A CASE OF MULTIPLE AUTOIMMUNITY COMPLICATED BY SIADH

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ABSTRACT

Central nervous system (CNS) vasculitides are rare, often severe diseases, difficult to diagnose for the lack of specific symptoms and with a poor outcome. We report a case of CNS vasculitis in a 57-year-old patient suffering from multiorgan dysimmune syndrome characterised by celiac disease, ulcerative colitis and diabetes mellitus. Cognitive deterioration, gait impairment and balance loss were the main clinical findings, and the patient was able to walk in 3 years. Moreover, inappropriate secretion of adiuretin syndrome occurred, making the patient's treatment more complex. Methylprednisolone and monthly intravenous pulse of cyclophosphamide boosters were administered; plasma-exchange, intravenous immunoglobulins and rituximab were sequentially used with no benefit.

Keywords*: Autoimmunity, Vasculitis- CNS Vasculitides-Multiorgan dysimmune syndrome-SIADH-Immunosuppressors.*

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Introduction

Vasculitides are rare and severe conditions that are difficult to diagnose because of nonspecific symptoms. They are characterised by inflammation affecting blood vessel walls and damage to the integrity of the vessels, causing alterations in blood flow. The vessels involved may be of a different type or affecting one or more organs or systems. The resulting clinical syndromes are mostly a consequence of tissue ischaemia, vascular damage and inflammation.

There is also a primary and isolated vasculitic involvement of the central nervous system (CNS) (primary CNS vasculitis): this is a rare disease characterised by inflammation of the blood vessels in the brain and medulla without evidence of vasculitis symptoms outside the CNS[(1-5)].

Here, we present a case of CNS vasculitis in a 57-year-old patient suffering from a multiple autoimmune syndrome, associated with a (SIADH).

Clinical case

A female patient, aged 57 years, was admitted to our hospital on September 2013. The patient had multiple autoimmune syndrome characterised by ulcerative colitis for 15 years, celiac disease for 5 years and diabetes mellitus treated with oral drug therapy for 2 years. The patient's clinical history began in April 2010 with an episode of fever associated with abnormal gait, which was diagnosed as myelitis, regressing after 2 weeks after high-dose steroid therapy as an inpatient. In April 2011, the patient experienced a sudden onset of confusion,

space-time disorientation and marked asthenia. An encephalopathy was diagnosed (Fig.1), and the patient was treated with cyclophosphamide (6 cycles at about 750 mg/day).

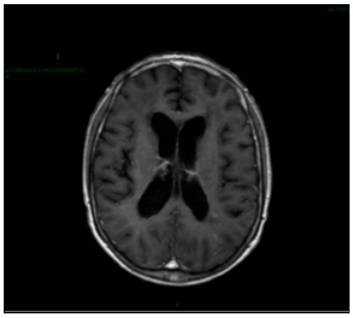

Fig. 1: Axial post-gadolinium T1-weighted MRI.

Another episode with similar features was reversed after high-dose steroid treatment in November 2012. A head magnetic resonance imaging (MRI) scan showed multiple small faint hyperintense foci, on long TR sequences, in the middle cerebellar peduncles and cerebellar dentate nuclei, peri- and supraventricular white matter and in both sides of the frontal subcortical region of the CNS (Fig. 2A).

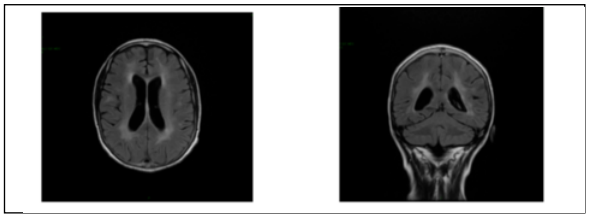

Fig. 2 A: Axial and coronal FLAIR MRI (November 2012).

At the end of December 2012, the patient's condition again worsened. According to her husband, she showed severe memory impairment, inability to perform habitual actions and unusual behaviour. She underwent a new head MRI scan, which showed new gadolinium-enhanced lesions (Fig. 2B).

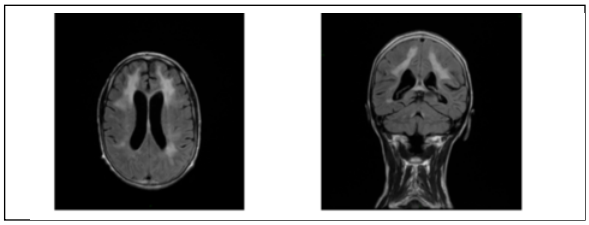

Fig. 2 B: Axial and coronal FLAIR MRI (November 2013).

