

Neuroleptic syndrome among patients receiving antipsychotic drugs-review

Síndrome neuroléptica entre pacientes recebendo drogas antipsicóticas- Revisão

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ABSTRACT

Neuroleptic Malignant Syndrome is occasional but deadly reaction, which results from treatment with antipsychotic medications. Risk aspects include the following: dehydration, agitation, and history of neuroleptic malignant syndrome. Despite the fact that Neuroleptic Malignant Syndrome has been described as adverse effect from treatment with antipsychotic medications, patients suffering with chemical imbalance of brain or mood disorders, especially when treated with lithium, fall in to higher risk group. Standard criteria for the diagnosis of Neuroleptic Malignant Syndrome highlight the following signs and symptoms: muscle rigidity, hyperthermia, alteration in mental status, and autonomic dysfunction. Syndrome usually lasts from 7 to 10 days in simple and uncomplicated patients who receiving neuroleptics orally. Early detection and diagnosis of syndrome are up the most importance, where discontinuance of triggering medication, managing of fluid balance, control of body temperature and close observation for complications takes place. Use of dopamine agonists should be advised in more complex cases. Electroconvulsive therapy has also been effective in a few cases. In this article author reviews the proposed pathology, symptoms, complications, and treatment of Neuroleptic malignant syndrome.

Key Words: Neuroleptic syndrome, Antipsychotic drugs, Diagnostic criteria, Side effects, Mental illness.

RESUMO

A síndrome neuroléptica maligna é a reação ocasional, mas mortal, o que resulta do tratamento com medicamentos antipsicóticos. Aspectos de risco incluem: desidratação, agitação e história de síndrome maligna por neurolépticos. Apesar do fato da síndrome neuroléptica maligna ter sido descrita como efeitos adversos do tratamento com drogas antipsicóticas, os pacientes sofrem com desequilíbrio químico dos transtornos cerebrais ou do humor, especialmente quando tratados com lítio, podem cair no grupo de risco mais elevado. Entre os critérios padrão para o diagnóstico de síndrome neuroléptica maligna, destacam os seguintes sinais e sintomas: rigidez muscular, hipertermia, alteração do estado mental, e disfunção autonômica. A síndrome geralmente dura de 7 a 10 dias em pacientes simples e não complicados que recebem neurolépticos por via oral. A detecção precoce e diagnóstico da síndrome são importantes, devendo ser providenciados: descontinuidade da medicação, balanço hídrico, controle da temperatura corporal e estreita observação de complicações. O uso de agonistas da dopamina deve ser aconselhado em casos mais complexos. Terapia electroconvulsiva também tem sido eficaz em alguns casos. Neste artigo os autores analisam a patologia, sintomas, complicações e tratamento da síndrome neuroléptica maligna.

Descritores: Síndrome neuroléptica maligna. Fármacos antipsicóticos. Critérios de diagnóstico. Efeitos secundários. Doença mental.

INTRODUCTION

Neuroleptic malignant syndrome is a potentially lethal syndrome associated with administration of neuroleptic medications. It has also been described as occurring on withdrawal of medications with central dopaminergic influences¹. Neuroleptic syndrome remains a significant source of morbidity and mortality among patients receiving antipsychotic medications². Data from the U.S. Agency for Healthcare Research and Quality indicate that about 2,000 cases of Neuroleptic syndrome are diagnosed annually in hospitals in the United States, incurring health care costs of 70 million, with a mortality rate of 10%.

The biggest risk factors include patients who are in the initiation of or increase in dose of neuroleptic medications³. When potent medications are used in a very high dose it may increase the risk for developing of Neuroleptic syndrome.

The congruent use of various neuroleptics, or adjuvant use of inductive drugs like lithium, also increases the risk for developing Neuroleptic syndrome ^{4,5}. In spite if Neuroleptic syndrome can develop at any time while patient on neuroleptic treatment, it is not likely to arise if a patient has been receiving a stable dose of their antipsychotic medications for prolong period of time and when patient is compliant with medication regimen ⁶.

A multitude of other risk factors have been recorded from case studies of Neuroleptic Malignant syndrome which combine dehydration, physical exhaustion, exposure to heat, hypernatremia, iron deficiency, malnutrition, trauma, thyrotoxicosis, alcohol, psychoactive substances, and presence of a structural or functional brain disorder such as encephalitis, tumor, delirium, or dementia ³. Males younger then 40 years of age are found to be at greater risk of developing Neuroleptic syndrome as well. Postpartum women may also be at slightly higher risk of developing Neuroleptic syndrome ⁷. Reports of identical twins and a mother and 2 of her daughters all presenting with Neuroleptic syndrome propose that a genetic risk factor for Neuroleptic syndrome may exist, ⁸ and some limited genetic investigations help support existence of genetic component to the condition ⁹, possibly through a genetically associated reduction in the function of the D2 dopamine receptor ¹⁰.

