ANTICONVULSANT HYPERSENSITIVITY SYNDROME: CLINIC CASE AND LITERATURE REVIEW

SÍNDROME DE HIPERSENSIBILIDAD A ANTICONVULSIVANTES: CASO CLÍNICO Y REVISIÓN DE LA LITERATURA

SÍNDROME DE HIPERSENSIBILIDADE ANTICONVULSIVANTE: CASO CLÍNICO E REVISÃO DE LITERATURA

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Treatment with anticonvulsant drugs can have as an infrequent consequence an adverse event called anticonvulsant hypersensitivity syndrome, of great importance due to the life-threatening risk that it may pose. It appears during the first 6-8 weeks of treatment, is more common in people who receive the drug for the first time, and is characterized by a skin rash accompanied by hepatitis or kidney failure. Here we present a clinical case of a young woman who also suffered from abnormalities in her white blood cells that were atypical for her treatment, oxcarbazepine.

Conceptos clave:

-Anticonvulsant hypersensitivity syndrome (AHS) is a rare and severe adverse reaction, most frequently caused by carbamazepine, phenytoin or phenobarbital.

-AHS is characterized by skin affection with infiltrated exanthema, edema most typically facial, or desquamation, adenopathies, hematological alterations and internal organ involvement. It has a 10% rate of mortality, usually caused by liver failure.

-Oxcarbazepine, described as a safe drug concerning hypersensitivity, is the cause of the patient's adverse event, and manifests with unusual traits, such as leukopenia.

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Abstract:

Introduction: The anticonvulsant hypersensitivity syndrome is a rare adverse reaction in which the skin, lymph nodes and internal organs are affected. It is usually caused by classic anticonvulsants such as phenytoin, carbamazepine or phenobarbital. Case report: Here we present the case of a 25-year-old woman from Córdoba, Argentina, who suffered a severe reaction to oxcarbazepine with a rash, lymphadenopathy, hepatitis and an unusual analytic. Clinical abnormalities were reversed after oxcarbazepine was terminated and treatment with diphenhydramine and dexamethasone was initiated. Discussion: DRESS syndrome is a hypersensitivity reaction that takes weeks to manifest, and is characterized by rash, leukocytosis with eosinophilia, adenopathies, liver involvement, and reactivation of the herpes virus 6, being more frequent in carbamazepine or phenytoin, and in rare cases to oxcarbazepine. Conclusions: In general, this strong medicine is not taken into account as a cause of hypersensitivity, reports suggest that it could be related to cases similar to this one, and studies that are more targeted are required, due to the morbidity and mortality of the syndrome.

Keywords: anticonvulsants; drug hypersensitivity; leukopenia.

Resumen:

Introducción: El síndrome de hipersensibilidad a los anticonvulsivantes es una reacción adversa rara en la que se ven afectados la piel, los ganglios linfáticos y los órganos internos. Generalmente es causada por anticonvulsivos clásicos como fenitoína, carbamazepina o fenobarbital. Caso clínico: Aquí presentamos el caso de una mujer de 25 años de Córdoba, Argentina, que sufrió una reacción severa a la oxcarbazepina con una erupción cutánea, linfadenopatías, hepatitis y un analítico inusual. Las anormalidades clínicas se revirtieron después de que se terminara la oxcarbazepina y se inició el tratamiento con difenhidramina y dexametasona. Discusión: El síndrome DRESS es una reacción de hipersensibilidad que tarda semanas en manifestarse, y se caracteriza por exantema, leucocitosis con eosinofilia, adenopatías, afectación hepática, y reactivación del virus herpes 6, siendo más frecuente ante carbamazepina o fenitoína, y en raros casos a oxcarbazepina. Conclusiones: Por lo general, este medicamento fuerte no se toma en cuenta como causa de hipersensibilidad, los informes sugieren que podría estar relacionado con casos similares a este, y se requieren estudios que sean más dirigidos, debido a la morbimortalidad del síndrome.

Palabras clave: anticonvulsivantes; hipersensibilidad a las drogas; leucopenia.

