciousness ranging from confusion to coma, and elevated creatine phosphokinase (CPK) levels (Velamoor et al., 1998). Studies suggest that the symptoms of NMS might progress in a predictable manner. It has been observed that mental status changes and muscle rigidity precede hyperthermia and autonomic dysregulation (Velamoor et al., 1994). This progression makes clinical sense as the rigidity might cause heat generation and lead to hyperthermia. However the presentation and course of NMS can be variable. NMS usually develops within 4 weeks of starting an antipsychotic treatment, but two-thirds of cases develop within the first week (Velamoor et al., 1994, 1998). Caroff and Mann reported that 16% of patients developed signs of NMS within 24 h of administration of antipsychotics, with 66% within the first week and 96% within the four weeks of antipsychotic therapy (Caroff and Mann, 1993). However, in some individuals, NMS also develops after having taken the same dose of antipsychotic medication for several months or even years.

Complications of NMS may include myoglobinuric renal failure, cardiac and respiratory failure, aspiration pneumonia, pulmonary embolism, disseminated intravascular coagulation, and persistent long term cognitive sequalae caused by hypoxia and prolonged hyperthermia.

2. Pathophysiology

There is compelling clinical evidence for D2 receptor blockade in the pathogenesis of NMS. The cornerstone of the evidence is that all antipsychotics including atypicals can cause NMS, it has been successfully treated by dopamine agonists, withdrawal of dopamine agonists (as in Parkinsons) can precipitate NMS, and that other dopamine drugs e.g. metoclopramide, proclorperazine, promethazine can also cause NMS.

Central dopaminergic systems are involved in temperature regula-

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tion, muscle tone, and movement. Blockade of these systems offers the most compelling evidence for causation of NMS. Neuroleptic induced dopamine blockade in the nigrostriatal pathway is said to cause rigidity, and dopamine blockade in the hypothalamus may explain the impairment of the autonomic as well as central thermoregulation. Alteration of dopamine neurotransmission in the brainstem reticular activating system may be responsible for the alterations in consciousness, e.g., mutism, coma, and other disturbances in arousal.

However the view that NMS results solely from dopamine receptor blockade may be overly simplistic. Other cofactors may include imbalance of norepinephrine, gaba, and serotonin systems (Mann et al., 2000). Central dysregulated sympatho-adrenal hyperactivity has also been postulated as a likely explanation in the etiology of NMS (Gurrera, 1999). The hypermetabolic state is possibly a result of excess noradrenaline relative to dopamine when individuals are on dopamine antagonist therapy. Recent studies in pharmacogenetics implicate a role for genetic predisposition as well in the causation of NMS (Kawanishi, 2003). Obtaining a family history is therefore essential.

3. Diagnosis

Since about 2 decades, there is broad consensus among investigators that the four principal symptoms of NMS are hyperthermia, rigidity, mental status changes and autonomic impairment (see DSM4-TR, American Psychiatric Association, 2000). NMS is generally characterized by the presence of rigidity and hyperthermia following antipsychotic administration, as well as other symptoms which may include profuse sweating, tremor, incontinence, mental status changes, changes in heart rate and blood pressure, leukocytosis, and CPK elevation. The medical workup is otherwise usually negative. There is, however, lack of general agreement among experts about the diagnostic significance of these items. This impedes research and clinical management of patients. While classical full-blown forms are recognized, diagnosed, and treated in a timely manner, partial or milder forms may be missed. This heterogeneity in presentation, course, and response to treatment warrants development of specific criteria that can be applied uniformly across varying clinical presentations with confidence. There have been few attempts to test the validity, reliability, sensitivity, and specificity of the diagnostic criteria.

An international multispecialty expert panel (including psychiatrists, neurologists, emergency medicine specialists, and anesthesiologists) converged to establish critical values and offer guidance regarding the relative importance of individual diagnostic elements (Gurrera et al., 2011).

