

Neuroleptic malignant syndrome

Diagnostic and therapeutic dilemmas in a general hospital setting

Naseem A. Qureshi, MD, PhD.

ABSTRACT

المتلازمة الخبيثة للمهدئات العصبية (NMS) هي حالة نادرة تهدد الحياة، وتحدث عادة بسبب استخدام الأدوية المضادة للحالات النفسية من النوع المعتاد أو غير المعتاد. نستعرض هنا حالة امرأة متوسطة العمر، تعاني من اضطراب ثنائي القطب وألم حاد في الظهر بسبب سقوطها عدة مرات، أدخلت على إثرها إلى المستشفى العام قسم الإصابات. بعد ثلاثة أيام من دخولها على المستشفى، تطورت لديها علامات وأعراض المتلازمة الخبيثة للمهدئات العصبية (NMS) بشكل مفاجئ، والسبب غالباً الهالوبيريدول (haloperidol) وهي حقنة تعطى عند الحاجة، ولكن كان هناك سبب إضافي هو أولانزابين (olanzapine). تأخر التشخيص (NMS) لمدة ثلاثة أيام مما أدى إلى مضاعفات خطيرة والتي كان من الممكن منعها بالتدخل السريع الذي يركز على التشخيص المبكر حتى في حالة غياب شروط هذا التشخيص. تحسنت الحالة بشكل كبير مع التدخل العلاجي واستمرت في الغسيل الكلوي. توفيت المريضة بسبب المضاعفات الكلوية. يجب تنمية وصف المضادات النفسية عند الحاجة للمرضى النفسيين اللذين يتم إدخالهم إلى المستشفيات العامة.

Neuroleptic malignant syndrome (NMS) is a rare life-threatening condition, usually induced by typical and atypical antipsychotics. A middle-aged woman with bipolar disorder and acute back pain due to multiple falls was admitted to the trauma ward of a general hospital. After 3 days, she suddenly developed signs and symptoms of NMS possibly caused by PRN injectable haloperidol, although the additional role of olanzapine could not be ruled out. A 3-day delayed diagnosis of NMS led to serious complications, which could be prevented by its prompt management contingent on its early diagnosis, even in the absence of certain diagnostic criteria. Although she improved substantially with treatment interventions and continued to have dialysis, she died later due to renal complications. The PRN administration of antipsychotic medications needs to be avoided among such psychiatric patients admitted to general hospitals.

Neurosciences 2008; Vol. 13 (4): 445-449

From the Administration for Mental Health and Social Services and Medical Research, Ministry of Health, Riyadh, Kingdom of Saudi Arabia.

Received 28th January 2008. Accepted 14th July 2008.

Address correspondence and reprint request to: Dr. Naseem A. Qureshi, Consultant Psychiatrist and Head of Research Unit, Administration for Mental Health and Social Services, Public Health Specialist, Administration for Medical Research, Ministry of Health, Riyadh, Kingdom of Saudi Arabia. Tel. +966 (1) 4738269. Fax. +966 (1) 2918017. E-mail: qureshinaseem@live.com

The neuroleptic malignant syndrome (NMS) is characterized by high grade fever, muscular rigidity, altered level of consciousness, autonomic dysfunctions, raised creatinine phosphokinase (CPK), and leukocytosis, and unpredictably induced by almost all typical and atypical anti-psychotics and some non-neuroleptics including antidepressants, which acutely shut down central dopamine D2 receptors and other neurotransmitters. Psychological stress, genetic vulnerability, and hyperactivity of the sympathoadrenal system also play an additional role in its development. In 7 published papers,¹ the author reviewed the epidemiology, etiologies, including the role of regulatory proteins, pathophysiology, diagnostic criteria, differential diagnosis, rating scales, challenge with neuroleptics, and outcome of NMS. Also, the author highlighted some vital implications of its early identification, prompt intervention, and re-initiation of appropriate neuroleptic therapy after 2 weeks hiatus therapy. This report has 2 objectives, 1) to clinically update NMS due to its ever changing parameters, and 2) to describe a patient with atypical NMS with serious complications developed due to delayed diagnosis in general hospital setting.