From January to August 2013, she was treated with an additional 8 cycles of cyclophosphamide. In September 2013, she was admitted to our unit because of clinical deterioration, including worsening balance that prevented walking without support, heightened confusion states, numerous episodes of space-time disorientation and severe physical fatigue.

On admission, the patient showed inability to wolk and stay upright without support, showed a marked ataxia of the trunk, postural and kinetic tremor, dysmetria, dysdiadochokinesia, weakness in four limbs, hyperexcitable tendon reflexes (especially in lower limbs) and bilateral presence of signs of Hoffmann and Babinski; furthermore, she exhibited impairment of both memory and executive functions. Routine blood tests did not show significant alterations (except an increase in glycosylated hemoglobin). The anti-DNA antibodies, anticardiolipin IgM, anticardiolipin IgG, anti-gliadin IgA and IgG, antiendomysium, anti-tissue transglutaminase antibodies, antigastric parietal cells, cytoplasmic antineutrophil/perinuclear antibodies, extractable nuclear antigen screen and antireticulin were negative; anti-Saccharomyces cereinsiae antibody, Anti-Herpes 1 A, and Anti-Herpes 2 IgA were all negative. Finally, one of the last head MRI scans performed in May 2014 showed worsening of the lesions extending to almost the entire hemispherical surface symmetrically (Fig. 2C).

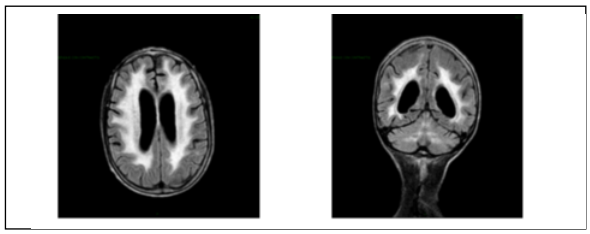

Fig. 2 C: Axial and coronal FLAIR MRI.

Marked hyponatremia [sodium: 127 mmol/l (135-150)] and mild hypokalaemia [potassium: 3 mmol/l (3.5-5)] where found. High proteinuria was observed: 1840 mg in 24 hours (normal 50-100) . Cerebrospinal fluid (CSF) examination showed protidorrachia [121 mg/dl (9-46)], intrathecal IgG synthesis [8.30 mg / day (<3.3)] and increased concentration of albumin [91 mg/dl (13.9 to 24.6)]. There were no oligoclonal bands. A spinal MRI, in the same period, showed blurred and scattered hyperintense areas in the medullary cord, with a tendency to converge in the dorsal tract. Intravenous administration of gadolinium showed dotted foci intramedullar impregnation in these areas (Figs. 3 A,B).

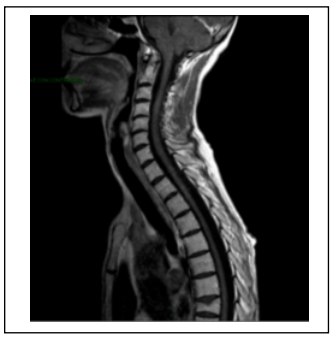

Fig. 3 A: cervical post-gadolinium T1-weighted MRI.

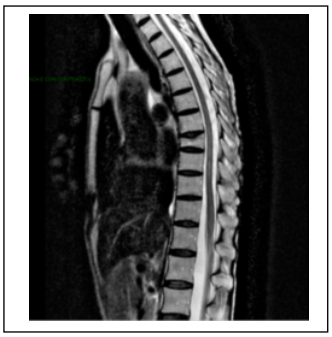

Fig. 3 B: dorsal T2-weighted MRI.

The cerebral angiography[6,7] showed delayed circulation of the right angular artery in its distal cortical tract, in capillary/venous phase as well as the precentral terminal branches again on the right; also, the PICA in its post-tonsillar branch shows a stenosis, making the inferior vermian and cerebellar branches slightly evident (Figs. 4 A,B).

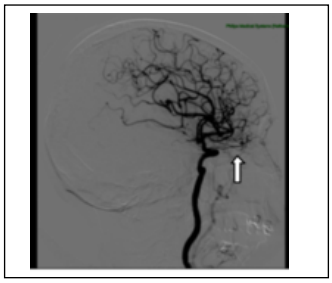

Fig. 4 A: Cerebral angiography.

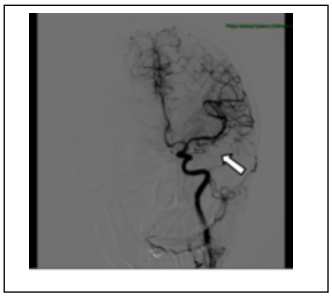

Fig. 4 B: Cerebral angiography.

