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Treatment-associated posterior reversible encephalopathy syndrome in an adolescent with Crohn's disease: A case report

Manuel Feuerstein[1], *Micaela Salas Victoria*[1], *Cynthia Slaifstein*[1], *Estanislao Díaz Pumará*[1]

ABSTRACT

Posterior reversible encephalopathy syndrome (PRES) is a type of leukoencephalopathy that usually presents symptoms such as headache, altered consciousness, seizures, blurred vision, and imaging signs such as subcortical white matter edema, predominantly in the parieto-occipital lobes. Numerous risk factors have been identified, which involve impaired cerebral blood flow autoregulation and vasogenic edema. We present the case of a 14-year-old female patient who, in the context of an induction treatment for Crohn's disease with high-dose corticosteroids, azathioprine, and infliximab, presented with posterior reversible encephalopathy, a rare complication in patients with inflammatory bowel disease.

Keywords: *Crohn's disease; inflammatory bowel disease; posterior leukoencephalopathy syndrome; pediatrics.*

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[1] *Unit 6 Pediatric Clinic, Hospital General de Niños Ricardo Gutiérrez, Autonomous City of Buenos Aires, Argentina.*

Correspondence to *Cynthia Slaifstein: css.clases@gmail.com*

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INTRODUCTION

Crohn's disease (CD) is an inflammatory bowel disease (IBD) whose incidence increases progressively throughout childhood, peaking between the ages of 12 and 14.[1] Extraintestinal manifestations are present in up to one-third of patients at onset and are more common in children than in adults.[2] Neurological involvement is rare (approximately 3%)[3] and is probably underreported,[4] although it has become more relevant in the era of biological treatments.[5] Peripheral neuropathy is the most common neurological involvement.[5] The pathophysiology of neurological manifestations is primarily immune-mediated, although gut-brain axis dysfunction, nutritional deficiency, prothrombotic state, and adverse effects of medication also contribute.[6] The following is the case of a 14-year-old adolescent who developed posterior reversible encephalopathy syndrome while receiving induction treatment for a recently diagnosed CD.

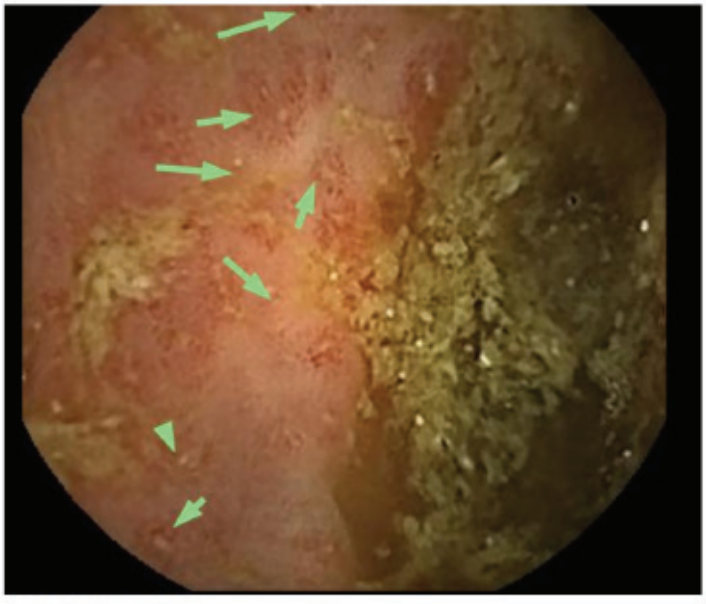
CLINICAL CASE

We present a 14-year-old female patient with celiac disease who has been followed up since the age of 2 with good adherence to a gluten-free diet. She was admitted to our institution due to the onset of CD with extensive intestinal involvement (duodenitis, severe inactive ileitis, colitis, and mild chronic rectitis), as evidenced by upper and lower videoendoscopy (*Figure 1*). Extragut manifestations included leukocyturia and hematuria secondary to tubulointerstitial damage and episcleritis. Immunological testing showed positive p-ANCA and ASCA antibodies, with IgG, IgA, and IgM and complement within normal limits, suggesting multisystem involvement secondary to the underlying disease.