The syndrome is accompanied by a number of symptoms. For example, it is characterized by hyperthermia and muscle rigidity. In other cases, patients experience significant changes in their cognitive abilities ⁹. Professionals regard the syndrome as a deadly mental condition, although alterations of the antipsychotic prescriptions have helped to reduce the number of reported cases.

In the larger field of psychiatry, patients with this condition receive various forms of medications in efforts to alleviate their symptoms. Depending on the nature of the diagnosed condition, practitioners prescribe medications intended to control or minimize the effects of the syndrome on the overall health of the patient. One such psychiatric disorder is psychosis. Patients who suffer from this mental disorder tend to experience hallucinations and delusions ¹⁰. The medication given to such patients is what constitutes the antipsychotic drugs ¹¹.

There are two types of antipsychotic medications. They include the first and the second-generation drugs. When administered to a patient, they tend to localize their action to the brain's dopamine pathways¹². They achieve this by blocking the receptors in this region. Clozapine and olanzapine are two common examples of antipsychotic drugs¹³. Neuroleptic syndrome resulting from these drugs is more evident in cases where typical antipsychotic medication is used.

A Review of Neuroleptic Syndrome

Research is ongoing to determine the pathophysiology of neuroleptic syndrome¹⁴. Studies reveal that the aforementioned blockage of receptors in the brain of the patient is what contributes to the development of the disorder¹⁵. The receptors that are affected by this blockage include the D₂.

Butwicka et al²⁵ carried out a study to examine the syndrome among patients with a CYP2D6 deficiency. Adolescents were the participants in this study. The findings made indicated that the patients had high concentrations of antipsychotic drugs in their systems. The symptoms exhibited by the patients indicated that the neuroleptic syndrome afflicted them. As a result, the researchers established a link between the drugs used by the patients and the disorder.

Diagnosis

Like in any other medical disorder, a patient suffering from neuroleptic syndrome will exhibit certain symptoms unique to the condition. The most common symptom involves sustained mental instability^{11,16}. Such patients generally display some sense of unease in their normal levels of 'stability'. In addition, the condition is characterized by extrapyramidal symptoms. In such cases, a patient is unable to initiate movement owing to impediments in their locomotive abilities^{16,10}. Another trait associated with neuroleptic syndrome is hyperpyrexia. In this case, the patient experiences an extremely high fever⁹. Detection of any of these symptoms is enough grounds to carry out a diagnosis.

Compared to other common neurological conditions, diagnosis of neuroleptic syndrome is not straightforward. The most obvious reason for this absence of a proper diagnosis framework is the lack of consensus among practitioners with

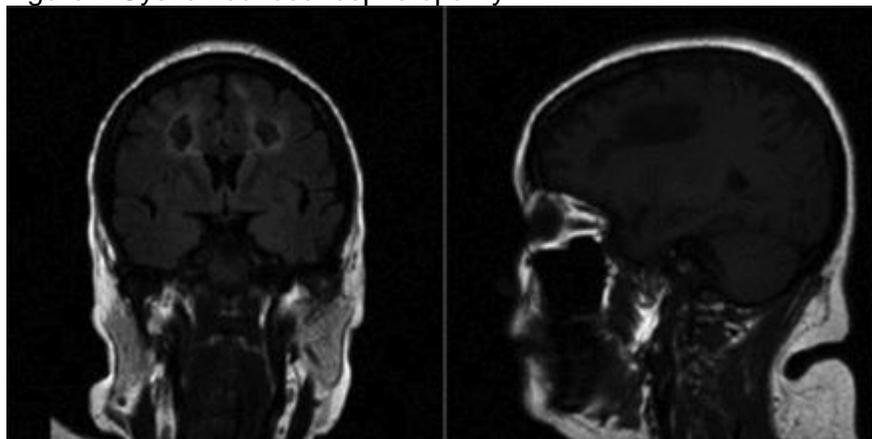
regards to the most preferred approach ¹⁷. However, there are few publications that make reference to the criteria used in diagnosing this condition. In most cases, clinicians are able to identify the disorder by relying on the symptoms presented.

