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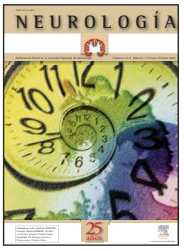

LETTERS TO THE EDITOR

Posterior leukoencephalopathy syndrome associated with amyloid angiopathy

Síndrome de leucoencefalopatía posterior en relación con angiopatía amiloide

Dear Editor:

In 1996, Hinchey et al1 described the reversible posterior leukoencephalopathy syndrome in relation to arterial hypertension, renal disorders and immunosuppression. Since then, numerous entities have been added as potential triggers. Connective pathologies, haematological diseases, drugs, angiography, blood transfusions, haemodialysis or acute intermittent porphyria are some of examples.2 Recently, there have been some reported cases involving amyloid angiopathy.3-7 We wish to add the case of a patient with this syndrome, who also showed the same underlying disease.

This was a hypertensive 73-year-old woman, who had undergone a kidney transplant due to polycystosis, and who was treated with prednisone, tacrolimus, mycophenolate mofetil and atenolol. The baseline study showed no alterations in cognitive function and a normal neurological status. On two occasions, before transplantation, in a state of advanced renal failure, she had presented some episodes of reversible language alterations in the context of elevated blood pressure. Three years after transplantation, she presented for 18 months sudden, recurrent episodes of incapacity for speech and language comprehension, which remitted in about a week. These were not accompanied by headaches or visual alterations; she maintained a good level of consciousness, and the episodes were not associated with strikingly elevated blood pressure or severe renal function alterations. The clinical manifestations were similar in all episodes. We conducted a complete analysis, autoimmunity studies, cerebrospinal fluid, vascular studies (supra-aortic trunks duplex, transcranial Doppler, echocardiography, ECG, Holter, cerebral angiography), electroencephalogram (EEG), magnetic resonance imaging (MRI), brain SPECT and brain biopsy. The arteriography revealed an ulcerated plaque in the left internal carotid artery (symptomatic), which did not condition haemodynamic alterations. The cranial MRI, in addition to parenchymal atrophy, revealed hyperintensity in the parieto-occipital region on FLAIR and T2-weighted sequences, predominantly on the left side, with a moderate enhancement after contrast administration, and a normal study with dissemination techniques (fig. 1). On the EEG and video-EEG, we observed a spike-wave focus in the left hemisphere and some electric crises with no clinical correlation. Other tests performed before the biopsy did not reveal any significant findings. The patient was admitted to the hospital repeatedly during each of these episodes, and subsequent therapeutic measures were taken due to their recurrence. Firstly, she received antiplatelet therapy, initially with aspirin and then with clopidogrel. Upon the later discovery of the ulcerated carotid plaque, which was not considered a subsidiary of surgery, anticoagulation was established, as well as treatment with statins. Given the the EEG findings and the lack of response to these therapies, empirical anticonvulsant treatment was prescribed, first with phenytoin and then with lamotrigine later on. Everolimus was also given as a replacement for tacrolimus,[8] despite not having found toxic levels of the drug. However, the patient still had recurrent language alterations (up to six episodes), and during the last two, showed residual aphasia. To establish a diagnosis and rule out infectious, neoplastic and inflammatory processes, a brain biopsy was performed; this revealed amyloid in the leptomeningeal vessels (fig. 2). A mild gliosis in the white matter was observed in the brain parenchyma, as well as scarce diffuse cortical plaques, with an absence of neuritic plaques and neurofibrillary tangles. We detected no inflammatory changes or tumour proliferation.

In the case presented, the clinical signs and symptoms initially pointed to vascular episodes of a stroke-like nature due to its acute onset. Despite this, CT and MRI studies never showed parenchymal necrosis, but only non-specific signal changes, hyperintense on FLAIR and T2 sequences. Tacrolimus was replaced because of known potential side effects of this drug, such as encephalopathy and language disorders.[9,10] The patient, despite the residual language impairment, did not present memory deficits or other additional cognitive impairments. Amyloid angiopathy is a vascular disease, common in the elderly, which often manifests as lobar haemorrhages. However, sometimes it may do so only as leukoencephalopathy, along with a Binswanger-type periventricular distribution, more associated with atrophy, or located in the U-fibres, at an immediately subcortical level. In this case, it is usually associated with oedema and has a more reversible nature. On the other hand, the deposition of amyloid material tends to be more intense in occipital lobes.[11] The most widely accepted pathophysiological explanation for posterior

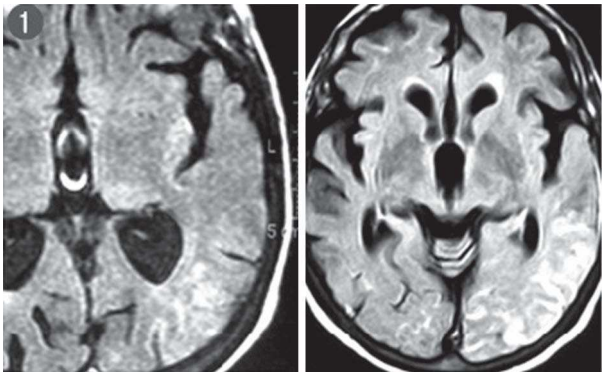

Figure 1 Cranial MRI: FLAIR sequence showing hyperintensity in the left parieto-occipital region. In the picture on the left, it is possible to see how the lesion shows enhancement after contrast.