Clinical update. Evidently, the decrease in the incidence (0.02-12.2% to 0.07-0.2%) and mortality (20-30% to 5-11%) of NMS, was attributable to increased awareness, preventive strategies, early detection, and

treatment interventions targeting reported causes of death including myoglobinemic renal failure. Notably, almost all atypical antipsychotics including ziprasidone, perospirone, olanzapine, risperidone, paliperidone, quetiapine, amisulpiride, clozapine, and aripiprazole tend to induce atypical NMS, especially absence of muscle rigidity and no elevation in CPK, hence it should be suspected among medical patients of all age bands on atypical antipsychotics who do not manifest one or 2 core symptoms of typical NMS.²⁻⁶ Clinical wisdom suggests that none of these drugs should be used among patients with active NMS. Kato et al⁷ demonstrated this in patients with NMS having Cytochrome P450 (CYP) 2D6 gene deletion allele (CYP2D6*5) linked with 2 CYP2D6 genotypes (*5/*10 and *1/*5), which decrease CYP2D6 activity with drug accumulation. Neuroleptic malignant syndrome is not dose-dependent, however, rapid escalation of an offending antipsychotic may cause NMS. Abrupt withdrawal of fava beans containing levodopa also causes NMS among patients with Parkinson's disease.⁸ The rare occurrence of NMS among patients with physical diseases including burn, toxic epidermal necrolysis, dementias, Parkinson syndrome, and others posits diagnostic difficulties, and delayed treatment that frequently results in multiple serious complications including acute renal failure. Neither acute renal failure, nor known risk factors of NMS were correlated linearly to death coupled with NMS.⁹

Case Report. A 59-year-old lady was admitted to Rashid Hospital, Dubai under the care of the trauma team in late year 2005, due to fracture of L4-5 attributed to recent recurrent falls associated with ataxic gait. A brief review of her past psychiatric records revealed that she was admitted to the psychiatric department for the management of an acute manic phase of bipolar disorder for the first time in the year 2001. She was also found to have ataxic gait, recurrent falls, slurred speech, and right-sided hemiparesis, and was thoroughly investigated on the advice of a consultant neurologist who prescribed her antiepileptic treatment. She had marked cerebellar atrophy on CT suggestive of suspected brain focal parenchymal lesions. She was followed initially in the neurology clinic only for a few months after discharge from the psychiatric division.

From 2001 to late 2005, she had multiple psychiatric admissions due to manic relapses, and had multiple CT of brain for aforesaid neurology complaints with no additional findings. On each admission, she was treated either with risperidone, 4-6 mg daily or olanzapine, 10 mg daily with depakine chrono, 500-1000 mg daily, and procyclidine, 10-15 mg/day with good improvement. Her last visit to the psychiatric clinic was on the 12th of November 2005, and her condition was stable. The

maintenance treatment was olanzapine, 10-15 mg/day, and depakine chrono, 1000 mg daily.

