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LETTERS TO THE EDITOR

Mild cerebral oedema in a patient with vascular encephalopathy due to varicela-zoster virus: an unexpected complication

Edema cerebral difuso en una paciente con encefalopatía vascular por el virus de la varicela-zoster: una complicación inesperada

Dear Editor:

The reactivation of the varicella-zoster virus (VZV) can produce a variety of neurological syndromes. Large vessel or unifocal vasculopathy affects mainly immunocompetent patients aged over 60 years and is expressed in the form of acute meningoencephalitis associated with focal neurological deficits by the involvement of one or more large vessels of the anterior or posterior cerebral circulation. In cases of extensive vascular damage, it reaches a high mortality. The development of diffuse cerebral oedema in this context is a very rare complication; we present a case in this situation.

Female, 62 years old, with a history of diabetes and obesity, who started with fever and dorsalgia with right anterior radiation an

dicular characteristics 10 days before admission; 48 hours earlier, headache, vomiting and impaired level of consciousness were added so her admission was decided. As background of interest, a granddaughter who lived with her had presented varicella one week before the clinical onset of the case. On admission, bradypsychia, time-space disorientation, stiff neck and tetraparesis were observed, with preserved and symmetrical bone-tendon reflexes. The analysis showed a slight leukocytosis (12,000/μl), with the rest of the biochemistry being normal; ANA, anti-DNA antibodies, ELA, ANCA, RPR and serology for HIV, HBV and HCV were negative. Computed tomography (CT) brain scan was performed, showing left cerebellar hypodensity of 12 mm (fig. 1A), as well as cerebral magnetic resonance imaging (MRI) that showed alterations in signal intensity, without perilesional oedema, producing restriction in post-diffusion sequences, in the left cerebellar hemisphere, both hippocampi and in the subcortical region of both parietal lobes in relation to diffuse pathological enhancement of the meninges (figs. 2B, 2C and 2D). Lumbar puncture showed clear cerebrospinal fluid with 120 cells/μl, and glycorrhachia, 78 mg/dl (blood glucose 203 mg/dl); the rest of the parameters could not be included. Treatment with ceftriaxone, ampicillin, acyclovir and dexamethasone was initiated, and a gradual improvement in the level of awareness and general condition were observed. On the fourth day, she presented varicella-type lesions in the thorax characteristic of herpes zoster, which spread over the course of admission, also affecting the extremities. On the sixth day, she suffered a transient episode of headache and time-space disorientation; a new cerebral CT scan was therefore performed, revealing a hemorrhagic transformation of the cerebellar lesion and persistence of the other injuries. On the ninth day of admission, her general condition deteriorated after developing a new headache and stupor, so a new cerebral CT scan was conducted, which showed diffuse cerebral oedema (figs. 2C and 2D).

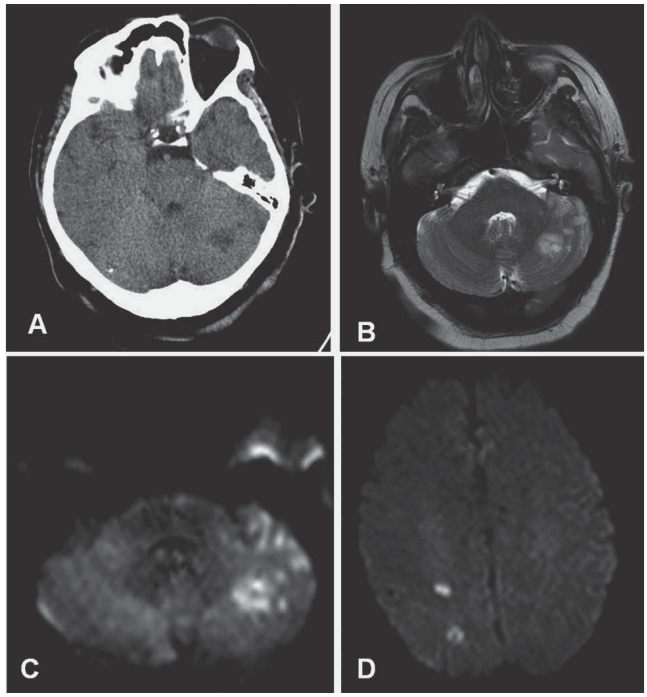

Figure 1 A: CT scan performed at the time of admission, showing parenchymatous hypodensity in the left cerebellar hemisphere. B, C and D: MRI scan performed on admission. B (T2-weighted image): signal hyperintensity in the left cerebellar hemisphere can be observed, which restricts diffusion (C), compatible with an acute ischemic stroke. At the supratentorial level (D), other acute lacunar infarctions can be observed in the right corona radiata.

