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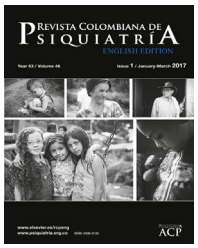

Case Report

Neuroleptic malignant syndrome associated with atypical antipsychotics: A case report

Johana Patricia Mogollon Díaz[a], *Linda Yurani Lizcano Toloza*[b,*], *Angie Yarlady Serrano García*[b], *Camilo Andrés Alquichire Luna*[b], *Diego Fernando García Bohorquez*[b], *María Fernanda Chaparro Durán*[b], *María Valentina Cáceres Valero*[b]

[a] *Departamento de Salud Mental, Universidad Industrial de Santander, Colombia*
[b] *Universidad Industrial de Santander, Colombia*

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ABSTRACT

Introduction: Neuroleptic malignant syndrome (NMS) is uncommon, with an incidence of 0.01%–3.23%, and is associated with the use of drugs that intervene with dopamine, causing hyperthermia, muscular rigidity, confusion, autonomic instability and death.
Case report: A 35-year-old man with a history of catatonia, refractory epilepsy and functional impairment, required frequent changes in his anticonvulsant and antipsychotic treatment, due to adverse effects. During 2019, in the month of July, clozapine was changed to amisulpride, in September he developed fever, muscle stiffness, stupor, diaphoresis and tachypnea over a two-week period; paraclinical tests showed elevated creatine phosphokinase (CPK) and leukocytosis, so NMS was considered. The antipsychotic was withdrawn and he was treated with bromocriptine and biperiden, with a good response. Ten days after discharge, he began treatment with olanzapine, which generated a similar episode to the one described in December, with subsequent management and resolution.
Discussion: The diagnosis is based on the use of drugs that alter dopamine levels, plus altered state of consciousness, fever, autonomic instability and paraclinical tests showing leukocytosis and elevated CPK. Differential diagnoses must be ruled out. Early diagnosis generally leads to total remission, although some patients will suffer complications, long-term sequelae or recurrences. The recurrence in this case derived from the early reintroduction of the neuroleptic after the first episode. Treatment should be individualised according to severity to avoid mortality.
Conclusions: Atypical antipsychotics are rarely suspected of generating NMS. Moreover, the time to reintroduction after an episode must also be taken into account.

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* *Corresponding author.*
E-mail address: lindalizcano903@gmail.com (L.Y. Lizcano Toloza).

Síndrome neuroléptico maligno asociado a antipsicóticos atípicos: a propósito de un caso

Palabras clave:
Síndrome neuroléptico malign
Antipsicóticos
Efectos adversos

RESUMEN

Introducción: El síndrome neuroléptico maligno (SNM) es infrecuente, con una incidencia del 0,01 al 3,23%, y tiene relación con el consumo de fármacos que interfieren con la dopamina; genera hipertermia, rigidez muscular, confusión, inestabilidad autonómica y la muerte.
Caso clínico: Un varón de 35 años, con antecedentes de catatonía, epilepsia refractaria y deterioro funcional, en tratamiento anticonvulsivo y antipsicótico, requirió cambio frecuente por efectos adversos de este. En julio de 2019 se cambió la clozapina por amisulprida; en septiembre se inicia un cuadro de 2 semanas de fiebre, rigidez muscular, estupor, diaforesis y taquipnea; los paraclínicos mostraron aumento de la creatininasa (CK) y leucocitosis, por lo que se consideró SNM. Se retiró el antipsicótico y se trató con bromocriptina y biperideno, que obtuvieron buena respuesta. A los 10 días del egreso, se inició tratamiento con olanzapina, que generó en diciembre un cuadro clínico similar al descrito, con posterior tratamiento y resolución.
Discusión: El diagnóstico se basa en la toma de fármacos que alteren la dopamina, más alteración del estado de conciencia, fiebre e inestabilidad autonómica, junto con paraclínicos como leucocitosis y elevación de la CK. Se debe descartar diagnósticos diferenciales. El diagnóstico temprano generalmente lleva a la remisión total; algunos tendrán complicaciones, secuelas a largo plazo o recidivas. La recurrencia en este caso derivó de la reintroducción temprana del neuroléptico después del primer episodio. El tratamiento se debe individualizar según la gravedad para evitar la muerte.
Conclusiones: Rara vez se sospecha que los antipsicóticos atípicos generen SNM; a su vez se debe tener en cuenta el tiempo a la reintroducción después de un episodio.