The findings of the panel of experts based on a formal consensus procedure (Delphi method) included exposure to dopamine antagonist, or dopamine agonist withdrawal, within the past 72 h; hyperthermia ($>$ 100.4 °F or 38.0 °C on at least 2 occasions measured orally), rigidity; mental status alteration (reduced or fluctuating level of consciousness); creatine kinase elevation (at least 4 times the upper limit of normal); sympathetic nervous system lability, defined as at least 2 of the following:

blood pressure elevation (systolic or diastolic $\geq$25% above baseline)

blood pressure fluctuation ($\geq$20 mmHg diastolic change or $\geq$25 mmHg

systolic change within 24 h); diaphoresis; urinary incontinence; hypermetabolism, defined as heart-rate increase ($\geq$25% above baseline) and

respiratory rate increase ($\geq$50% above baseline); and negative workup for infectious, toxic, metabolic, or neurological causes.

This consensus study criteria have been validated in a study recently published (Gurrera et al., 2017). The latest edition of DSM5 (American Psychiatric Association, 2013) has replicated the above mentioned consensus diagnostic criteria in the general clinical review of NMS under the heading of diagnostic features. This will hopefully advance research in the field, as well as the clinical management of patients with NMS.

The criterion of negative medical workup is critically important in the elderly in view of the presence of concomitant medical disorders and morbidities. Laboratory abnormalities in NMS generally include elevated creatine kinase levels as stated above, leukocytosis, metabolic acidosis, elevated catecholamines, and electrolyte changes (Velamoor, 1998; Strawn et al., 2007). A prospective study revealed that patients with NMS have a low serum iron level by as much as 10 μmol/l or even lower in 96% of the cases analyzed (Rosebush and Mazurek, 1991). This suggests that iron deficiency may possibly have a role in NMS as a risk factor. This may be especially relevant in developing countries in Asia due to nutritional deficiency of iron (Patil et al., 2014). Another study in India identified a higher incidence of coexisting medical and neurological issues, higher mean neuroleptic dosing, as well as the use of fluphenazine decanoate as contributing risk factors (Chopra et al., 1999).

4. Differential diagnoses

NMS is a diagnosis of exclusion. It is therefore important to rule out various medical and neurological conditions that may mimic this condition. This is especially essential in the elderly. Sewell and Jeste (1992) study of 34 hospitalized patients with suspected NMS found that 24 of those patients had NMS while the symptoms of the remaining 10 patients were more likely attributable to other acute medical conditions. A stroke, especially involving the brainstem and basal ganglia can simulate NMS. Recent studies have indicated that elderly patients undergoing treatment with second-generation antipsychotics are at an increased risk of stroke (Hall et al., 2005, 2006). Another important condition to consider while diagnosing NMS is Parkinsonism Hyperthermia Syndrome seen in patients with Parkinson's disease and other disorders of the basal ganglia (Mizuno et al., 2003). These patients can develop rebound parkinsonian symptoms resembling NMS such as hyperthermia and rigidity due to abrupt withdrawal of dopamine agonist treatment. This, according to Caroff et al. is analogous to inhibiting dopamine activity with antipsychotics. Another possible differential diagnosis to consider is Neuroleptic Sensitivity Syndrome in patients with lewy body dementia. In these patients, any exacerbation of psychotic symptoms is often managed with multiple antipsychotics. Over a period of time, repeated use of these antipsychotics can sensitize the patients to neurological side effects of medications (Caroff et al., 2007). Like NMS, neuroleptic sensitivity syndrome, if not managed, could be fatal as the patient can rapidly deteriorate with increased confusion, rigidity, fixed flexion posture and dehydration. It is important to note that anticholinergic agents do not reverse these symptoms and might actually make it worse (Hall et al., 2006).

The relationship between catatonia and NMS has been studied by several authors. Clinical onset, signs and symptoms may be similar. Views range from the two being considered as two distinct entities, to NMS possibly being an antipsychotic aggravated form of catatonia (Mann et al., 1986; Topka and Buchkremer, 1996).

Heat stroke and Serotonin Syndrome are also confused with NMS as the clinical presentations may be similar. However, there are important differences. Patients with heat stroke present with hyperthermia but with a dry skin and loss of muscle tone. Hyperthermia in NMS on the other hand is usually associated with muscle rigidity and diaphoresis (Caroff et al., 2007). The use of polypharmacy in patients, especially a combination of SSRI's and other medications can cause the serotonin syndrome. Although they present with hyperthermia and autonomic changes as seen in NMS, they also manifest gastrointestinal symptoms, myoclonus, and hyperreflexia, which are not characteristic of NMS (Velamoor, 1998). Malignant hyperthermia resembles NMS, but occurs only in surgical settings following anesthesia.