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Olazapine induced neuroleptic malignant syndrome

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The neuroleptic malignant syndrome (NMS) is an idiosyncratic, serious and potentially fatal disorder observed in patients who receive treatment with neuroleptics. It was first described in 1968 by Delay and Deniker[1] as a clinical picture characterized by hyperthermia, muscular rigidity and altered mental status[2]. The incidence of NMS related with typical neuroleptics is 0.02% to 2.44%[3], however, it is not well-known with atypical neuroleptics.

Since Johnson and Bruxner published the first case of NMS associated to olanzapine in 1998[4], there have been several reviews published in this sense, the most recent done by Patricia I. Rosebush et al. with 36 cases[5]. The interest of the following case is because the patient had a NMS after continued treatment with olanzapine without association of other drugs or dose changes.

This is a 73 year old woman with personal background of high blood pressure, hypercholesterolemia, type 2 diabetes mellitus and depressive syndrome. She had been operated on for cataracts, appendix and uterine curettage. She was allergic to penicillin and received treatment with atorvastatin, enalapril, citalopram, reboxetine, clonzepam and olanzapine (5 mg daily) without changes in dosage or introduction of new drugs in the last year. The patient was admitted due to a 3-4 day long picture consisting in high fever (>40 ºC) accompanied by sweating, shivering and temporal-spatial disorientation without apparent infectious focus. She was drowsy, disoriented, with fair general condition and had cogwheel rigidity and loss of glabellar reflex. The rest of the examination was normal.

Laboratory analyses done showed: 15,900 leukocytes (78% neutrophils); ESR (erythrocyte sedimentation rate), 46 mm/1 h; C-reactive protein, 16 mg/l; glucose, 190 mg/dl; GOT (aspartate aminotransferase), 41 U/l; GPT (alanine aminotransferase), 43 U/l; LDH (lactate dehydrogenase), 584 U/l; CK (creatinkinase), 442 U/l; CKmb (CPK isoenzyme MB), 16 U/l. Renal function, ions, thyroid hormones, coagulation study, cerebrospinal fluid (CSF), urine analysis and X-ray tests (chest X-ray, abdominal ultrasonography and computed tomography-normal), blood cultures and urine cultures were normal. Arterial blood gases showed partial respiratory insufficiency with respiratory alkalosis.

Faced with the suspicion of a neuroleptic malignant syndrome, all psychiatric medication was discontinued and treatment was initiated with dantrolene. On the third day of her admission, she had an episode of bronchoaspiration, and had to be moved to the ICU and required orotracheal intubation with mechanical ventilation. Subsequent course of the patient was favorable with disappearance of fever and neurological symptoms with resolution of the clinical symptoms. On discharge, she was receiving treatment with clonazepam, citalopram and enalapril.

NMS is a rare, but potentially serious complication of treatment with neuroleptics. It occurs in 66% of the cases during the first week of treatment[2,6] and in greater frequency when previous doses are increased[9] and when several drugs of the same group[8], tricyclic antidepressants[7,9], lithium salts are associated and when they are used by the parenteral route[6].

NMS initiates with a prodromic state of anxiety, that precedes awareness disorders (stupor and negataivism) and the appearance of extrapyramidal symptoms[1]. The fundamental clinical data are hyperthermia and plastic muscular rigidity that may cause dysarthria, dysphagia, sialorrhea, hypoventilation and dyspnea that is sufficiently serious so as to require mechanical ventilation. Vegetative abnormalities such as tachypnea, tachycardia, diaphoresis, skin paleness, sphincter incontinence and fluctuation of blood pressure are also typical. Awareness level varied from a state of alertness with obnubilation and mutism to stupor and coma. It is frequent to find elevated CPK, leukocytosis, hyper- or hyponatremia, thrombocytosis, decreased serum concentrations of iron, calcium and magnesium and elevation of alkaline phosphatase as well as myoglobinuria and proteinuria in the complementary examinations[1].

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In all the cases, CT scan and CSF are normal, it being possible to find that the electroencephalogram may be normal or show specific abnormalities such as generalized slowdown of the waves without focal signs. Rhabdomyolysis secondary to hyperpyrexia and muscular rigidity appears in one out of every three patients.

Treatment consists in elimination of the neuroleptic medication, antipyretics of the group of pyrazolones, fluid replacement, bromocriptine or dantrolene[5,10].

The natural course of the disease is toward cure although the appearance of complications casts a shadow over the prognosis. Among these, renal failure due to rhabdomyolysis and dehydration, acute respiratory failure secondary to embolism, pneumonia, bronchoaspiration, adult respiratory distress syndrome and pneumothorax, hepatic and cardiac failure, seizures and disseminated intravascular coagulation are found1. Although less seriousness was attributed initially to MNS induced by typical neuroleptics8, subsequent reviews have not confirmed this information9.

It is important to consider the possibility of relapse of the picture when treatment with neuroleptics is re-initiated. Thus, we should not use them for the next two weeks after the resolution of the symptoms and, if necessary, they should be reintroduced using those having less potency, at lower doses and associating antiparkinsonian medication.

Although, as previously mentioned, it is more frequent for it to appear in the first weeks or after a change in dosage, it may also appear after long-term treatments, a case of olanzapine induced MNS in a patient who received this treatment for more than two years having been published[10].

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