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C. Cores Bartolomé[a,*], E. Rubio Nazábal[a], M.J. Sobrido[b], C. Pérez Sousa[a]

[a] *Servicio de Neurología, Complexo Hospitalario Universitario de A Coruña (CHUAC), Coruña, Spain*
[b] *Instituto de Investigación Biomédica de A Coruña (INIBIC), Servicio Galego de Saúde, Coruña, Spain*

* Corresponding author.
E-mail address: cores_15@hotmail.com (C. Cores Bartolomé).

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Neuroleptic malignant syndrome induced by aripiprazole depot

Síndrome neuroléptico maligno por aripiprazol depot

Dear Editor:

Aripiprazole is a second-generation antipsychotic drug indicated for schizophrenia. Extended-release injectable (ERI) formulations of aripiprazole were approved by the European Medicines Agency in 2013-2015.[1]

Neuroleptic malignant syndrome (NMS) is an infrequent but severe complication of first- and second-generation antipsychotics. It represents a neurological emergency[2]; diagnostic criteria include administration of an antipsychotic in the prior 72 hours, hyperthermia, rigidity, and altered level of consciousness (major criteria), and the presence of at least 3 of the following signs: tachycardia, diaphoresis, urinary incontinence, tachypnoea, blood pressure fluctuations, elevated creatine kinase (CK) level, and leukocytosis, after exclusion of other causes. NMS manifests 24-72 hours after the intake of antipsychotics, although it may take several days to present. It presents a monophasic course, with duration ranging from one to 44 days.[3]

NMS is less frequent and severe when caused by second-generation antipsychotics, and ERI formulations are not associated with increased frequency or mortality.[4,5]

We present an atypical case of NMS after the administration of ERI aripiprazole.

Our patient is a 37-year-old man with history of a psychotic episode of unknown origin 14 years earlier, who attended the emergency department due to delusional symptoms. The patient started treatment with antipsychotics and benzodiazepines, but due to suspicion that he was not taking the medication, 800 mg of ERI aripiprazole were administered.

At 30 days after the injection, the patient developed parkinsonian symptoms with severe rigidity and bradykinesia. He started treatment with oral diazepam, showing little response. At 4 days, he presented diaphoresis, tachypnoea, fever of up to 39°C, leukocytosis, and CK elevation of up to 630 U/L; level of consciousness was preserved. After diagnosis of possible NMS, he was transferred to the ICU and started treatment with dantrolene (60 mg/6 h intravenously) and bromocriptine (5 mg/8 h), after lumbar puncture ruled out focal systemic or central nervous system infection. Progression at the ICU was favourable, with good control of body temperature, improvement in parkinsonian symptoms, and normalisation of CK levels; at 10 days, he was transferred to the neurology ward. Subsequent progression was torpid, with fever of up to 40°C and exacerbated rigidity, but no CK elevation; a full-body CT scan yielded normal results. The patient was eventually transferred back to the ICU, where hyperthermia was managed with intravenous dantrolene. After showing good progression, he was transferred once more to the neurology ward.

Oral treatment with dantrolene (100 mg/8 h) had to be maintained, and dopaminergic agonists were replaced with levodopa to minimise psychiatric complications. We requested a blood analysis including antineuronal antibodies, and brain MRI and DaTSCAN studies; all tests showed normal results. The patient's condition improved progressively over the 3 following weeks, although strange utterances and obsessive thought persisted. Parkinsonian symptoms remitted at 6 weeks.

Given the good subsequent progression, no such therapeutic options as amantadine or electroconvulsive therapy were considered.

NMS is a neurological emergency, with incidence ranging from 0.02% to 3% of patients treated with antipsychotic drugs.[5,6]

ERI formulations are useful in avoiding relapses in patients with schizophrenia,[5] although they are less frequently used than oral formulations due to their higher cost and the fear of such adverse effects as NMS. However, there is no evidence showing a higher risk of NMS with ERI than with oral formulations.[3] There is evidence that the clinical course of NMS associated with ERI formulations is more severe.[5]

This case is an example of NMS associated with ERI aripiprazole. The delayed onset and the prolonged, biphasic course of NMS in our patient are atypical features with respect to classical descriptions of the disease.

NMS cases associated with aripiprazole present fewer motor complications and shorter duration due to the drug's pharmacodynamics (partial dopaminergic/serotonergic agonism).[7] However, the initial symptom in our patient was generalised rigidity, and lasted weeks.

These peculiarities in the progression of NMS may be due to the complex pharmacodynamics of ERI aripiprazole[8,9] and the doses used. Although NMS is an idiosyncratic reaction,

there is evidence that high doses of aripiprazole are associated with higher frequency of NMS.[10]

In conclusion, we may state that NMS may appear as a complication of ERI formulations of aripiprazole. The delayed onset after administration of the drug and the severity and duration of symptoms are the result of the complex pharmacodynamics of these formulations.

Author contributions

ACC and ED collected data and drafted the manuscript. JGD and FG critically reviewed the manuscript. All authors approved the definitive version.

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A. Contreras Chicote[a,b,*], E. Díaz[a,b], J. García Dominguez[a], F. Grandas[a,b]

[a] *Servicio de Neurología, Hospital Universitario Gregorio Marañón, Madrid, Spain*
[b] *Facultad de Medicina, Universidad Complutense de Madrid, Madrid, Spain*

[*] Corresponding author.
E-mail address: anacontreraschicote@hotmail.com (A. Contreras Chicote).

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A new CYP27A1 mutation in a case of cerebrotendinous xanthomatosis

Una nueva mutación CYP27A1 en un caso de xantomatosis cerebrotendinosa

Dear Editor,

Cerebrotendinous xanthomatosis (CTX) is a rare autosomal-recessive lipid storage disease caused by mutations in the CYP27A1 gene. Clinical manifestations of CTX are so broad and diverse that diagnostic delay or under-diagnosis happened frequently, especially in the early disease phase.

We present the case of a 31-year-old Chinese woman presented with gait disturbance for more than 1 year. She developed recurrent diarrhea since birth and suffered from frequent coughing and fever since the age of 4. She had learning difficulties and was poor at sports throughout childhood. At 10 she developed progressive vision loss, and had operation due to bilateral cataracts 6 years later. Cholecystectomy was performed for cholecystitis with cholecystolithiasis at the age of 27. Recently, she was found short-tempered and difficult to communicate.

Her physical examination demonstrated bilateral ptosis, decreased myodynamia of lower limbs (grade 4), ataxia, knee and ankle hyperreflexia, positive ankle clonus and positive bilateral pathological signs. The protuberance on her achilles tendons are visible and palpable on both sides. Her Mini-Mental State Examination score was 24.

Our patient's serum lipid level was normal while both chenodeoxycholic acid (CDCA) and ursodeoxycholic acid (UDCA) were decreased. The brain MRI revealed hyperintensity lesions on bilateral cerebellar dentate nucleus and deep medulla (Fig. 1A). MRS showed that NAA and Cho peak decreased, and lipid peak and lactate peak increased at