

# Difficulties in diagnosing neuroleptic malignant syndrome

Monica S. Zolezzi, B.Pharm, MSc, Abdullah M. Al-Hathloul, MD.

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## ABSTRACT

This report describes a recent case of neuroleptic malignant syndrome, a rare adverse effect of antipsychotic medications. Assessment of the neuroleptic malignant syndrome was carried out by using the Naranjo Algorithm Probability Scale which resulted in a highly probable reaction to haloperidol. The difficulties in establishing the diagnosis in this patient lead to late intervention resulting in a slow recovery and prolonged hospitalization. Our objective in this presentation is to highlight the importance of early recognition of this potentially fatal adverse drug reaction.

**Keywords:** Neuroleptic malignant syndrome, antipsychotics, adverse drug reactions.

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Neuroleptic malignant syndrome (NMS) is a potentially fatal form of idiosyncratic drug-induced hyperthermia.<sup>1</sup> It is usually rare, the exact incidence is unknown but it may possibly occur in around 0.02% to 3.2% of patients receiving neuroleptics,<sup>1,2</sup> death rates are reported to be 14% for oral antipsychotics and 38% for depots.<sup>3</sup> These rates may be reducing due to increased awareness, early intervention and reduction in risk factors.<sup>3,4</sup> It occurs with the older neuroleptic agents as well as with the newer atypical agents.<sup>5</sup> Failure to identify cases of NMS and lack of reliable epidemiologic data make this figure uncertain. Apart from hyperthermia, the presenting characteristics of NMS include severe muscle rigidity, dysphagia, altered blood pressure, elevated creatine kinase levels, elevated white blood cell count, altered mental status, and autonomic dysfunction.<sup>2,3</sup> The exact cause or mechanism for the development of this reaction is not known, it is thought to be a sudden over-blockade of dopaminergic function leading to disruption of the thermoregulatory center.<sup>3</sup> Because NMS is potentially life-threatening, treatment should be

immediate and intensive. In this report, we present another case of haloperidol-induced NMS and address the difficulties encountered in establishing the diagnosis, which often delay the implementation of additive treatment.

**Case Report.** A 17-year-old Saudi female, was admitted to the psychiatric ward on March 2000 with symptoms of rigidity and retarded movements, specifically lack of flexibility, cogwheel rigidity, perplexed, frightened look in her eyes, semi-mute, admitted with the initial diagnosis of catatonia. Upon investigation, it was recorded that approximately 2 weeks prior to this admission, the patient was presented to Accident and Emergency (A&E) due to a change in her behavior, such as agitation, fearful, isolatory, with query hallucinations, seeing a man in her room, and ideas of reference - family and friends talking with regards to her. When she was brought to the hospital A&E, her behavior became aggressive and required an intramuscular injection of haloperidol and lorazepam to settle her down before

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From the Departments of Pharmaceutical Services (Zolezzi) and Psychiatry (Al-Hathloul), Armed Forces Hospital, Riyadh, Kingdom of Saudi Arabia.

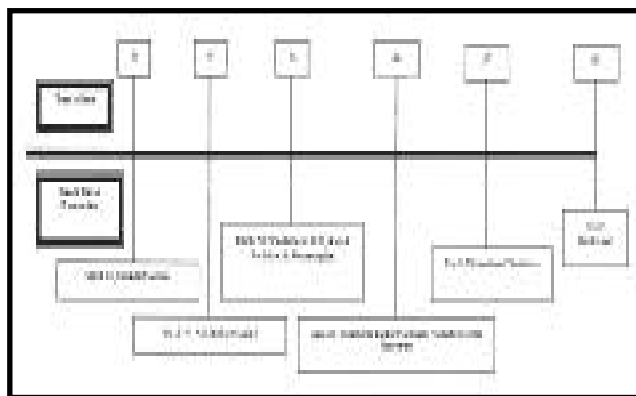
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Address correspondence and reprint request to: Dr. Monica Zolezzi, L-532 MODA, PO Box 7897, Riyadh 11159, Kingdom of Saudi Arabia. Tel/Fax. +966 (1) 4777714 Ext. 3432. E-mail: monizolezzi@yahoo.com