The present episode of recurrent falls forced her to visit the emergency room (ER), and the admitting trauma doctor requested urgent psychiatric consultation on the pretext that she is a known psychiatric case. The psychiatrist examined the patient in the ER, and continued the same maintenance treatment, namely, olanzapine 10 mg/day and depakine chrono, 1000mg/day. It was learned from her relatives that she was not using any other medications, and recently no alterations in her drug regimen were carried out. At that time, there was no evidence of fever, muscular rigidity, confusion, high or low blood pressure, except she had abnormal, involuntary movements of her lower limbs, and mild agitation, and restlessness. The next day, the patient was again reviewed by the psychiatrist for reported continuing agitation, pulling intravenous tubes, and tendency to frequently get up from, and leave the bed as observed by the nurses. Olanzapine were increased to 20 mg/day, and depakine chrono to 1500 mg/day, to prevent a possible manic relapse. According to the trauma team, she needed complete immobilization, and was frequently restrained. Such strategies put pressure on the psychiatrists to give PRN doses of psychotropic medications. On day 3, she was referred to the medical specialist for evaluation of one day high-grade fever. On days 1 to 3, this patient received injectable PRN medications including haloperidol (total 15 mg), lorazepam (total 6 mg), midazolam (total 30 mg), and procyclidine (total 15 mg), which were recommended by psychiatric residents on emergency calls. She was also examined by the neurologist for the jerky movements of lower extremities, and was prescribed symptomatically dilantin sodium, 300 mg/day. According to the medical evaluation, she was semiconscious, and her orientation was impaired. She was restless, irritable, sweating profusely, and jumps on the bed, however, no obvious extrapyramidal manifestations were observed. Her pulse was 129 beats per minute, and the recorded temperature was 40°C and blood pressure was normal. Systemic examination showed that she had good air entry with occasional crepitations, and cardiovascular system was normal. Abdominal examination showed a lower mid line old scar, otherwise it was soft, non-tender, and no signs of visceromegaly. Assessment of the CNS was difficult as the patient was constantly moving, and restrained. Neck rigidity was voluntary, and the plantar reflex was flexor. Based on medical evaluation, several medical conditions were entertained such as, meningitis/encephalitis, cerebral malaria, thyroid storm, heat stroke, seizure disorder, malignant hyperthermia, lethal catatonia, serotonin syndrome, and NMS. Consequently, a variety of laboratory investigations

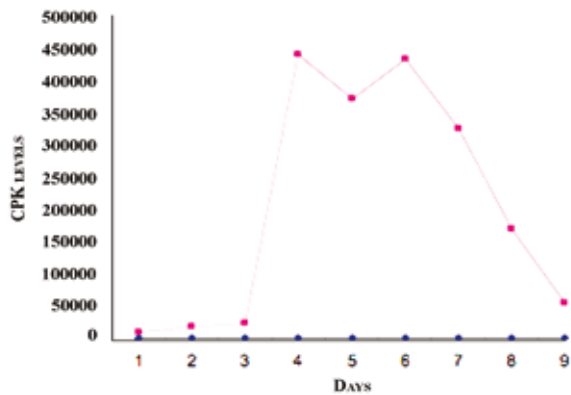


Figure 1 - Distribution of creatinine phosphokinase (CPK) levels by days.

were carried out and the results were as follows, white blood count (WBC) 12500/mm³ (4500-11000/mm³), hemoglobin 11.8 g/dl (12-16 g/dl), platelets 278,00/mm³ (150,00-400,000/mm³), urea 26 mg/dl (7-20 mg/dl), creatinine 1.2 mg/dl (0.5-1.4 mg/dl), sodium 143 mEq/L (135-146 mEq/L), and potassium 3.6 mEq/L (3.5-5.5mEq/L). The blood and urine culture and sensitivity was negative; the mid stream urine (MSU) test showed no WBC, red blood cells, protein or epithelial cells; the brain CT scan showed no significant additional findings; the thyroid function tests were normal; and the malarial parasite test was negative. Based on these laboratory results, and the emerging clinical manifestations, the diagnosis of NMS was retained, and several other clinical diagnoses in terms of fever due to respiratory tract infection, urinary tract infection, and sepsis and nosocomial infections were considered. In the light of further deteriorating course of the patient NMS leading to severe rhabdomyolysis, acute renal failure, and systemic infections was considered. The relevant investigations carried out on the third day, and subsequently to further confirm the most suspected diagnosis of NMS were as follows; repeat CPK levels on multiple days (normal range 96-140 U/L) were 9646 U/L, 18550 U/L, 23692 U/L, 442240 U/L, 371800 U/L, 434300 U/L, 327000 U/L, 170000 U/L, 54200 U/L (Figure 1); lactic dehydrogenase, 1014 IU/L (50-150 U/L); aspartate aminotransferase (AST or SGOT) - 90 U/L (5-40 U/L); alanine aminotransferase (ALT or SGPT) - 48 U/L (7-56 U/L); urea - 240 mg/dl; creatinine - 7.8 mg/dl; potassium - 5.8 m mol/l; calcium - 8.5 mg/dl, 8 mg/dl, and 4.4 mg/dl (8.5-10.5 mg/dl). Myoglobin was detected in the urine. Repeat MSU showed *Escherichia coli*. Blood and sputum culture and sensitivity showed growth of acinetobacter, and she was confirmed to have