Therapeutic history

The patient was treated with cyclophosphamide[8] associated with methylprednisolone: 6 cycles of 750 mg/day (4500 mg) from October 2011 to March 2012 and from January 2013 to August 2013, totalling about 16 grams. She was then treated with a cycle of plasma-exchange (five sessions), and subsequently a complete cycle of intravenous immunoglobulin (20 g/day for 5 days). Since the patient responded poorly to previous treatments, Rituximab[9] was administered in 2 intravenous infusions of 1000 mg at 1-month intervals with no benefit.

Discussion

Our case describes a multiple autoimmune syndrome complicated by (SIADH). Presently, an association between SIADH and multiple dysimmune syndrome also associated with cerebral vasculitis has never been reported. Criteria for the diagnosis of primary CNS vasculitis[1] were proposed by Calabrese and MalleK and are based on three prerequisites:

i) the detection of an acquired neurological deficit of unknown origin after initial basic evaluation;

ii) cerebral angiography with typical characteristics of vasculitis or a brain biopsy sample showing vasculitis elements;

iii) no evidence of systemic vasculitis or other diseases in which angiographic or pathologic characteristics may be secondary.

These criteria have been established for both adults and children[10] and, although not entirely validated, are currently used in clinical practice. No sufficiently sensitive and specific laboratory test exist to confirm or exclude the diagnosis[9]. The patient presenteding with a radiologic and angiographic picture very suggestive of vasculitis had an inflammatory cerebrospinal fluid (characterised by the presence of hyperproteinorrhachia) without oligoclonal bands.

There were also no signs of vasculitis in other sites or serologic tests with evidence of the presence of autoantibodies. It was not possible to perform a biopsy of the encephalic lesions due to the patient's poor health. During hospitalisation, a severe hyponatraemia was studied by determination of plasma and urine osmolarity, which indicated decreased plasma osmolarity (<275 mOsm/kg) and

increased urine osmolarity with normal renal function.

Urinary excretion of sodium was high (300 mmol/24h), with normal intake of sodium and water. As a first hypothesis, this condition seemed attributable to a syndrome of inappropriate ADH secretion. This is a biochemical and clinical syndrome of euvolaemic hyponatraemia, which occurs due to the increased antidiuretic actions of arginine vasopressin[11,12], and hyponatraemia is the most common electrolyte abnormality. Hyponatraemia is a consequence of an excess of extracellular water. SIADH's aetiology is extremely varied. Numerous pathologic conditions affecting the CNS may cause SIADH (such as inflammatory or neoplastic diseases, degenerative/demyelinative diseases, Guillain-Barré syndrome, multiple sclerosis, traumatic brain injury, hydrocephalus, vasculitis and cerebrovascular accident), but many drugs may cause it, either because they increase the release of ADH (such as morphine, carbamazepine, haloperidol, tricyclic antidepressants) or because they increase sensitivity to the hormone (e.g., nonsteroidal anti-inflammatory drugs, cyclophosphamide)[13].

In our case, it is possible that treatment with cyclophosphamide contributed to SIADH's development but the onset of the syndrome coincided with the worsening of the patient's neuroradiology picture, and for two years, during the drug treatment, the patient showed no sign of hyponatraemia in the analyses that were carried out repeatedly. For this reason, during hospitalisation, the patient was first treated with fluid restriction, but this option was unsuccessful because hyponatraemia was only slightly reduced[14]. Therefore, she was treated with a vasopressin V2-receptor antagonist[11,12,14,15], an aquaretic-promoting excretion of water alone, which led to normalised serum sodium levels in a few days, with a simultaneous transitory improvement in clinical symptoms.

In the following months, the patient progressively evolved to a severe worsening of cognitive performance; she also lost any voluntary motor ability; irreversible dysmetabolic and electrolytic abnormalities occurred, and the patient , with severe dementia, anarthria and dysphagia died a few weeks later.

Conclusion

We believed that reporting this case is worthwhile to reiterate the notion-by no means unprecedented, though certainly relevant-that the finding in a patient, more frequently in a female patient, of an autoimmune disease should lead to a suspicion of the coexistence of other autoimmune manifestations, as in this case, characterised by a gradual onset of ulcerative colitis, celiac disease, diabetes and cerebral vasculitis, constituting a kind of autoimmune synergy[16-18].

Another important aspect was the finding of a certainly uncommon condition of reduced sensitivity to ADH resulting in hyponatraemia, with severe manifestation of symptoms, such as to seriously compromise not only the quoad valetudinem but also quoad vitam prognosis[19].

A third aspect that deserves to be highlighted was the possibility of the etiologic treatment of one of the many patient's symptoms, such as hyponatraemia by syndrome of inappropriate antidiuretic hormone secretion, which showed a surprising sensitivity to treatment with a V2 vasopressin receptor antagonist, so that a decisive regression of part of the patient's recent symptoms was obtained before its final aggravation and exitus.

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