she was discharged home. During the following few days, the patient was noted not eating, withdrawn from family members, she showed difficulty in speaking, with severe muscle spasms in the neck and tongue protrusion. Soon after admission she was treated with intravenous fluids and occasional use of lorazepam or procyclidine for stiffness and drooling. She was investigated for possible catatonia, but her condition deteriorated over the next few days after admission, for which she required a transfer to the Intensive Care Unit (ICU). The following summarizes the laboratory findings upon transfer to ICU: Temperature, fluctuating from 37.3-40°C, increased creatine kinase: 460 (normal 50-170) increased alkaline phosphatase: 349 (normal 98-279) blood pressure, fluctuating from 126/90 to 100/50 blood culture: no growth. All other investigations normal (including lumbar puncture, computerized tomography, magnetic resonance imaging and electroencephalogram) No other significant findings. Six days after her admission, she was started on Dantrolene IV 50 mg every 6 hours and oral bromocriptine 2.5 mg twice daily, which was further increased to 5mg 3 times daily. A naso-gastric tube was inserted for feeds. She showed a gradual improvement in rigidity and was able to return to the psychiatric ward in April 2000. Intravenous dantrolene was switched to oral and tapered down until it was discontinued. She was maintained on Bromocriptine 5mg 3 times daily until just before discharge in June 2000, having fully recovered from her rigidity and mental condition.

Use of the Naranjo Adverse Drug Reaction (ADR) Probability Scale<sup>6</sup> indicated a highly probable relationship, between the development of the NMS-associated symptoms and the administration of haloperidol in this patient.

**Discussion.** Neuroleptic malignant syndrome is a diagnosis of exclusion;<sup>9-11</sup> thus, numerous other disorders must first be ruled out, in particular lethal catatonia which may be indistinguishable from NMS. Diagnostic criteria for NMS, such as the one provided by the Diagnostic and Statistical Manual of Mental Disorders (DSM),<sup>12</sup> may be useful for the practical clinician to clarify or solidify the diagnosis of NMS and promptly initiate treatment. Although the optimal treatment for NMS has not been fully established, prompt intervention is necessary, including the discontinuation of the offending drug(s) and rapid initiation of supportive care to stabilize respiratory, renal, and cardiac systems, such as correction of the dehydration and the hyperthermia. Sedation with benzodiazepines may also be useful.<sup>3</sup> All these measurements were promptly initiated in the patient, however, due to the diagnosis of NMS not being clearly established from the beginning, additional drug treatment was delayed until the 6th day after her admission (9 days after symptom



**Figure 1** - Time course of patient's neuroleptic malignant syndrome and its management.

initiation). The patient presented most of the DSM IV diagnostic criteria for NMS.

The benefit of adding specific therapies to supportive measures in the treatment of NMS has been controversial.<sup>7</sup> Most of the available reports, however, support that treatment with dantrolene, bromocriptine, or both, usually leads to a more rapid clinical response.<sup>7,8</sup> Neuroleptic malignant syndrome is a relatively rare complication of neuroleptic exposure. The literature has consisted of case reports rather than controlled studies. As a consequence, optimal treatment and prognosis remain controversial. The patient's response to dantrolene and bromocriptine was slow, but led to full recovery after 60 days of continuous treatment. Although speculative, the delay in initiation of additive drug treatment may have contributed to the delay in the resolution of the symptoms presented by the patient, in particular the muscle rigidity.

The time course of this patient's NMS presentation and its management is outlined in (Figure 1), showing that it took 86 days for a complete resolution of the syndrome. This case illustrates that NMS continues to be a diagnostic challenge to physicians primarily due to its diverse presentation, which may cause delays in the diagnosis and, consequently, treatment. Physician awareness and prompt initiation of specific therapy may be able to make a significant difference in the resolution of this clinical syndrome.

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