On admission, she presented normocytic normochromic anemia, hypoalbuminemia, and increased acute phase reactants: white blood cells 11 600/mm^3, hemoglobin (Hb) 9.2 g/dL (mean corpuscular volume [MCV] 84 fl, mean corpuscular hemoglobin [MCH] 28 pg, mean corpuscular hemoglobin concentration [MCHC] 33 g/dL), hematocrit (Hct) 27%, platelets 253 000/mm^3, albumin 2.3 g/dL, and C-reactive protein 46 mg/L. Upon confirmation of the diagnosis by intestinal biopsy, she started with hydrocortisone 400 mg/day and azathioprine 50 mg/day, combined with oral antibiotic therapy to manage dysbacteriosis. Exclusive parenteral nutrition was indicated for one month due to persistent gastrointestinal bleeding, with good tolerance.

During his hospitalization, she presented hypovolemic shock secondary to lower gastrointestinal bleeding (Hb 4.5 g/dL). She required treatment in the critical care unit and was stabilized after expansion with crystalloids and multiple red blood cell transfusions. Given the lack

Figure 1. Video colonoscopy



Superficial ulcers in the colon mucosa.

of response to corticosteroids, infliximab at 5 mg/kg was added to the induction treatment in weeks 0, 1, and 4. In this context, she developed difficult-to-manage hypertension (HTN) with a maximum systolic blood pressure (BP) of 153 mmHg and sustained high records, requiring combined treatment with amlodipine and enalapril. Renal Doppler ultrasound was performed within normal limits, and HTN was assumed to be secondary to high-dose corticosteroid therapy.

Twenty-one days after starting corticosteroid treatment and three days after the first infusion of infliximab, she had a generalized tonic-clonic seizure lasting four minutes. The immediate postictal ionogram showed a sodium level of 139 mmol/L and an ionic calcium level of 1.11 mmol/L, a blood glucose level of 104 mg/dL, and hydroelectrolytic or metabolic disorders were ruled out. A contrast-enhanced brain MRI was performed, which showed increased T2 signal with a corticosubcortical pattern over the frontal, parietal, and bilateral occipital convexity, images consistent with PRES (*Figure 2*).

Treatment with phenytoin was initiated, which, with normal electroencephalographic controls and no new episodes, was gradually reduced until it was discontinued. She remained stable, continuing the original infliximab protocol without repeating seizures, and progressed without neurological sequelae.

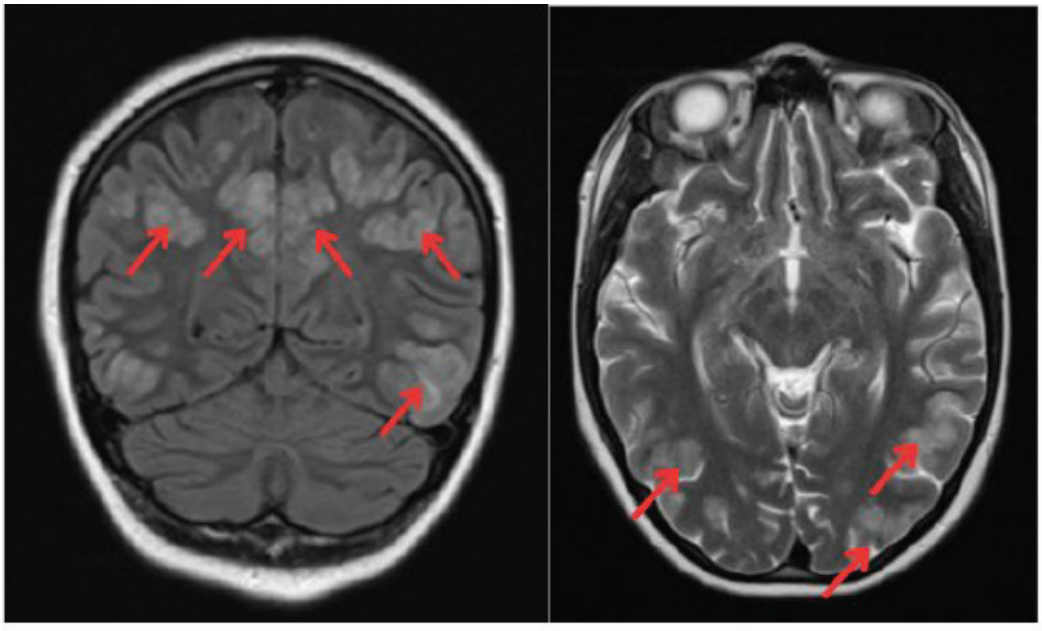
To date, no new control images of the central nervous system have been performed.

