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Neuroleptic Malignant Syndrome - review of pathophysiology, clinical presentation, differentiation and management

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Abstract

Introduction and purpose: The number of invented and produced medications has increased over recent years. Besides their positive impact on health, they invariably provide various kinds of side effects. This review is focused on malignant neuroleptic syndrome, a rare condition with no fully confirmed pathogenesis, which at least partially can be explained as an adverse effect of blocking dopamine receptors. Even though it usually affects psychiatric or neurological patients, doctors of all medical specializations should stay alert, as the condition can often lead to premature death.

Brief description of knowledge: The main symptoms associated with NMS are hypertonia, hyperpyrexia, autonomic instability and altered consciousness. They can appear in any configuration, sometimes followed by less characteristic manifestations. It should be primarily differentiated from serotonin syndrome, malignant hyperpyrexia and catatonia, mostly through the interview of those who have taken medications and undergone surgeries, as there are not any specific lab tests available. Fundamental treatment methods consist of neuroleptic withdrawal, intensive supportive care, drug administration and eventually ECT.

Summary: NMS is an uncommon, severe disease that should be carefully considered in patients treated with neuroleptics. Due to its rarity and sudden onset, it appears to be problematic to conduct widespread research and studies, so there are still no concrete, consistent and unquestioned guidelines on recognizing and treating the condition.

Key words: “neuroleptic malignant symptom”; “NMS”; “adverse effect”; “neuroleptics”

Introduction

In this day and age, the pharmacy industry evolves very rapidly, providing newer and newer treatment possibilities – diseases that were not curable some years ago can be successfully healed today, or at least clinical manifestations may be alleviated. However, great possibilities go along with adverse effects which throw the idyll off. They can vary from common and not potentially lethal symptoms like rash, headache or abdominal pain to life-threatening ones. Malignant neuroleptic syndrome is a perfect example of the latter. It usually occurs due to the use of typical antipsychotics or the abrupt cessation of dopamine agonists. Although its

prevalence has decreased comparatively to the 1990s, when the incidence was put at ~0.2%–3.23%.[1] and fluctuates between 0.02 and 0.03% in recent studies [2], the mortality rate still comes to 5.6%. [3] Despite the fact that it is not a quotidian condition, the medics should make an effort to recognise the early onset of symptoms in order to provide the best medical help and avoid death.

Aim

The aim of this article is to gather information about malignant neuroleptic syndrome, beginning with its history and pathophysiology, through diagnostic directions, and ending with present treatment possibilities.

History

The first discussion about concurrent manifestation of altered consciousness, muscle rigidity, hyperthermia and autonomic dysfunction connected with the use of dopamine receptor blockers appeared in 1960 in France, when Delay and colleagues focused on the haloperidol effect. For the observed disorder, they provided the name "syndrome malin des neuroleptiques", which was afterwards translated into NMS. [4]

Pathophysiology

Even though NMS is an object of interest to many researchers, its exact, complete base still remains undiscovered. Therefore, some quality theories associated with clinical presentation have been made. They do not exclude one another and can be eventually put together. Initially, attention was focused on the inhibitive effect that neuroleptics have on the central nervous system. They are D2 receptor antagonists; therefore, the treatment leads to blockage in the mesocortical–nigrostriatal pathways and the hypothalamic nuclei [5], so the genesis and consequently the symptoms are in alignment with Parkinson's disease. In patients with PD, a paramount problem is midbrain's neurodegeneration, which includes precisely dopamine neurons in the substantia nigra. Thus, they suffer from lead-pipe rigidity, fine tremor, and hypertonia - comparatively with NMS patients.[6] General treatment for PD involves increasing dopaminergic transmission with D2 receptor agonists. In this regard, sudden drug withdrawal is the next most common cause of NMS.[7] On the other hand, the origin of all the symptoms

which constitute NMS can not be explained by the dopamine activity restriction theory. Additionally, triggering NMS by medications which do not affect dopamine transmission also does not fit into the pattern. Although most cases are associated with typical antipsychotic use, other types of medications can be responsible for developing severe manifestations too, in particular atypical neuroleptics (olanzapine, clozapine, risperidone) mood stabilizers (lithium and carbamazepine) antidepressants (paroxetine, sertraline, amitriptyline) and antiemetic agents (metoclopramide).[8] As so the other theory focusing on the skeletal muscle system came into being. There have been experiments conducted in vitro which showed the direct toxicity of neuroleptic chlorpromazine, which resulted in muscle contracture. Its activity relies on increasing release of calcium from the sarcoplasmic reticulum, eventually provoking NMS symptoms. However, these results were not confirmed during in vivo studies, and it is agreed that in vitro findings do not correspond with clinical presentation. Last but not least, the idea is also connected with calcium release, but it relates to genetic susceptibility to neuroleptics, which allows a rise in calcium ion use, leading to hyperthermia, rhabdomyolysis and rigidity.[9]