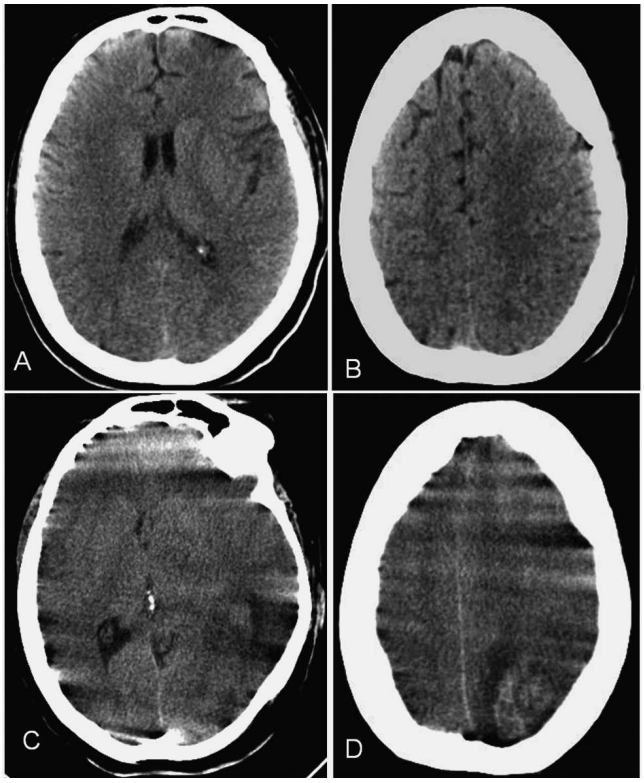

Figure 2 Computed tomography (CT) scan performed at the time of admission, at the level of the basal ganglia (A) and the convexity (B). Cranial CT scan performed at 9 days of admission, at the level of the basal ganglia (C) and the convexity (D). Despite the motion artefacts present in the study due to the patient's poor clinical condition, it is possible to observe a generalised decrease in sulci and ventricle size in relation to diffuse cerebral oedema.

The patient died after 6 hours. Blood cultures of urine and cerebrospinal fluid (CSF) were negative; serology in CSF: IgG herpes type I, 1.39 index; IgM herpes type I, 0.43 index; IgG VZV, 0.64 index; IgM VZV, 0.1 (normal indices <1). Polymerase chain reaction (PCR) was not carried out on CSF.

VZV-induced unifocal vasculopathy mainly affects immunocompetent patients older than 60 years after the cutaneous reactivation (usually cranial zoster, mainly trigeminal or cervical); the vasculopathy is expressed as a focal neurological deficit from involvement of one or more large vessels of anterior or posterior brain circulation, generally associated with acute or subacute meningoencephalitic condition[1,2]. Imaging studies (CT and MRI) often reveal ischemic lesions in the white matter or at the junction of white and grey matters[3]. Hemorrhagic transformation of these lesions due to rupture of aneurysms (mycotic), formed after the vascular deterioration by the virus is rare but possible[4,5]. The diagnostic confirmation of VZV-mediated vasculopathy requires finding VZV DNA through PCR or the detection of anti-VZV IgG antibodies in the CSF, although the serological absence in the CSF can occur in a substantial proportion of patients[3]. In the absence of laboratory confirmation, the clinical diagnosis in this patient was based on the epidemiological history, with varicella in a cohabitant, and the development of generalised skin lesions characteristic of VZV infection, in the context of abnormalities observed through radiographic techniques (ischemia, infarction and cerebral haemorrhage) and pleocytosis in the CSF[3,6-8]. While cutaneous lesions were not initially presented, cerebral vasculopathy, in the absence of that background, occurs in 40% of cases[1,3].

Despite the treatment established, the patient evolved poorly due to an extremely rare complication in this context: diffuse cerebral oedema. The latter has been identified as an expression of other viral encephalitis; for example, type I herpes simplex[9,10], although its development in the context of VZV-induced vascular damage has not been described. The main pathophysiological mechanism for its development could be the vasogenic oedema secondary to endothelial dysfunction caused by viral vascular invasion, leading to a loss of cerebrovascular autoregulation and blood-brain barrier integrity[2,4,8]. The cytotoxic oedema that often accompanies acute meningoencephalitic cases (bacterial and viral) and the initial cerebral ischemia could probably be involved in this case[8].