methicillin-resistant *Staphylococcus aureus* detected in the intensive care unit (ICU) of Rashid Hospital. The attending senior medical registrar presented this case for thorough discussion in the morning meeting of the medical department attended by all staff including the invited specialist senior psychiatric registrar. All staff members reached a consensus diagnosis of NMS with multiple secondary complications. This discussion was held when the patient was in the Nephrology section of Dubai Hospital.

Management. In view of the deteriorating clinical course associated with serious complications and supported by laboratory investigations, there was a very high index of suspicion of NMS. On day 4, the attending psychiatrist reviewed the case, and all antipsychotic medications were discontinued immediately. A plan of management was discussed with the medical team. Hydration was started to balance the intake-output. Electrolyte imbalance was also corrected. Cold sponging was carried out to reducing body temperature. Rocephine, 2 gm twice/day was started empirically to treat secondary systemic infections. Despite aggressive medical management, she remained irritable, restless, and continued to deteriorate medically. She was electively intubated after 2 days, and was shifted to the ICU with high fever. With continuing supportive treatment, she also received other antibiotics, however, her urine output kept on dropping. She was transferred to the ICU of Dubai Hospital for continuous veno-venous hemodialysis, which was continued for 4 days. Later she was kept on regular hemodialysis. She was extubated on the 17th of December 2005. She continued to have mild fever, cognitive changes, and involuntary movements. In addition to the enumerated management, she was simultaneously given bromocriptine, 7.5 mg/day, and dantrolene 25 mg, 3 times a day, relatively specific drugs for the treatment of NMS. Her condition improved over 8-10 days. Nephrologists consulted the treating psychiatrist for starting antipsychotic medications, who was advised to give only clonazepam, 2-4 mg/day, for residual mild agitation, involuntary movements, and insomnia. Her overall condition improved further, however, she later died due to renal complications.

Discussion. The patient suffered from severe atypical NMS as shown by clinical manifestations, laboratory results, and associated life-threatening complications. This patient did not develop any extrapyramidal symptoms (EPS) such as increased muscle rigidity, catatonic features, drooling of saliva, tremors, and dystonia, reportedly one of the salient diagnostic criteria of typical NMS. This atypical presentation was possibly induced by olanzapine instead of haloperidol. This finding supports the results of other researchers,⁶ and

suggests that all patients with NMS induced by atypical antipsychotics may not develop EPS, and even then the physicians should have a high index of suspicion of atypical NMS, simply based on its other consistent clinical and laboratory criteria. It is important to know that only 80-100% of patients treated with first generation antipsychotic medications develop EPS, and therefore the role of haloperidol administered PRN to this patient cannot be ruled out. It is speculated that both olanzapine and haloperidol might have contributed to the development of NMS in this case. Arguably then was, why this patient did not develop NMS when she was treated with olanzapine alone over the last 5 years. However, there are reports of atypical NMS caused by 2 antipsychotic drugs given simultaneously.¹⁰ The implications of these findings are 1) PRN use of antipsychotics from different pharmacological groups should be used cautiously among vulnerable psychiatric inpatients with neurological insult, and 2) the strategies to manage agitation should include proper restraint and the judicious short-term use of benzodiazepines instead of antipsychotics. Notably, a single case report is not enough to suggest those kinds of implications, however, NMS is a rare entity. A number of risk factors of NMS shown in this patient were dehydration, agitation, exhaustion, inconsistent use of PRN antipsychotics, and rapid escalation of their doses, and psychological stress of physical disease. A constellation of neurological signs and symptoms revealed in this patient also were reported to predispose patients to develop NMS, when they are exposed to antipsychotic medications. Drug-induced or idiopathic chronic involuntary movements were also reported to be a risk factor of NMS. According to some researchers, the surviving NMS patients tend to show a variety of neuropsychiatric sequelae such as cognitive changes including amnesia, insomnia, agitation, and restlessness, and retardation, or catatonia. Some of these were shown in this case, which will assume clinical importance, and should have the focus in future research to reduce their occurrence.¹¹ The implication of these findings is that the risk factors of NMS should be identified prior to giving any antipsychotic medications, which is mostly possible in in-patient settings instead of in the ER, as this exercise requires both a comprehensive evaluation and review of the entire medical records of the patient. From the treatment perspective, early recognition of NMS, immediate discontinuation of all offending medications including neuroleptics and non-neuroleptics, correction of volume depletion, hypotension, and electrolyte imbalance, and control of temperature are most important steps in the management of NMS. The use of relatively specific drugs such as bromocriptine, dantrolene, and amantadine depend on the severity of NMS that could be assessed by using