Risk factors

NMS is generally considered to be an idiosyncratic disorder, resulting in problematic forecasts. Neither drug potency nor treatment duration can provide certainty for patients' safety. It is also remarkable that after bringing themselves back to health, some patients are subjected to antipsychotic rechallenges, sometimes even to the offending one, with no repeat of adverse effects. [10] There are still some situations which make the patients more vulnerable. They can be grouped into four main categories. [8]

The first one should be connected with pharmacological treatment details, like the initiation or increasing quantity of medication or its instability. Additionally, FGAs are more likely to cause NMS than SGAs, but the latter, especially those commonly used like olanzapine, quetiapine, or risperidone can also be guilty.[11,12] There is no agreement on the importance of depot or non-depot forms of administration, whereas the number of intramuscular or parenteral injections is claimed to be a risk factor. [11,13,14] NMS, which is worth emphasizing, has been described at all standard doses and in all routes of administration. Moreover, it is also proven that antipsychotic polypharmacy and simultaneous use of medications which predispose to NMS, like lithium and carbamazepine, are also bad predictors. [15]

Another group of agents are environmental ones, including high pulse, systolic and diastolic blood pressures, temperature, physical restraint or exhaustion, hot weather, malnutrition and iron deficiency. [14,16,17] It is well established that NMS afflicts more often young (peaking at 20–25 years old) men than women (ratio 1.47:1) - this fact is probably related to the higher necessity of administering neuroleptics in this population. Moreover, questions arise about the lack of compliance in this group of patients, leading to a labile drug dosage.[18,19] A further problem is the presence of pre-existing structural brain damage such as tumors, functional difficulties like delirium, dementia or other psychiatric disorders, for example, bipolar disorder or schizophrenia. [20]

In connection with a case report that showed NMS occurrence in family clusters [21], some research was conducted, confirming the genetic component of NMS. It is connected with a reduction in the function of the D2 dopamine receptor due to the presence of A1 and A2 alleles. Studies have found that the probability of developing NMS is 10.5 times higher in A1 allele carriers than in non-carriers, as they present an alteration of dopaminergic activity. [22–24]. Additionally, patients who experienced NMS are at greater risk of developing it once more. [8]

Clinical presentation

The onset of the symptoms usually takes place 1-3 days after the initiation of the treatment, but it can also occur a few weeks later or after a rapid increase in the dose of medication. Principal symptoms include altered consciousness, lead-pipe rigidity, hyperthermia, and autonomic dysfunction. They may occur simultaneously, but on the other hand, not all of them must appear to recognise the syndrome. To check the pattern of presenting symptoms, Velamoor and colleagues carried out a study, which resulted in describing a consistent pattern for 82.3% of examined patients, sequencing the chance of mental status and rigidity arising before hyperthermia and autonomic dysfunction.[25]. High temperature (over 38-40 °C) without chills usually doesn't respond well to antipyretic drugs. It is related to dopamine receptor antagonists influencing the CNS and causing heat loss anomalies. Muscle rigidity, also involved in producing excess heat, varies from mild to severe, opisthotonic tone, followed by trismus, nystagmus, or dysphagia. The abnormal function of the autonomic system results in extreme diaphoresis, an accelerated heartbeat, labile hypertension, sialorrhea, and urinary incontinence. Hallmark symptoms also include wavering of mental status, mutism or kinetic agitation. It is worth emphasizing that NMS associated with SGA is usually less severe and

more difficult to recognise than NMS caused by FGA. It manifests with more restricted muscle rigidity and a much smaller creatinine kinase level. [26]

Complications

As mentioned at the beginning, the mortality rate comes to 5.6%, which is a decrease compared to previous studies. [27] Rhabdomyolysis occurs in about one-third of patients and is considered to cause myoglobinuric acute kidney injury. Myoglobinuria, hyperkalemia, hyperphosphatemia, hypercalcemia or hyperuricemia can be detected in lab tests.[18,28] Sialorrhea and dysphagia carry a greater risk of pneumonia induced by aspiration. A prolonged stay in an intensive care unit can sometimes lead to sepsis transformation, multiorgan failure and DIC.[29] Regarding autonomic dysfunction, the patients can also present Takotsubo cardiomyopathy and cardiac arrhythmias may occur as coexisting neuroleptic side effects or due to electrolyte imbalance.[18]