Introduction

Neuroleptic malignant syndrome (NMS) is a rare condition, with an incidence of 0.01%–3.23%[1] and mortality calculated at 11.6% of cases.[2] It is therefore considered a medical emergency. This neuropsychiatric condition is associated with taking medications that alter dopamine levels and is characterised by hyperthermia, severe muscle rigidity, confusion, and autonomic instability.[2,3] It usually occurs at the start of treatment (from the first 24 h to one week after initiation), although other risk factors have been associated.[1]

Therefore, since it is a syndrome of low incidence but with severe neurological and systemic manifestations that can lead to death, we present the case of a patient on chronic treatment with typical and atypical antipsychotics and anticonvulsants who had two episodes of NMS two months apart.

Case report

A 35-year-old male, with a history of catatonic episodes since he was seven years old, epilepsy diagnosed at age 12 and treated on an outpatient basis with phenytoin, valproic acid, levetiracetam, and lacosamide, had progressive functional impairment from the age of 20 until he was completely dependent on his caregiver at 29 years old. Due to his disorganised behaviour, he required the prescription of antipsychotics from that age.

Treatment by psychiatry was on an outpatient basis, and the prescribed antipsychotics were modified due to adverse effects or therapeutic failure multiple times in the prior two years, as described below. In January 2018, he started with olanzapine 10 mg/day, which did not control the aggressive behaviour and worsened it upon reaching a dose of 20 mg/day. Therefore, in March, he was switched to risperidone 2 mg/day, which caused severe extrapyramidal symptoms (spasticity and rigidity of the muscles of both upper extremities, the neck, and the jaw, with inability to swallow, tremor at rest, and Parkinsonian gait), leading to the withdrawal of the drug in June and a change to low-dose clozapine, which was continued for several months. However, he presented with an exacerbation of the aggressiveness and irritability, so in July 2019, treatment with amisulpride was started and progressively increased up to a dose of 400 mg/day.

After two months of treatment with amisulpride, in September 2019, the patient was taken to the emergency department due to a two-week history of symptoms characterised by febrile peaks of 39 °C, marked rigidity of the axial and appendicular musculature, altered state of consciousness with a tendency towards stupor, distal tremor especially in the upper extremities, hyporexia, diaphoresis and tachypnoea along with productive cough. On hospital admission, elevated creatine kinase (CK) (742 U/l) and leukocytosis were documented. Due to his respiratory symptoms, a chest CT

scan was performed, which showed no evidence of consolidation or pleural effusion. Due to the elevation of CK and the patient's symptoms, a diagnosis of NMS was considered, for which reason the antipsychotic was withdrawn and the patient was treated with bromocriptine and biperiden, with an adequate response. He was discharged nine days later and referred to a mental health institution for control of the underlying psychiatric disorder, and in October it was decided to restart treatment with the antipsychotic olanzapine 20 mg/day, which in December generated a clinical picture of similar characteristics, diagnosed as NMS, and appropriate treatment was initiated.

The patient consulted nine days after the last discharge. The physical examination revealed generalised rigidity, drowsiness, loss of balance while standing, gait instability, mutism, irritability, and aggressiveness (requiring restraint measures). In addition, his caregiver reported that the patient refused to take his medication or food, which is why he was admitted to the emergency department of the mental health institution, and treatment with CRET was indicated without modifying his anticonvulsant treatment.

Discussion

NMS is a rare clinical entity that occurs in patients treated with drugs that alter dopaminergic concentrations. Epidemiological data report that it occurs more frequently in men than in women, at a ratio of 2:1.[1] Different incidences have been reported. Schönfeldt et al. indicate an overall incidence of 0.01%–3.23%. For their part, Vargas et al. report an incidence of 0.2% with first generation antipsychotics, without establishing differences with second generation antipsychotics. They also determined that the risk of recurrence of NMS can be 30% with typical and 0.2% with atypical antipsychotics.[2] Data regarding the occurrence of NMS with each atypical antipsychotic is scarce. The search carried out in the literature for the analysis of this case reported 20 NMS events associated with olanzapine between 1998 and 2009 and five due to amisulpride up to 2009.[4] The case of a male patient who suffered two episodes of NMS, one due to olanzapine and another due to amisulpride, is reported.

The evaluation of possible NMS begins with the review of the mechanism of action of the psychoactive drugs administered in relation to the blockade of dopamine receptors, and the appearance of clinical characteristics such as motor symptoms, altered state of consciousness, fever/hyperthermia and autonomic instability, in addition to paraclinical findings such as leukocytosis, elevated CK, proteinuria, myoglobinuria, transient elevation of nitrogenous levels, increased alkaline phosphatase, bilirubin, aminotransferases—especially aspartate aminotransferase (AST)—and serum aldolase, as well as electrolyte disturbances.[5] In this case, in addition to the fact that he was taking antipsychotics, the patient presented with all the aforementioned symptoms along with various laboratory data compatible with NMS, such as elevated CK and leukocytosis.