Resumo

Introdução: A síndrome de hipersensibilidade anticonvulsivante é uma reação adversa rara na qual a pele, os linfonodos e os órgãos internos são afetados. Geralmente é causada por anticonvulsivantes clássicos como fenitoína, carbamazepina ou fenobarbital. Relato de caso: Apresentamos o caso de uma mulher de 25 anos de Córdoba, Argentina, que sofreu uma reação grave à oxcarbazepina com erupção cutânea, linfadenopatia, hepatite e uma analítica incomum. As anormalidades clínicas foram revertidas após o término da oxcarbazepina e o tratamento com difenidramina e dexametasona foi iniciado. Discussão: A síndrome de DRESS é uma reação de hipersensibilidade que leva semanas para se manifestar e é caracterizada por erupção cutânea, leucocitose com eosinofilia, adenopatias, envolvimento hepático e reativação do vírus do herpes 6, sendo mais frequente na carbamazepina ou fenitoína e, em casos raros, a oxcarbazepina. Conclusões: Em geral, este medicamento forte não é levado em consideração como causa de hipersensibilidade, os relatórios sugerem que pode estar relacionado a casos semelhantes a esse e são necessários estudos mais direcionados, devido à morbidade e mortalidade da síndrome.

Palavras-chave: anticonvulsivantes; hipersensibilidade a drogas; leucopenia.

Introduction

Anticonvulsant hypersensitivity syndrome (AHS) is a rare drug adverse reaction, which can lead to complications that include death. AHS occurs in 1 in 1000 to 10000 treaties, 1-8 weeks after contact with the anticonvulsant drug. It is characterized by skin affection with infiltrated exanthema, edema most typically facial, or desquamation, adenopathies, hematological alterations and internal organ involvement[1]. This type of adverse event has a 10% rate of mortality, usually caused by liver failure. Human leukocyte antigen (HLA) B*40:02, HLA-DRB1*04:03[2] have been involved in this syndrome. It has been addressed a defect on metabolism, an abnormal epoxide hydroxylase enzyme, responsible of aromatic anticonvulsants degradation, also linked to activation of herpes viruses[3].
This is a case about a 25-year-old woman from Córdoba, Argentina, who experienced severe symptoms of hypersensitivity, after six weeks of treatment with oxcarbazepine in increasing doses.

Clinical case

A 25-year-old woman from Córdoba, who had a record of absence crisis-type epilepsy diagnosed one year ago, was medicated with levetiracetam 1 gr per day. After the crisis professedly had not stopped, her neurologist began to replace the drug adding oxcarbazepine 300 mg per day for one month, increasing dose to 600 mg after 15 days, while levetiracetam dose was decreased (500 mg per day). She presented herself through the emergency department (ED) in a general hospital 6 weeks after she had begun the new treatment, with three-week worsening symptoms: diffuse pruritic morbilliform rash, generalized edema including facial angioedema, cervical and axillary adenopathies (figure 1). She complained that during the week prior to consultation, she had had fever (maximum 39.5°C- 103.1° F) and whitish vomiting, data that was objectified in the ED. The symptoms worsened after dose of oxcarbazepine was duplicated. Blood analysis revealed hepatitis and leukopenia: Red-cell count 4310000/ul, white-cell count 3400/ul (normal 4500-9000), (granulocytes 1598), AST 413 ALT 367, platelet count normal, serology tests for VDRL/ HIV/ HBV/ HCV were performed, they were negative. Naranjo's algorithm was used to determine adverse drug reaction (ADR) probability, obtaining a score of 8/10 (probable)[4]. Anticonvulsant hypersensibility syndrome was diagnosed and the patient was hospitalized. Oxcarbazepine was suspended, while levetiracetam was continued at 1 gr per day, diazepam intravenous was indicated in case of seizure, which was not necessary. The patient was rehydrated; dexamethasone and diphenhydramine were administrated intravenous during hospitalization. After five days she was discharged due to her improvement; at this time blood tests revealed white-cell count 11800 (50/0/0/4/0), AST 61, ALAT 250, GGT 197. Maintenance treatment was based on fexofenadine 540 mg per day orally divided in three doses of 180 mg and meprednisone 40 mg day, which at day 7 of discharge were adjusted to 180 mg per day and 20 mg per day, respectively. Previous symptoms did not relapse, she was cited to weekly medical supervision for one month; after three weeks, the rash had disappeared while adenopathies, though had diminished, still persisted; the patient or her family didn't refer she suffered from seizures after levetiracetam was re-established as the treatment for her absence-type epilepsy.