Diagnostic criteria

There is no one unified diagnostic criteria to distinguish NMS. Over the years, an extensive list of guidelines has been provided. The most common ones are the DSM-5 criteria[30] and Levenson's criteria[31]. They are followed by Adityanjee et al.'s criteria, Pope et al.'s criteria, Caroff and Mann's criteria, Addonizio's et al.[30,32]

According to the DSM V criteria, muscle rigidity, fever, diaphoresis and neuroleptics exposure are major symptoms, while autonomic disturbances, worsened mental status, motor symptoms and laboratory findings are categorized as minor ones. On the other hand, Levenson's criteria do not include antipsychotic administration or rigidity as a criterion, which makes this criteria more useful for recognising an atypical NMS process. There are not many differences between the symptoms included in several types of criteria; nevertheless, thereis as disparity in their importance. All sets of criteria emphasize that the NMS diagnosis is above all the exclusion of other conditions, and in majority those criteria consider muscle rigidity and hyperthermia as cardinal symptoms for the differential diagnosis.

Differential diagnosis

The examination process should be focused on verifying whether the presented syndrome is actually NMS or whether another disease is more likely. There are a number of conditions

which can reveal themselves with similar symptoms. Starting from endocrinopathies such as pheochromocytoma and thyrotoxicosis through mixed connective tissue diseases or other autoimmune disorders, and finally coming on to the negative influence of stimulants, hallucinogens, alcohol or sedative withdrawal. A closer look should be first and foremost taken at serotonin syndrome, malignant hyperthermia, malignant catatonia, anticholinergic syndrome, infectious diseases of the CNS, tetanus infection, and severe lithium intoxication. [9,33]

Serotonin syndrome is connected to an increased level of serotonin as a result of misguided drug choices or self-poisoning attempts.[34] It is usually compared to NMS as it may occur through the simultaneous use of antipsychotics and antidepressants, provoking difficulties in the correct treatment.[35] Even though these conditions share their hallmarks, gastrointestinal symptoms, shivering, hyperreflexia, myoclonus and ataxia remain fundamental distinctions.

Malignant hyperpyrexia is a genetic muscle membrane disorder that usually develops after exposure to inhaled anesthetics or succinylcholine. In view of similar symptoms, the main possibility to differentiate one from another is through a precise interview.[18]

Malignant catatonia is mainly characterized by hyperpyrexia and rigidity. The presence of prodromal behavioral or motor symptoms, such as psychosis, agitation, dystonia or stereotypic movements can help to differentiate it from NMS. The aforementioned are however very difficult to distinguish.

No tests allowing to verify NMS diagnosis are yet available. Still, some lab tests might give important clues. Firstly, the CPK increase has significant meaning as it usually reaches above 1,000–10,000 UI/L when NMS develops. Other situations, such as physical restraint or intramuscular drug administration can also increase the CPK level, but it is usually below 600 UI/L. Apart from that, in patients suspected of the discussed conditions, it is recommended to run a morphology, coagulogram and general urine test, check the levels of creatinine, urea, electrolyte, transaminases and cardiac markers. If required, medical imaging (MRI, TK), cerebral fluid examination and toxicology should be considered to avoid any delay in the treatment of CNS infection. Furthermore, there is a nonfocal generalized slowing in 54% of performed EEG.[36] The results of blood tests are usually the following: leukocytosis, thrombocytosis, decreased iron level and dehydration. Electrolyte imbalance comes out as hyperphosphatemia, hyperkalemia, hypocalcemia, hypomagnesemia, hypo or hypernatremia.