One such publication that makes reference to possible diagnostic criteria is *The Diagnostic and Statistical Manual of Mental Disorders*. The manual explains that an analysis of the condition should begin with the identification of the main symptoms associated with it ^{11,18}. Thus, when a patient complains of a high fever, which is accompanied by severe rigidity of their muscles after using antipsychotic drugs, there are enough grounds to believe that they might be suffering from the disorder.

A complete diagnosis must ensure that the patient exhibits additional symptoms. Such other symptoms include mutism, elevated blood pressure, and dysphagia. Incontinence and diaphoresis are also evident among such patients ^{12,13}. A complete diagnosis requires a patient to exhibit two of the additional symptoms ¹⁹. When presented together with fever and muscle rigidity, such traits as leukocytosis make for a strong diagnosis.

Figure 1 below is an illustration of a scan to verify leukocytosis that is associated with the condition. Such scans help practitioners to detect the syndrome early enough to minimize fatalities.

Figure1: Cystic Leukocencephalopathy



Source: Smail et al. (2012)¹⁰

Fatality in neuroleptic syndromes is associated with cystic leukocencephalopathy. Figure1 is an MRI of a patient who had an overdose of

olanzapine, venlafaxine, quetiapine, and propranolol. The four are common antipsychotic drugs. As evidenced by the white matter in the MRI, the patient has developed cystic leukoencephalopathy ¹⁰.

A test for the leukocyte count in an individual helps to strengthen the diagnosis. The reason is that a reduced count increases the possibilities of the syndrome's presence. It is important to appreciate that neuroleptic syndrome can be experienced in various degrees. As such, a practitioner is advised to adopt a critical diagnostic approach.

Diagnostic Criteria for Neuroleptic Syndrome

The information below is based on information from the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, Washington, DC, American Psychiatric Association, 2013.

A	The development of severe muscle rigidity and elevated temperature associated with the use of antipsychotic medication.
B	Two (or more) of the following:
	1 diaphoresis
	2 dysphagia
	3 tremor
	4 incontinence
	5 changes in level of consciousness ranging from confusion to coma
	6 mutism
	7 tachycardia
	8 elevated or labile blood pressure
	9 leukocytosis
10 laboratory evidence of muscle injury (e.g., elevated CK)	
C	The symptoms in Criteria A and B are not due to another substance (e.g., phencyclidine) or a neurological or other general medical condition (e.g., viral encephalitis).
D	The symptoms in Criteria A and B are not better accounted for by a mental disorder (e.g., Mood Disorder with Catatonic Features).

In the paragraph above indicates the symptom corresponding to the degree of the syndrome's manifestation. However, it is important to note that the said diagnosis should be arrived at under certain circumstances. It should be made in the event that toxicology report suggests the presence of a particular antipsychotic

drug ²⁰. Such an approach confirms that neuroleptic syndrome is a side effect of antipsychotic drugs.

Sa et al. carried out a study to determine the relationship between olanzapine and the malignant form of neuroleptic syndrome. In their study, they found that schizophrenic patients using the antipsychotic drug exhibited symptoms that suggested they had acquired the syndrome. The study confirmed that neuroleptic syndrome results from the use of such antipsychotics. Patients suffering from schizophrenia and psychosis are usually given the same drug, albeit in different doses ²¹.

In a literature review, Croarkin et al⁴ sought to determine whether the symptoms are exhibited differently or not depending on one's age. The information obtained was limited to patients below 18 years. The study by Croarkin et al⁴. revealed that between 1991 and 2007, prevalence of the syndrome was higher among adults compared to teenagers. The findings established a link between the condition and age. To this end, the study indicated that the symptoms associated with this disorder were similar among adults ¹².

Regardless of the prevalence disparities between adults and children, psychiatrists are advised to exercise caution when making antipsychotic prescriptions to young patients ¹⁵. The argument is based on the undeniable fact that neuroleptic syndrome is closely associated with the unintended effects of these drugs. Antipsychotic medication poses health risks to children given their low levels of immunity. As such, practitioners in this field are encouraged to handle their young patients with a lot of care.

CONCLUSION

The malignant version of neuroleptic syndrome is quite rare ^{17, 22}. However, the risk of fatality is high regardless of whether the condition is malignant or not^{23,24}. Due to this, questions are raised with regards to the preferred treatment approach. The mere fact that one can be accurately diagnosed with the condition is not enough to address these concerns. In their study, Berman¹ points out that the first

step in dealing with this syndrome is to ensure that the effects of the causative agent are dealt with as soon as possible. The treatment option should be implemented fast enough to reduce chances of fatality.

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