leukoencephalopathy syndrome is the failure of the capacity of the cerebral arteries to self-regulate, which is more prominent in posterior regions due to the lower density of sympathetic innervation in the vertebrobasilar territory.[12] In a study comparing arteries with and without amyloid,[13] it was found that the arteries infiltrated by this protein presented thinning and degeneration of their middle layer, which is the most important for self-regulation. These findings would explain the potential ability of amyloid angiopathy to trigger posterior leukoencephalopathy syndrome. The relationship between these entities has previously been reported in patients who had no background of other classic promoters, such as those which occurred in our case (hypertension, renal disease, immunosuppressants, and seizure activity). The interaction of all of them could have participated in the development of the episodes and could justify the resistance observed to the therapeutic changes. The biopsy taken from the left posterior parieto-occipital region did not show the presence of the parenchymatous oedema characteristic of the syndrome

Figure 2 Brain biopsy: intense immunostaining in the wall of meningeal vessels with the antibody against beta-amyloid protein.

apart from an amyloid deposition in the vessels. The biopsy did show a mild gliosis in the white matter (already described in another publication[14]), which may be a reflection of the brain damage caused over time by repeated episodes and is probably related to the residual language disorder that has appeared in recent months.

Gliosis in white matter may be related to prior oedema. Although seizure activity may also lead to gliosis, in these cases it tends to be located in the cortex. The biopsy showed no neuropathological signs of Alzheimer's disease, as no neuritic plaques or neurofibrillary tangles were evidenced. The small sample size does not let us eliminate the possibility that they were present in other brain areas. The presence of diffuse plaques is attributable to the patient's age. Some authors propose carrying out cranial MRI with hemosiderin sequences to identify cases of leukoencephalopathy of unknown cause, seeking juxtacortical microbleedings that can back up amyloid angiopathy, although these do not necessarily have to be present. The possibility of steroid treatment in cases where the biopsy shows an inflammatory component in relation to amyloid angiopathy[5,15] has also been raised; this was not detected in our patient sample.

In short, posterior leukoencephalopathy syndrome is an entity that, in addition to being caused by hypertensive encephalopathy, may be a manifestation of many different diseases, and we must include amyloid angiopathy among them. In cases where there are no radiographic changes characteristic of this disease, it is necessary to perform a brain biopsy for its diagnosis.

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Sleep disorders and restless legs syndrome in an adult with Asperger's disorder, a case report

Alteraciones del sueño y síndrome de piernas inquietas en un adulto con síndrome de Asperger, a propósito de un caso

Dear Editor:

Asperger syndrome[1] is a pervasive developmental disorder (PDD), whose prevalence ranges from 0.1 to 3.6 cases / 1,000 children, with predominance in males. It is characterised by restrictive and repetitive interests and altered social relations.[2] Common symptoms are motor clumsiness, difficulty in planning, sequencing of motor tasks and coordination alterations.[3] It is often associated with other neuropsychiatric syndromes: anxiety disorder, obsessive-compulsive disorder, bipolarity, depression, attention deficit and hyperactivity disorder, Gilles de la Tourette syndrome, epilepsy, movement and sleep disorders.[4] Disturbances of sleep architecture are usually functional, in sleep stability and efficiency; structural alterations are not frequent.[5] Melatonin has been used to treat such disturbances with moderate effectiveness.[6]

Restless legs syndrome (RLS) is characterised by a restlessness that requires moving the legs to relieve the symptoms, which worsen in the evening. Its incidence in the general population is 5-10%.[7] Some 80% of patients with RLS have periodic leg movements (PLM) that hinder sleep.[8] The delay time from inception to diagnosis may be elevated.[9] The first-line drugs are dopamine agonists and L-Dopa, although benzodiazepines and anticonvulsants have also been used; the most effective include gabapentin, clonidine, opioid agonists and beta blockers.[8,9] The typical symptoms of Asperger syndrome, RLS and sleep disorders overlap, thus complicating diagnosis and treatment.

We present the case of a 25-year-old male who attended consultation due to insomnia and hypothymia. At age 16 he was diagnosed with Asperger syndrome and depression, after his academic performance dropped and he complained of fatigue, sadness, hyphedonia, conciliation insomnia and mnemonic and concentration difficulty. Serotonergic antidepressant treatment was initiated, with partial improvement. From age 16 to age 20 he consulted various specialists for apathy, nervousness and conciliation insomnia, receiving antidepressant treatments, benzodiazepines and melatonin. At age 21 he attended consultation because the depressive manifestations remained, as did the difficulty in sleeping from discomfort and an internal feeling of tension in the lower extremities, which appeared at bedtime and which forced him to wander about, preventing relaxation. No temporal relationship was found between symptoms (suggestive of RLS) and the establishment of drug treatment. Physical and analytical examinations were normal. Magnetic resonance imaging, electroencephalogram, magnetoencephalography and cranial spectroscopy did not detect any significant abnormalities. Polysomnography detected, repeatedly, in two tests carried out at 1-year intervals, unstable sleep, very low percentage of deep sleep and a small proportion of REM sleep (table 1). PLMs were also observed. Treatment with escitalopram, 20 mg / day, and alprazolam, 1 mg / day, were started, with partial remission of RLS and depressive symptoms. Subsequently, gabapentin was added up to 600 mg / day, with only slight

Table 1 Polysomnographic recordings from 2004 and 2005

Polysomnography	2004	2005
Total sleep (%)*		
Phase 1	15.6	80
Phase 2	48.5	
Phase 3	18.7	11
Phase 4	17.2	3
REM	0	6
Sleeping time (min)	421	430
Sleep latency (min)	11	56
Sleep efficiency (%)	84	23.46
Awakenings (n)	7	Numerous
Intra-sleep awake time (min)	39	66

*Normal conditions of total sleep: NREM 1 (4%), 2 (25%), 3 and 4 (45%) and REM (25%).