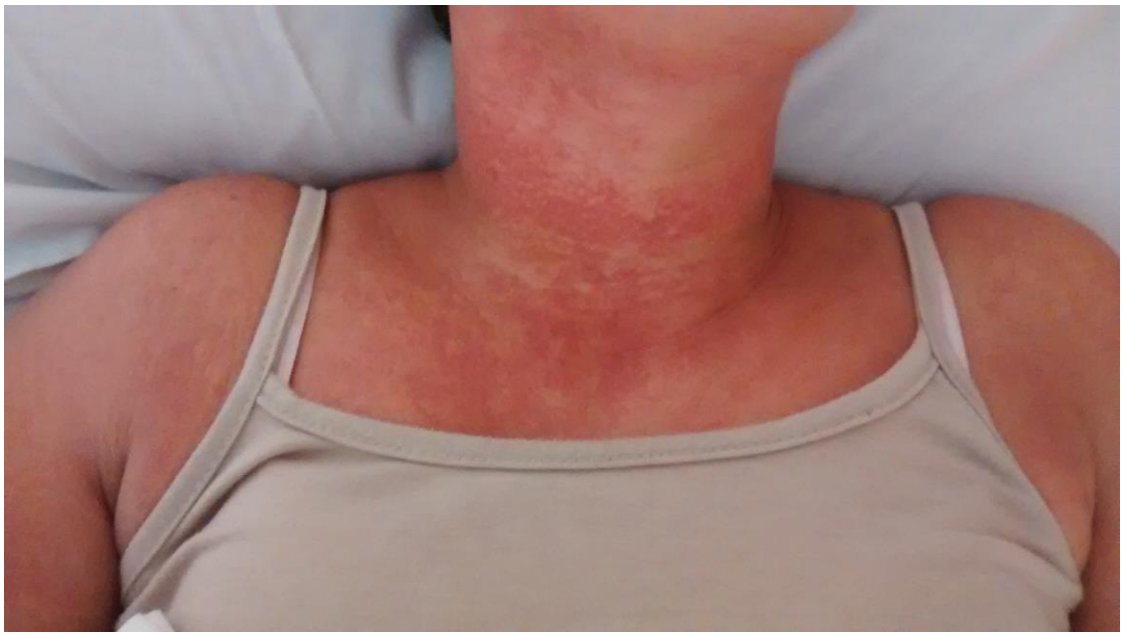

Figure N° 1. Maculopapular lesions in the neck and thorax in a 25-year-old woman with hypersensitivity syndrome to anticonvulsants.

Discussion

Anticonvulsant hypersensitivity syndrome is most frequently caused by carbamazepine, phenytoin, or phenobarbital[5], due to the aromatic ring that takes part on their structure[6,7]. This entity is also known as DRESS Syndrome, which has been agreed must meet the following criteria: 1) Maculopapular rash starting after three weeks of treatment; 2) clinical symptoms that last for two weeks after the suspected drug was retired; 3) fever; 4) abnormalities detected on liver function; 5) leukocytosis > $11x10^9$/L, at least 5% of atypical lymphocytes, or eosinophilia >$1.5x10^9$/L; 6) lymphadenopathy; 7) human herpes virus 6 reactivation[8].
The peculiar aspect on this case relays on the fact that there was no leukocytosis or eosinophilia, but leukopenia, which was objectified and it reverted after suspected drug withdrawal. Although neutropenia has been associated with oxcarbazepine[9], leukopenia is a more rare reaction that can take place after weeks of treatment, according to reports; this adverse event also has been found along with hyponatremia[10]. On the report we present, white cells count returned to normal when this anticonvulsant was suspended. On the other hand, hepatitis has been associated with oxcarbazepine use for partial epileptic seizures, and reverts after withdrawal as well[11].
Once the correct diagnose has been established, treatment requires discontinuing the anticonvulsant, use of antihistamines, corticosteroids and nutritional support. Laboratory test including hepatic enzymes, renal function and complete blood count must be performed. If it is considered necessary, a skin biopsy can be done if there are blisters or pustular lesions[5].
According to this case as in previous reports, Anticonvulsant Hypersensitivity Syndrome is an entity that manifests through diverse but serious manifestations, including the probability of liver failure.

Although leukopenia is rare, blood alterations are found frequently. Anticonvulsants with aromatic rings on their structure need control blood tests in order to prevent and diagnose adverse reactions in early stages.

Conclusions

AHS is a rare adverse reaction that affects skin with polymorphic lesions, lymphadenopathies, and internal organ involvement, like hepatitis or kidney failure. Death rate can reach up to 10% if not diagnosed and treated correctly. Although newer drugs like oxcarbazepine have been initially reported as safe, many reports induce us to believe further investigations and pharmacological epidemiology studies must be initiated in order to determine true incidence of severe adverse reactions like AHS.

Limitaciones de responsabilidad
La Facultad de Ciencias Médicas, la Universidad Nacional de Córdoba o el Policlínico Policial no se hacen solidarios con las opiniones de este trabajo.

Conflictos de interés
No existen conflictos de interés de ninguna clase a declarar.

Fuentes de apoyo
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Originalidad del trabajo
Este trabajo no ha sido publicado previamente, total ni parcialmente en ninguna revista.

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