

The treatment of this disease is difficult and disappointing. The remarkable effect of inhibition of IL-1 has led to new expectations for these patients.<sup>5–7</sup> There is currently no Anakinra available in Argentina.

The interest of this article lies in the presence of a monoclonal IgG variant, together with the clinical and histological lesions and the subsequent progression to multiple myeloma.

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## **Listeria monocytogenes Meningoencephalitis During the Treatment With Rituximab and Mycophenolate Mofetil in a Patient With Pediatric-onset Systemic Lupus Erythematosus\***



### **Meningoencefalitis por Listeria monocytogenes durante el tratamiento con rituximab y micofenolato de mofetilo en una paciente con lupus eritematoso sistémico de inicio pediátrico**

Mr. Editor:

We have pointedly read the excellent review of cases of central nervous system (CNS) due to *Listeria monocytogenes* (*L. monocytogenes*) infection in patients with systemic lupus erythematosus (SLE published by Horta-Baas et al.<sup>1</sup>) and would like to describe an additional case of meningoencephalitis in pediatric onset SLE (pSLE) during treatment with rituximab and mycophenolate mofetil (MMF).

A 12 year old girl from Ecuador, residing in Spain since the age of 4, with a history of uncomplicated hydrocephalus was diagnosed with pSLE in August 2008 at the age of 10, based on fever, anemia, oral ulcers, finger vasculitis, joint pain, pericarditis, pneumonitis, positive ANA and anti-DNA antibodies. She was initially treated with prednisone 2 mg/kg/day in a descending dose and hydroxycloquin 200 mg/day with a good response but later developed type IV nephritis, pericarditis, constitutional symptoms, neurologic involvement (headache and psychiatric alterations) and type B insulin resistance syndrome (hyperinsulinism, hypoglycemia, acantosis nigricans and polycystic ovaries). She received 3 monthly boluses of cyclophosphamide (500 mg/m<sup>2</sup> iv) between February and April 2009 without improvement and therefore was treated with rituximab (375 mg/m<sup>2</sup>/week iv 4 doses) starting in May and, since July, with MMF (1.5 g/day) plus prednisone 35 mg/day, with renal function and disease activity improvement ( $\Delta$ SLEDAI 18→6), administering a new cycle in October. She underwent an oophorectomy in November because the increase in size of annexal masses carried a high risk of complications or malignancy, the latter excluded by histopathological analysis. During this internment the patient presented bacteremia associated to a urinary catheter caused by *Candida parasilopsis* and a relapse in lupus activity, being treated

with 3 boluses of methylprednisolone (30 mg/kg iv) and increasing oral prednisone to 45 mg/day (1 mg/kg/day). A month after this episode she came to the emergency room due to fever, forceful vomiting which had lasted for 12 h, with no prior symptoms. At the time she was using the same dose of MMF and prednisone 35 mg/day, but maintained important lupus activity (SLEDAI 10). Upon examination she was hypotensive, with pus coming out of the subclavian catheter insertion site, a reduced consciousness level (Glasgow 13), meningeal irritation signs and asymmetric bilateral paresia of the VI pair. Blood tests showed hemoglobin 10.8 g/dl, leukocytes 20.100/mm<sup>3</sup> (neutrophils 94.5%), C reactive protein 103 mg/dl and procalcitonin 12 ng/dl. Cerebrospinal fluid (CSF) analysis showed pleocytosis (200/mm<sup>3</sup>, 80% mononuclear and 20% polymorphonuclear), hypoglucorrachia (2 mg/dl), hyperproteinorrachia (1.07 g/l) and a Gram stain that was negative for microorganisms. She was hospitalized, receiving empirical treatment with cephotoxim, vancomycin and iv steroids (methylprednisolone 50 mg/day). *Staphylococcus epidermidis* was isolated in the subclavian catheter and *Staphylococcus aureus* in a blood culture, while the CSF culture was positive for *L. monocytogenes*. The diagnosis of rhomb encephalitis was proposed, due to the neurologic focalization, but the cranial magnetic resonance image (MRI) did not demonstrate compatible alterations on the brain stem or cranial nerves. Antibiotics were changed to gentamycin for 7 days plus ampicillin for 4 weeks, afterward receiving amoxicillin for two weeks after discharge. Vancomycin was maintained for coverage of catheter associated infection. The patient's consciousness level improved 24 h after hospitalization, but the oculomotor affection took longer, until the fourth week. MMF was suspended definitely, but the patient required 3 additional cycles of rituximab in May 2010, January and June 2011 for control of nephritis. She later presented other infectious complications, including herpes zoster and subdural empiema due to *Streptococcus pneumoniae*, dying as a consequence of the latter in January 2012.

