Neuroleptic malignant syndrome with slight elevation of creatine kinase in serum: a brief review

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Dear Editor

Neuroleptic malignant syndrome (NMS) is the most severe adverse effect that can be caused by antipsychotics. It is an acute potentially fetal and idiosyncratic reaction that may be produced with any medication affecting the central dopaminergic system with an estimated frequency of 0.5-1% of the neuroleptic-treated patients.[1] Its four main clinical manifestations are hyperthermia, severe muscle rigidity, autonomic nervous system dysfunction and altered level of consciousness.[2] Laboratory findings consist in elevation of the creatine kinase (CK) plasma levels and leukocytosis. Specifically, elevation of CK in plasma has been described in more than 90% of the cases.[3,4] NMS more frequently occurs with first generation neuroleptics. However, it is believed that it can be caused by any antipsychotic drug.[5] The physiopathological mechanism causing it is still unknown. It has been suggested that a marked reduction in central dopamine activity resulting from D2 receptor blockage in the nigrostriatal pathway, in hypothalamus, in the mesolimbic and mesocortical pathway can explain some of the symptoms (as the rigidity, hyperthermia and mental status dysfunction).[6,7] The diagnosis is clinical, and when a patient under treatment with antipsychotics has fever and muscle rigidity, CK plasma levels should be determined since they are a useful marker for the early detection of NMS.[8] The cases that do not occur with elevation of CK in plasma are rare, and as far as we know, only three cases have been reported in which this elevation has not occurred.[9-11]

Clinical case

A case of NMS with minimum elevation of CK in plasma is presented herein. The patient was male, 67 years old, without any somatic background of interest, diagnosed with bipolar type I disorder since 1978 after admission to an acute unit for manic symptoms. Since then, he has been admitted into the acute unit eight times, mostly due to manic decompensations, which had been treated with haloperidol, quetiapine and olanzapine. He was followed-up in the area Mental Health Center, with good response to olanzapine 20 mg/day and lithium 1000 mg/day. In May 2015, he was readmitted to the acute unit of a monographic hospital due to a new manic decompensation with psychotic symptoms (megalomanic delusion and harm ideation) due to poor therapeutic compliance. Treatment was initially reestablished with olanzapine 20 mg/day, but due to lack of response, the olanzapine was replaced with risperidone at a dose of 6 mg/day, maintaining lithium as a mood stabilizer (levels of 0.81 mmol/l with 1000 mg/day). Risperidone was increased up to 12 mg/day due to persistence of severe manic symptoms. Twenty-four days after his admission, he had a fever peak of 38ºC without a focus, accompanied by confusion symptoms, with the persistence of significant irritability and behavior loss of control. The decision was made to transfer him to a tertiary hospital with an acute unit. On arrival, he was evaluated by internal medicine. The physical examination study showed fever over 38ºC, cervical rigidity, symptoms of confusion with fluctuation in level of consciousness and diaphoresis. Standing out in the initial analysis was leukocytosis of $20.9x10^3$/ul with neutrophilia and CK of 342 IU/L (upper normality limit being 200 IU/L). A spinal tap was performed, obtaining a pleocytosis of 46 cells/ml without high protein level in CSF, with normal sugar content and gram stain that did not show microorganisms. Thus, the patient was admitted to internal medicine with a diagnostic orientation of possible viral encephalitis. At four days of his admission to internal medicine, the patient continued to be febrile, with fluctuations in level of consciousness and joint rigidity. In the analysis, the CK (163 IU/L) had become normal and the leukocytosis had abated ($6.8x10^3$/ul). The result of the CRP in cerebrospinal fluid, which was negative for herpes virus and enterovirus, was obtained. The differential diagnosis was proposed between encephalitis and neuroleptic malignant syndrome and it was decided to withdraw the antipsychotic treatment and initiate intravenous dantrolene at a dose of 1 mg/kg every 6 hours. At day seven of being in internal medicine, the patient continued with treatment resistant fever (axillary temperature >40ºC), tachycardia at 100-110 beats per minutes without muscle rigidity. In the laboratory analysis, the CK and leukocytes continued to be within normality (107 IU/L and $6.17x10^3$/ul, respectively). He presented deterioration of consciousness that required his transfer to the Intensive Care Unit (ICU). During his stay in this department, the diagnosis of encephalitis was initially ruled out, and the antimicrobial treatment was withdrawn. After, the diagnosis of neuroleptic malignant syndrome was also ruled out, based on the absence of muscle rigidity and of frank elevation of CK in plasma (he was hospitalized for three days in the ICU). On the first day, the concentration ranged from 40 IU/L to 189 IU/L. The second day, it increased to 222 IU/L and on the third day to a maximum of 366 IU/L with subsequent normalization. For this reason,