Muscle damage due to rigidity and hyperpyrexia explains the elevated levels of CK, liver function tests and lactate dehydrogenase.[18]

Treatment

All pharmacological and nonpharmacological treatment methods are not well evaluated because of limited NMS prevalence and its acute onset. The best way to improve a patient's recovery forecast is fast symptom recognition and the discontinuation of neuroleptics.[37] Aggressive, supportive care should be taken over sufferers, including inserting intravenous channels for fluid or drug administration. Dehydration due to hyperpyrexia and malnutrition should be managed, as they can lead to renal failure. With the use of intensive hydrating, there is also the possibility of rebalancing electrolyte disturbances, especially hypokalemia. As the patients with NMS usually remain in a coma, strict monitoring for complications such as cardiorespiratory failure, aspiration pneumonia, thromboembolism and renal failure is demanded. Within supportive care, oxygen should be administered at a fiO2 in the range of 24-28% though oxygen masks, as well as a nasogastric tube might be essential to nourish patients whose health has not improved for a long time. Prophylactic endotracheal intubation should be considered to prevent aspiration pneumonia and dysphagia in patients with sialorrhea. On the other hand, a non-invasive way to reduce the risk of aspiration pneumonia is a semi-recumbent position (defined as elevation of the head of the bed to 45 degrees). [38] Moreover, even though physical measures to control temperature, such as application of wet cooling blankets and ice packs have not been systematically evaluated, they carry low risks and can help to prevent fever. Since the patients remain in a coma or need physical restraint, it is also essential to administer low-weight heparins and promote early mobilization to prevent the occurrence of pulmonary thromboembolism. Thanks to appropriate care, most patients recover fully in 2 to 14 days.

Treatment recommendations for NMS are sometimes conflicting. The four main drug groups which appear to have a positive impact are benzodiazepines, dantrolene, bromocriptine, and amantadine. If there is no improvement, ECT ought to be carefully considered, as the particular duration of drug administration is not defined in the guidelines.[30]

Benzodiazepines are said to abate illness and quicken recovery. Lorazepam in doses of 1-2 mg intravenously every 4-6 hours, accompanied by supportive care is usually the first clinical intervention in patients with acute NMS, decreasing rigidity and fever within 24-48 hours. [36]

Dopamine receptor agonists, like bromocriptine and amantadine are often preferred, because of the dopamine blockade hypothesis of NMS. Their advantages include reversing parkinsonism in NMS, reducing hospitalization time and mortality rates. [5] They are both taken orally with a recommended starting dose of 200-400 mg daily of amantadine and 5-7,5 mg of bromocriptine. Bromocriptine should not be dechallenged within 10 days after remission because recurrence may come from premature discontinuation. [39]

Dantrolene is a hydantoin derivative that acts on peripheral skeletal muscle, inhibiting calcium release from the endoplasmic reticulum. For this reason, it can be more helpful in patients presenting with extreme rigidity and fever.[40] It must be emphasized that popular choices to control labile hypertension are calcium channel blockers (verapamil and diltiazem), which should not be served simultaneously with dantrolene, since their combination can lead to hyperkalemia and cardiovascular collapse. [41] It is administered intravenously at a dose of 1-10 mg/kg body weight or per os at 50-600 mg qd.

Kuhlwilm and colleagues prepared a systematic review of 405 NMS cases in which they compared the effect of treatment in patients who got medications or ECT with those who received only supportive care. It was shown that in severe NMS, supply of dantrolene, bromocriptine or usage of ECT compared to supportive care, decreased mortality rates, contrary to mild to moderate NMS, where no relevant difference was noticed. [42]

Therapy should be postponed for at least 14 days or more if the syndrome was caused by long-acting drugs. If there is an underlying condition which requires neuroleptic rechallenge, low dose of SGA should be given, along with careful monitoring. Moreover, intravenous and intramuscular administration forms, as well as lithium in conjunction are denied, as they carry greater risk. The chance of redeveloping NMS is 30% after restarting antipsychotic treatment.

Electroconvulsive therapy

Shock treatment, in turn, is usually considered when there is no health improvement during the first 2-3 days of treatment. It was also found to be effective, especially in severe cases of NMS, so decisions about ECT ought to be made without any delay. The total recommended treatment consists of 6-10 sessions, but the response occurs on average after 4 sessions.[43] Furthermore, it turned out that ECT can treat some underlying conditions, such as residual catatonic or parkinsonian states, when neuroleptics usage is abandoned. While the procedure

is performed, it is required to monitor muscle injury and kalium level.

Conclusion

Neuroleptic Malignant Syndrome is a rare and life-threatening condition, which for the meantime is not well fathomable. Its symptoms are not specific and can be easily overlooked or mistaken with other conditions. Yet there are still no tests which help one to explicitly make a diagnosis. All the aforementioned reasons should draw clinicians' attention to vigilant guarding over patients treated with neuroleptics and encourage immediate withdrawal if there are any suspicions about developing NMS.

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