However, the abovementioned findings are not pathognomonic of NMS and other diseases such as central nervous system infections, drug toxicity, catatonic syndromes, malignant hyperthermia, heat stroke, tetanus, hypocalcaemic tetany, strychnine or cocaine intoxication, decerebrate posture with hypertonia, intracranial masses, *status* epilepticus, mesodiencephalic lesions and serotonin syndrome.[3,5] All these conditions were ruled out in the patient.

In the literature, the pathogenesis of NMS is not clear. However, there are different hypotheses about its aetiology, and the most widely accepted is that of drug-induced alteration of dopaminergic activity in the central nervous system. The involvement of the nigrostriatal pathway generates symptoms such as muscle rigidity and tremor; the deterioration of the mesocortical and tuberoinfundibular pathways triggers thermal dysregulation at the central level. In the same way, hyperactivity of the sympathetic autonomic system and at the muscular level is generated, and the frequent contractions along with the rigidity generates muscle fibre oedema that adds to necrosis.[2,5]

Alterations in dopamine concentration will depend on the level at which the drug acts, which can be presynaptic, synaptic, or postsynaptic. Likewise, NMS can appear due to the *de novo* administration of central dopamine receptor blocking agents, due to abrupt withdrawal of dopamine agents, overdose, rapid dose escalation, parenteral drug administration (e.g., intramuscular), and frequent drug changes, among others. In addition, there are case reports associated with anticonvulsants such as phenytoin and valproic acid.[2] Our patient was already taking anticonvulsants chronically before the first episode, so they can be ruled out as triggers for the clinical picture. The development of NMS was influenced by the continuous change of antipsychotics (clozapine, risperidone and amisulpride in 12 months).

NMS can be recurrent, as already mentioned. Risk factors for recurrence include: taking high-potency antipsychotics, short interval between episode and re-introduction of neuroleptics, high doses of antipsychotics, and concomitant use of lithium carbonate.[2] The patient in this case was restarted on antipsychotics early, 10 days after discharge due to the first NMS, which could have triggered the second episode. According to the literature, it is recommended that the reintroduction of antipsychotics take place at least two weeks after resolution of the symptoms.[6,7]

There is no reference pattern for the treatment of NMS, so it must be individualised based on the severity of the symptoms. However, the procedure indicated by Schönfeldt-Lecuona et al. in their comparative analysis of international recommendations on the treatment of NMS is as follows: *a)* immediate discontinuation of the antipsychotics; *b)* symptomatic treatment to avoid life-threatening complications such as electrolyte disturbance, dehydration, rhabdomyolysis and acute kidney failure, aspiration pneumonia, deep vein thrombosis, seizures, sepsis, or cardiac arrest; *c)* centrally acting pharmacotherapy (benzodiazepines), peripherally acting muscle relaxants (dantrolene) and dopamine agonists (bromocriptine, amantadine), and *d)* electroconvulsive therapy (ECT).[1] The first three measures were applied in our patient.

If diagnosed early, most patients will have complete remission of symptoms, but about 30% of patients may present with complications such as kidney failure, difficulty swallowing associated with altered mental status, residual catatonia,

mutism, and motor dysautonomia, which can last from weeks to months after acute control of NMS symptoms.[2,3] The prevalence of long-term sequelae has been estimated at 3.3%, and they include: contraction of the extremities, permanent dysphonia, polyneuritis and neurocognitive alterations. Different authors have reported brain damage with clinical manifestations of ataxia, dysmetria and dysarthria.[3] The patient had various underlying cognitive and motor disorders that worsened with the NMS.

Regarding mortality, it has been estimated at between 20% and 30%. The most common causes of death are cardiorespiratory failure, pneumonia, pulmonary embolism, sepsis, and hepatorenal failure. Among the predictive complications of mortality are myoglobinuria and kidney failure, which were not found in our patient.[3]

Conclusions

NMS is an uncommon diagnostic entity, so it is important for the clinician to take into account the history of administration of drugs that intervene in dopamine metabolism, such as atypical antipsychotics, along with the symptoms and laboratory tests. The patient's outcome will depend on the time to diagnosis; if it is late, there may be sequelae, or even death. Treatment must be individualised based on the severity of the symptoms, and precautions must be taken when reintroducing the drugs that have triggered the syndrome to avoid recurrences.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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