The mean age of the 26 patients in the series of CNS infection due to *L. monocytogenes* in SLE by Horta-Baas et al. was 33.5 ± 11.8 years.<sup>1</sup> The only pediatric case corresponded to a patient of 16 years of age previously treated with steroids, azathioprine and methotrexate, who presented meningitis with a confusional state, bilateral diplopia, nistagmus, VII cranial nerve paralysis and weakness of the upper right extremity.<sup>2</sup> Alterations in consciousness appear in 75% of cases of meningitis due to *L. monocytogenes* and the focal neurologic signs appear in 35%–40%, with the term "meningoencephalitis" being more adequate.<sup>3</sup> Cranial neuropathies most commonly seen affect cranial nerves III, VI, VII, X and XI,<sup>2</sup> but

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there appearance forces the clinician to consider the possibility of rhombencephalitis.<sup>4</sup> Regarding immunosuppressive treatment of the patients in the series by Horta-Baas et al., five cases had previously received MMF but none rituximab.<sup>1</sup> Four cases of meningitis/encephalitis due to *L. monocytogenes* associated to rituximab have been published, all of them in adult patients with an underlying hematologic malignant process.<sup>5,6</sup> Infection with *L. monocytogenes* in pSLE is rare, found in the literature only in a 5 year old patient with type IV lupus nephritis, neurologic alterations and antiphospholipid syndrome who developed bacteremia due to *L. monocytogenes*, treated and solved with ampicillin.<sup>7</sup> One aspect that is also interesting in our patient is the subsequent appearance of other severe neurologic infections after the administration of rituximab.

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## Genetic Characteristics of Rheumatic Patients Developing Inflammatory Skin Lesions Induced by Biologic Therapy<sup>\*</sup>



### Características genéticas de pacientes reumatológicos que desarrollan lesiones cutáneas inflamatorias inducidas por fármacos biológicos

Dear Editor,

The appearance of inflammatory skin lesions (ISL), induced by biological drugs, mainly cutaneous psoriasis, has been extensively described.<sup>1–3</sup> The hypothesis is that in patients with genetic susceptibility present an activation of alternative inflammatory pathways such as interferon- $\alpha$  1.2, but this has not been demonstrated and no genetic studies in these patients exist.

We conducted a prospective observational study analyzing genetic data from patients of the Rheumatology Department of the Hospital del Mar (Barcelona) who developed *de novo* ISL due to biological therapy between January 2008 and December 2012.

The demographic and clinical variables evaluated were: age, sex, diagnosis of ISL, rheumatic disease and duration (in years), biologic drug employed and time from onset to the start of the drug (weeks). Genetic variables were the presence of HLA-B27, HLA-DR1, HLA-DR4 and HLA-DR7 alleles (detected by standard PCR), HLA-CW6 (Sanger sequencing using the indirect marker rs4406273) and the deletion of two genes *late cornified envelope* (LCE), LCE3C.LCE3B-del (with a multiplex PCR experiment<sup>4</sup>). Fifteen patients who developed ISL (prevalence 2.5%) were included. They had a mean age of 43.9 $\pm$ 12.4 years and 73.3% were female. The diagnoses of ISL were: seven skin psoriasis (five palmoplantar pustulosis, one with psoriasis *vulgaris* and one with *guttata*), three alopecia areata, two cutaneous lupus, one eczema, one suppurative hidradenitis

and one with erythema multiforme. Rheumatological diagnoses were: three rheumatoid arthritis, ankylosing spondylitis 6, four non-radiological axial spondyloarthritis and two psoriatic arthritis, mean disease duration of 13.1  $\pm$  7.4 years. Biologic drugs were eight cases using adalimumab, etanercept in four, infliximab in two and abatacept in one, with a mean time of onset of 57.1  $\pm$  62.1 weeks.

Genetically, seven patients had HLA-B27, four were HLA-CW6 positive (26%), only one with psoriasis, one positive HLA-DR1, another HLA-DR4 and six HLA-DR7 positive patients (40%), three with psoriasis. In four patients (26.7%) two LCE3C-LCE3B deleted alleles were detected and 11 (73.3%) had one deleted allele (Table 1). LCE3C.LCE3B allele frequency was 63.6%.

The low proportion of patients with the presence of HLA-CW6 and HLA-DR7 alleles (especially in cases of psoriasis) stands out, lower than that found in populations of cutaneous psoriasis,<sup>5–7</sup> which could be due to the predominant type of psoriasis, palmoplantar pustulosis, since the average age of patients was older than 40 years (HLA-CW6 and HLA-DR7 alone have been associated with type I psoriasis, with an onset before 40 years of age, and with the *vulgaris* and *guttate* subtypes<sup>5</sup>).

In our series, the presence of the deletion of the two LCE genes (allele frequency of 63.6%) was consistent with the frequently seen in population samples with inflammatory diseases (62%–70%) but higher than that reported in control populations (55%–60%).<sup>4,8–10</sup> But what stands out is that all patients with ISL had at least one copy of the LCE3C.LCE3B deleted alleles (absence of non-deleted homozygous individuals). In the general population, the frequency of non-deleted homozygotes is around 18%<sup>4,9,10</sup> and disruption of the skin barrier occurs in relation to the number of copies of LCE3C.LCE3B, being undetectable in carriers of the homozygous deletion<sup>4</sup> and reduced in heterozygotes.

This observational study of a series of cases of ISL induced by biological drugs and is the first to include genetic data, although further studies are needed with larger numbers of patients and a control group to better study this process and help establish if there a pattern of genetic susceptibility as in the case of LCE3C.LCE3B deletions.

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