DISCUSSION

Extraintestinal manifestations of CD occur in 10% of patients at onset and 30% during the first few years of the disease.[7,8] Cutaneous-mucosal, ocular, hepatobiliary, and osteoarticular involvement are the most common;[1] neurological involvement is rare and more frequent in the first few years after diagnosis. It can manifest as peripheral neuropathy (the most common, with an incidence of around 2%),[9] myelitis, vestibular involvement, myasthenia gravis-like symptoms, and cerebrovascular accidents (CVA). Focal or generalized seizures have also been reported: most are acute symptomatic seizures secondary to metabolic disturbances or stroke.[6]

PRES is an acute clinical-radiological syndrome characterized by an insidious onset of symptoms such as headache, seizures, blurred vision, confusion, and decreased level of consciousness. Characteristic findings on neuroimaging are consistent with edema of

Figure 2. Brain MRI



Left: extensive signal alteration with a cortico-subcortical pattern on the frontal, parietal, and bilateral occipital convexity. Right: increased T2 signal with no signs of diffusion restriction or bleeding. The images suggest signs of vasogenic edema.

the posterior cerebral white matter, particularly in the parieto-occipital lobes, although variations may occur.[10,11] Triggers include hypertension, renal failure, salt and water retention, and immunosuppressive drugs such as corticosteroids, cyclosporine, and tacrolimus, even at non-toxic blood levels. Alteration of the cerebral blood flow autoregulation mechanism and endothelial dysfunction are the primary mechanisms involved in the pathophysiology of PRES.[10,11] Numerous theories attempt to explain this phenomenon, and multiple pathophysiological mechanisms probably coexist. The sudden development of high blood pressure may exceed the brain's ability to autoregulate blood flow, leading to hypoperfusion. The posterior brain is more vulnerable to this phenomenon because its circulation has less sympathetic innervation, which attenuates the response to reflex parasympathetic vasodilation. HTN, acute BP fluctuations, and autonomic activity can alter the thresholds of cerebral autoregulation. In turn, hypoperfusion can damage the blood-brain barrier, causing extravasation of plasma and other macromolecules into the interstitial space. The loss of endothelial junction integrity is exacerbated by the release of vasoactive substances such as nitric oxide, thromboxane A2, or endothelin 1.[11] With early recognition of the trigger and appropriate treatment, complete recovery is expected within days or weeks, although there are reports of neurological sequelae and even death in a few patients.[12]

Infliximab is a monoclonal anti-TNF alpha antibody widely used in various autoinflammatory and autoimmune diseases. The most common adverse effects are the development of severe infections, opportunistic infections such as tuberculosis, and lymphoproliferative syndromes such as non-Hodgkin's lymphoma.[10,12] The most frequently reported neurological complications are headache, followed by peripheral neuropathy and demyelination of the central nervous system.[12]

Neurological toxicity has been reported with metronidazole[9] and isolated cases of seizures and PRES secondary to infliximab in patients with CD. In these reports, seizures were described 3 to 7 days after the first and/or second infusion of infliximab in both pediatric and adult patients.[10,12-15]

The onset of seizures in a patient with IBD is a rare event that raises various differential diagnoses, such as stroke, electrolyte disturbances, secondary complications of the underlying disease, and adverse effects of treatment. In the case of the patient, who developed PRES in the induction phase of CE after 21 days of treatment with high doses of corticosteroids and 3 days after the first infusion of infliximab, a metabolic or electrolyte imbalance was ruled out, given normal blood glucose, natremia, and calcium levels during the seizure. As triggering mechanisms for PRES in our patient, we ranked significant BP fluctuations (which varied between sustained hypertension, hypovolemic shock secondary to lower gastrointestinal bleeding, and multiple episodes of anemia requiring transfusion), high-dose corticosteroid therapy, and infliximab infusion, given the temporal correlation. However, this is not described as a frequent adverse effect and did not recur in subsequent infusions.

The presence of neurological symptoms in patients with IBD is rare. In the case of the patient presented, who developed seizures in the context of induction treatment, a diagnosis of PRES was made. Considering the favorable evolution with anticonvulsant treatment, normalization of blood pressure, and progressive reduction of corticosteroid therapy, it is interpreted as probably associated with the coexistence of triggering factors such as hypertension and immunosuppressive drugs (corticosteroids, infliximab). Careful monitoring of BP should be maintained, paying close attention to variations, and other risk factors for PRES should be monitored in patients with CD. ■

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