scales.¹² This NMS rating scale has 6 domains (clinical and laboratory) with good reliability and validity, the later was reflected in a relationship of severity with duration and outcome. This scale measures the severity of NMS in the clinical setting for supporting diagnosis, monitors patients progress, also applicable to other neuroleptic malignant-like syndromes such as lethal catatonia, and atypical NMS. Obviously, the treatment of NMS associated with myoglobulinemic acute renal failure by dantrolene sodium and hemodialysis, or hemodiafiltration was reported to be effective, and in one study, all 6 patients improved.¹³ Early alkalization of the urine with IV sodium bicarbonate can prevent renal failure. Electroconvulsive therapy is a good option for resistant NMS among patients with medical diseases, psychosis and severe depression.¹³ Notably, Strawn et al¹⁵ have comprehensively discussed several issues of NMS including treatment algorithm for NMS spectrum-related symptoms. Endovascular cooling has been reported to be effective in severe case of NMS.¹⁶ Re-initiating antipsychotic drugs among patients who have recovered from NMS as evidenced best by the return of CPK levels to normal range, is a challenging task. Most preferably an antipsychotic drug from different pharmacological group should be started in low dosages only after a 2-week hiatus therapy.¹⁵ Even with this strategy, approximately 25-30% of patients tend to show recurrence of NMS, and this special population needs to be the focus of future studies.

As also observed in this case, there is converging evidence that delayed recognition of NMS is accompanied by numerous potentially serious complications associated with high mortality, that is 30%, which could be as high as 50% in case of rhabdomyolysis and acute renal failure.¹⁵ Therefore, its early recognition and prompt intervention including discontinuation of suspected drugs are 2 essential steps. In the general hospital setting, the early diagnosis of NMS is shrouded in many difficulties such as: relative lack of awareness of NMS among medical and nursing staff, persistent stigma of mental disorders, and not seeking early psychiatric consultation, improper use of consultation-liaison services, communication and coordination difficulties among physicians, relatively exclusive medical orientation of physicians, and overlooking NMS in the continuing medical education (CME) programs of general hospitals. Therefore, some important steps are suggested: 1) an immediate psychiatric referral of medical patient with fever temporally related to the use of antipsychotics could help in early detection of NMS in a general hospital setting, 2) antipsychotic medications should be used cautiously among vulnerable medical patients with psychiatric disorders. Although a single case is not

enough to justify no use of PRN antipsychotic drugs, instead benzodiazepines might help better to control agitation and restlessness and symptoms of NMS without causing any serious complications, 3) both the general hospitals and psychiatric divisions should include NMS in their CME activities, 4) NMS is a rare syndrome and when it strikes a patient, and if remains unrecognized, death is the most probable course and, 5) NMS is a heterogeneous, iatrogenic drug-induced disorder, and needs to be differentiated from a variety of medical conditions and other disorders.¹⁵

Finally, in light of this case, general hospitals should have in place aforesaid preventive measures of NMS, and enhance its awareness among physicians and nurses, which are directly related to its early recognition with reduced mortality.