Table 1 DSM-IV-TR diagnostic criteria for NMS

A. Appearance of intense muscle rigidity and elevated fever associated with taking antipsychotic medication.
B. Two (or more) of the following symptoms:
   1. Diaphoresis
   2. Dysphagia
   3. Tremor
   4. Incontinence
   5. Changes in level of consciousness going from confusion to coma
   6. Mutism
   7. Tachycardia
   8. Elevated or fluctuating blood pressure
   9. Leukocytosis
   10. Laboratory findings indicating muscle injury (for example, elevation of creatine kinase serum concentration).
C. The symptoms of criteria A and B are not due to a substance or medical disease.
D. The symptoms of criteria A and B do not give a better explanation for the presence of a mental disorder.

treatment with dantrolene was also withdrawn. Once his fever abated and his level of consciousness normalized, he was discharged to the psychiatry ward without a specific diagnostic classification. In the psychopathologic study, temporal and spatial disorientation, verbosity were seen, incoherent speech with megalomanic content and marked psychomotor restlessness. It was decided to initiate electroconvulsive therapy (ECT). However, haloperidol at low doses was prescribed for behavior management (8 mg/day) until the first session could be carried out. At two days of reintroduction of haloperidol, once again he had fever above 38ºC that did not response to antipyretics. On the third day, he presented with muscle rigidity and a new decrease in the level of consciousness that required a new admission to the ICU. Treatment with haloperidol was withdrawn and physical antipyretic measures were initiated. CK serum concentration was monitored again, this ranging from 91 to 102 IU/L during the second stay in the ICU. When the fever abated and there was recovery of his level of consciousness, he was transferred again to the psychiatric ward with the diagnostic orientation of neuroleptic malignant syndrome. ECT was performed until completing 9 sessions, with progressive remission of the manic symptoms. Coadjuvant treatment was also initiated with low doses of quetiapine (25 mg/day) that was progressively increased up to 500 mg/day, with good tolerance.

Discussion

Diagnosis of NMS is clinical. In accordance with the DSM-IV-TR criteria, elevation of CK in plasma is a minor criterion and its presence is not necessary for the diagnosis (table 1).[12] However, given the high prevalence of CK serum elevation in the initial phases, it is considered an important criterion for early diagnosis (it is present in more than 90% of the cases).[3,4] Regarding NMS, day one is considered to be when fever appears without a focus. The maximum peak of CK in plasma appears at 24-48h, usually becoming normal on day 12. There is great variability regarding the maximum plasma concentration, although an elevation of at least four times the upper normality limit is generally observed.[13] The clinical case presented is an atypical presentation of NMS since the cases in which there is no elevation of CK are uncommon.[11,13] This case shows that the definitive diagnosis of NMS must be based on the clinical manifestations since the patient fulfills the diagnostic criteria of DSM-IV-TR. This case is a clear example that an atypical presentation may delay diagnosis, resulting in inadequate management of the patient (in the specific case of our patient, the consequence of the diagnostic delay was a second admission to the ICU). Regarding the few cases previously reported in which there was no elevation of CK, the reason why this did not occur is unknown. More cases of NMS with normal CK levels are needed to determine which factors may be related with this atypical presentation.

REFERENCES

1. Ananth J, Parameswaran S, Gunatilakem S, Buroyne K, Sidhom T. Neuroleptic Malignant Syndrome and atypical anti-psychotic drugs. Journal of Clinical Psychiatry. 2004;65:464-70.
2. Caroff SN, Mann SC. Neuroleptic malignant syndrome. Med Clin North Am. 1993;77:185-202.
3. Addonizio G, Susman VL, Roth SD. Neuroleptic malignant syndrome: review and analysis of 115 cases. Biol Psychiatry. 1987;22:1004-20.
4. Caroff SN, Mann SC. Neuroleptic malignant syndrome. Psychopharmacol Bull. 1988;24(1):25-9.
5. Trollor JN, Chen X, Sachdev PS. Neuroleptic malignant syndrome associated with atypical antipsychotic drugs. CNS Drugs. 2009;23:477-92.
6. Bhanushali MJ, Tuite PJ. The evaluation and management of patients with neuroleptic malignant syndrome. Neurologic Clin. 2004;22:389-441.
7. Strawn JR, Keck PE, Caroff SN. Neuroleptic malignant syndrome. Am J Psychiatry. 2007;164:870-6.
8. Nisijima K, Shioda K. Temporal changes in serum creatine kinase concentration and degree of muscle rigidity in 24 patients with neuroleptic malignant syndrome. Neuropsychiatr Dis Treat. 2013;9:853-9.
9. Singh R, Hassanally D. Neuroleptic malignant syndrome with normal creatine kinase. Postgrad Med J.1996;72(845):187.
10. Nielsen J, Bruhn AM. Atypical neuroleptic malignant syndrome caused by olanzapine. Acta Psychiatr Scand. 2005;112:238-40.
11. Nisijima K, Shioda K. A rare case of neuroleptic malignant syndrome without elevated serum creatine kinase. Neuropsychiatr Dis Treat. 2014;10:403-7.
12. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders: DSM-IV-TR. Washington DC: American Psychiatric Association; 2000.

13. Nisijima K1, Shioda K. Temporal changes in serum creatine kinase concentration and degree of muscle rigidity in 24 patients with neuroleptic malignant syndrome. Neuropsychiatr Dis Treat. 2013;9:853-9.