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Drug-resistant secondary headache associated with administration of biological drugs☆

Cefalea secundaria farmacorresistente asociada a fármacos biológicos

Dear Editor:

Headache has been reported as an adverse reaction to numerous biological drugs used to treat rheumatoid arthritis. More specifically, it is listed as an adverse reaction on the summaries of product characteristics for abatacept,[1] a human recombinant fusion protein that blocks the activation of T lymphocytes, and certolizumab pegol,[2] a Fab′ fragment of a humanised recombinant TNF antibody conjugated with polyethylene glycol.

We present the case of a 69-year-old woman who attended our headache unit due to exacerbation of existing tension-type headache. She consulted due to oppressive right temporal headache of moderate to severe intensity, with attacks occurring daily. She did not present nausea, vomiting, photophobia, or phonophobia, and headache was not aggravated by movement. The patient had history of asthma, treated with salmeterol and fluticasone; seronegative rheumatoid arthritis; and tension-type headache of mild intensity, which was well controlled with analgesics. Five days before consultation, she had started treatment with intravenous perfusions of 750 mg abatacept, to which she attributed the exacerbation of her headaches. She had history of arthritis, treated with hydroxychloroquine, methotrexate, leflunomide, rituximab, etanercept, adalimumab, and tocilizumab, which were withdrawn due to ineffectiveness or intolerance.

All neurological examination findings were normal, with no evidence of focal neurological signs; eye fundus and gait assessment and cranial palpation revealed no alterations. The results of a head CT scan, blood analysis, and a brain MRI scan were also normal. The patient was diagnosed with tension-type headache secondary to abatacept infusion; we started treatment with amitriptyline, observing no response at 4 months.

Given the temporal relationship between infusion of the drug and exacerbation of headache, we agreed with the patient to suspend abatacept for 3 months and subsequently reintroduce it with subcutaneous administration. The patient presented a distinct improvement in headache after the drug was suspended, and pain was controlled with pregabalin (75 mg every 12 hours), which she was using to treat pain associated with rheumatoid arthritis. With this treatment, pain became mild and the frequency of attacks reduced to less than 2 per month; headache did not interfere with the patient's daily life. When abatacept was reintroduced 3 months later, headache was reactivated. We therefore decided to withdraw the drug definitively and to maintain a watchful waiting approach with regard to the rheumatoid arthritis.

Three months later, arthritis worsened and we started treatment with golimumab. Response was good, with no effect on headache, but the drug had to be suspended a year later due to alopecia and weight loss of up to 7 kg. We subsequently started treatment with certolizumab pegol, which was also suspended due to continued weight loss and onset of facial flushing, palpitations, and pain of very similar characteristics to those of the headache associated with abatacept. Headache improved once more when the drug was withdrawn.

At 8 months without treatment, after a further worsening of the arthritis and with no further treatments available for the condition, the rheumatology department opted to administer abatacept once more. Treatment response was good but headache was exacerbated, despite trials with increased pregabalin dose (225 mg daily) and escitalopram, mirtazapine, and lacosamide.

Headache associated with rheumatoid arthritis is relatively common, either as the initial symptom,[3] associated with osteoarticular conditions, or secondary to cervical spondyloarthropathy or atlanto-axial subluxation.[4] As is the case with other biological drugs,[5] disease-modifying drugs for rheumatoid arthritis have been associated with headache. High incidence of headache is reported among patients receiving abatacept[6—8] or certolizumab pegol[9]; in both cases, pain is mild and is often associated with reactions when the infusion is administered.

Our patient had rheumatoid arthritis and presented headache with a clear temporal association with 2 disease-modifying treatments, with pain improving when the drugs were withdrawn and reappearing when they were reintroduced. The headache was drug-resistant, which influenced

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the therapeutic approach taken to arthritis and the patient's quality of life due to poor clinical control. These drugs do not have a shared structure: the first is a recombinant protein, whereas the second is a variable fraction of a humanised monoclonal antibody. Neither do they share a therapeutic target, with one acting on T lymphocytes[1] and the other on TNF-α,[2] fundamentally produced by macrophages.

In conclusion, headache secondary to treatment with biological drugs is a well-described entity that is usually mild and associated with infusion of the drug. Our patient presented tension-type headache and headache attributed to a substance, specifically 2 biological drugs (point 8 in the third edition of the International Classification of Headache Disorders[10]); pain was refractory to pharmacological treatment and presented chronic transformation, with a significant impact on the patient's quality of life. It is important to be aware of the possibility of this adverse reaction, and it should be considered in the diagnosis of new or exacerbated headache in patients receiving disease-modifying treatment for inflammatory/autoimmune conditions. New studies with these drugs, whose complex protein structures affect functions related to the immune system, should address the reasons why they trigger headache in certain patients.

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Guillain-Barré syndrome associated with Zika virus infection in the Americas: a bibliometric study☆

Síndrome de Guillain-Barré asociado a zika, experiencia americana. Estudio bibliométrico

Dear Editor:

We conducted an extensive bibliometric study into cohorts of patients with Guillain-Barré syndrome (GBS) associated with Zika virus infection. We searched numerous databases including Scopus, Medline/PubMed, Web of Science, Science Direct, Scielo, and Imbiomed.

We selected studies conducted in the Americas and grouped them by country and cohort size; evaluated the methodology used to identify infectious agents (selecting those that screened for Zika virus as a primary objective and other agents [viruses and bacteria] as a secondary objective); and analysed the percentage of patients testing positive for Zika virus, global or average incidence, and the nerve conduction findings reported. We excluded case reports, series of fewer than 5 cases, and cohort studies not reporting serology findings for Zika virus.

We identified 22 studies analysing cohorts of patients with GBS associated with Zika virus infection, published between 2014 and 2017; cohort size varied between studies. Brazil and Colombia had the most studies published (4 and 6, respectively), followed by Puerto Rico and Mexico (3 each), and Venezuela, Jamaica, Grenada, and Martinique (one study each). We found 2 multicentre studies, with parti-

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