Acknowledgment. *The author expresses sincere thanks to all the staff of Medical Department, Rasbid Hospital, Dubai, United Arab Emirates for inviting him to actively participate in the morning consensus meeting held for discussing this case and also to Janssen-Cilag Pharmaceutical for supporting this work.*

References

1. Qureshi NA. Neuroleptic malignant syndrome revisited! *Saudi Med J* 2002; 23: 1147.
2. Borovicka MC, Bond LC, Gaughan KM. Ziprasidone- and lithium-induced neuroleptic malignant syndrome. *Ann Pharmacother* 2006; 40: 139-142.
3. Nakagawa M, Matsumura T, Kato D, Kishida I, Kawanishi C, Tamura K, et al. Neuroleptic malignant syndrome induced by perospirone. *Int J Neuropsychopharmacol* 2006; 9: 635-636.
4. Chung DS, Kim BN, Cho SC. Neuroleptic malignant syndrome due to three atypical antipsychotics in a child. *J Psychopharmacol* 2005; 19: 422-425.
5. Dew RE, Rosenquist PB, McCall WV. Aripiprazole for agitation in a 13-year-old girl with neuroleptic malignant syndrome. *Int J Adolesc Med Health* 2005; 17: 187-188.
6. Picard LS, Lindsay S, Strawn JR, Kaneria RM, Patel NC, Keck PE Jr. Atypical neuroleptic malignant syndrome: diagnostic controversies and considerations. *Pharmacotherapy* 2008; 28: 530-535.
7. Kato D, Kawanishi C, Kishida I, Furuno T, Suzuki K, Onishi H, et al. Effects of CYP2D6 polymorphisms on neuroleptic malignant syndrome. *Eur J Clin Pharmacol* 2007; 63: 991-996.
8. Ladha SS, Walker R, Shill HA. Case of neuroleptic malignant-like syndrome precipitated by abrupt fava bean discontinuance. *Mov Disord* 2005; 20: 630-631.
9. Melli G, Chaudhry V, Cornblath DR. Rhabdomyolysis: an evaluation of 475 hospitalized patients. *Medicine (Baltimore)* 2005; 84: 377-385.
10. Strawn JR, Keck PE Jr. Early bicarbonate loading and dantrolene for ziprasidone/haloperidol-induced neuroleptic malignant syndrome. *J Clin Psychiatry* 2006; 67: 677.
11. Adityanjee, Sajatovic M, Munshi KR. Neuropsychiatric sequelae of neuroleptic malignant syndrome. *Clin Neuropharmacol* 2005; 28: 197-204.
12. Sachdev PS. A rating scale for neuroleptic malignant syndrome. *Psychiatry Res* 2005; 135: 249-256.
13. Sanai T, Matsui R, Hirano T, Torichigai S, Yotsueda H, Higashi H, et al. Successful treatment of six patients with neuroleptic malignant syndrome associated with myoglobulinemic acute renal failure. *Ren Fail* 2006; 28: 51-55.
14. Ozer F, Meral H, Aydin B, Hanoglu L, Aydemir T, Oral T. Electroconvulsive therapy in drug-induced psychiatric states and neuroleptic malignant syndrome. *J ECT* 2005; 21: 125-127.
15. Strawn JR, Keck PE Jr, Caroff SN. Neuroleptic malignant syndrome. *Am J Psychiatry* 2007; 164: 870-876.
16. Diedler J, Mellado P, Veltkamp R. Endovascular cooling in a patient with neuroleptic malignant syndrome. *J Neurol Sci* 2008; 264: 163-165.

Related topics

Khan FY, Qusad MQ. Neuroleptic malignant syndrome. *Neurosciences* 2006; 11: 104-106.

Zolezzi MS, Al-Hathloul AM. Difficulties in diagnosing neuroleptic malignant syndrome. *Neurosciences* 2002; 7: 131-133.