Appropriate management of diffuse cerebral oedema in the context of viral encephalitis caused by herpes simplex, even with decompressive craniotomy if necessary, has improved survival of patients with this entity[9,10], although there are no reports on VZV-induced deterioration. Keeping in mind the possibility that this complication could develop in such patients may encourage its early recognition and prompt treatment.

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Small-fibre polyneuropathy in Whipple's disease

Afección neurológica en la enfermedad de Whipple en forma de polineuropatía de fibra fina

Dear Editor:

Whipple's disease is a rare multisystemic disease caused by the bacterium *Tropheryma whippelii*. It typically causes rheumatic and digestive affectation, along with frequent neurological symptoms in the final stage of the disease[1,2], especially in the form of supranuclear ophthalmoplegia, cognitive impairment and confusion. In the neurological clinic, the affectation of the peripheral nervous system is one of the least described. We present a patient with fine fibre polyneuropathy caused by Whipple's disease.

The patient is a 58-year-old man, with no toxic habits, with a history of chronic seronegative oligoarthritis of more than six years of evolution, who attended the neurology service due to plantar dysesthesia with 1 year of evolution and a progressive course. On examination, segmental muscular balance was normal in both lower and upper extremities and bone-tendon reflexes were within normality. In terms of sensitivity, we detected sock hypalgesia, along with distally decreased pallesthesia.

Analysis revealed that the blood count, renal and liver function, clotting, tumour markers, thyroid function, autoantibodies (ANA, ENA ANCA, ECA, anti-smooth muscle), serology for hepatitis, syphilis, HIV, protein electrophoresis, cryoglobulins, vitamin B12 and folic acid were within the normal results. Only an erythrocyte sedimentation rate (ESR) of 70 mm in the first hour stood out, maintaining similar values in the following analytical controls.

Neurography showed a slight decrease in amplitude of sural sensory potentials (left, 10.73 μV; right, 8.69 μV. Reference values, according to Kimura, 17.2 ± 6.7 μV), with the rest of the study within the normal range, including coaxial electromyogram.

Given that they would explain the clinical manifestation of xerophthalmia, a Shirmer test and salivary gland scintillography were conducted, with negative results. A biopsy of subcutaneous fat was also performed, with no detectable amyloid deposits.

The clinical picture followed a sluggish course, with increasing dysesthesia and poor symptom control despite combination therapy (capsaicin, phenytoin, valproic acid, gabapentin, baclofen). A new, control electrophysiological study was performed again after one year, with no significant changes.

Eighteen months later, the patient consulted for continuous abdominal pain with vomiting and diarrhoea, having lost 10 kg. We performed a small intestine biopsy by endoscopy and detected macrophage infiltration with PAS-positive inclusions. We performed a sural nerve biopsy, which showed a reduction of unmyelinated fibres with preservation of the medium- and large-calibre fibres in the absence of inflammatory and vascular changes (anatomopathological method: fixation in glutaraldehyde, after fixation in osmium tetroxide, dehydration in ethanol and propylenoxide, inclusion in araldite).

Under the diagnostic guidance of Whipple's disease affecting joints, digestive tract and peripheral nervous system in the form of fine fibre polyneuropathy, we initiated treatment with intravenous ceftriaxone for 15 days and cotrimoxazole for 1 year. As for the analysis, ESR normalised and there was a marked improvement of digestive symptoms, although arthralgias and dysaesthesia persisted.

The literature reflects about 200 cases of Whipple's disease with neurological affectation; of these, we have found in approximately 5% peripheral neuropathy described in different forms: sensorimotor mixed polyneuropathy[3,4,5] (the degree of association in one of them is arguable because the patient was also a severe alcoholic[4]), polyneuropathy (predominantly motor)[5], bilateral wrist-drop[6], CPE paralysis[1,4] (the latter probably related to severe weight loss). Three of these patients underwent sural nerve biopsy: one showed a non-specific perivascular inflammatory infiltrate[6]; the second, a moderate loss of myelinated and unmyelinated fibres, with some macrophages, but without any bacilliferous inclusions[3], and the third showed bacilliferous particles, but no PAS-positive inclusions[7].

After reviewing the literature, ours seems to be the first reported case of fine-fibre polyneuropathy confirmed by sural nerve biopsy. Despite the absence of PAS-positive inclusions in our biopsy as well, it could not be attributable to other causes because of the negativity of the rest of the study. Also pointing to the prior manifestation of this disease is the fact that ESR was persistently elevated and became normalised after specific antibiotic treatment.

In the first neuropathies described in Whipple's disease, it was considered that they were secondary to hypo-absorption[4]. However, there were subsequent cases