



## SCIENTIFIC LETTERS

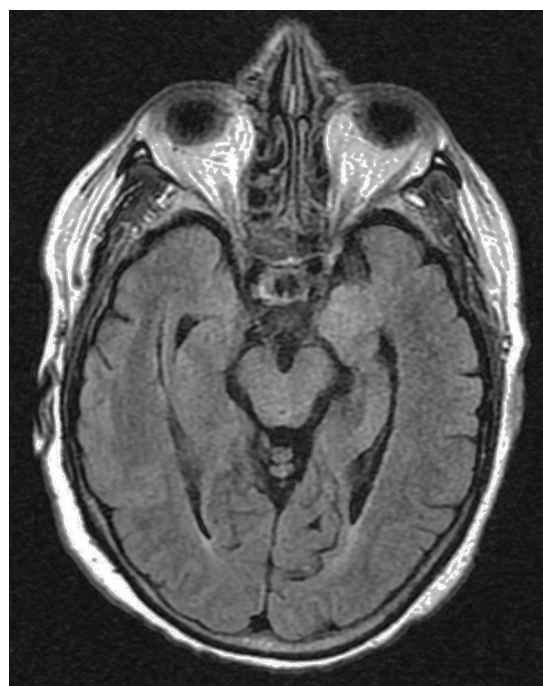
### Limbic encephalitis: The great unknown<sup>☆</sup>



### Encefalitis límbica: la gran desconocida

Limbic encephalitis (LE), described in 1960 by Brierley et al.<sup>1</sup> is a rare neurological clinical entity of subacute course that causes neuropsychiatric symptoms.

Hereby we present the clinical case of a seventy one year old female with dyslipidemia, hypothyroidism and breast ductal carcinoma with radical exeresis and treated with chemotherapy. She was admitted in the hospital following an event of sepsis due to methicillin-sensitive *Staphylococcus aureus* (due to reservoir infection). She suffers from progressive disorientation, repetitive talking, and sleepiness with progression towards status epilepticus, which is why she was admitted in the unit of intensive care medicine (ICM). The urgent cranial computed tomography (CT) scan performed did not show any significant findings. At admission her state is post-critical after the administration of intravenous (IV) benzodiazepines and her temperature is 38 °C; the rest of the device based-medical examination was normal. The blood sample showed platelet levels of  $22 \times 10^9/l$ , creatinine levels of 3.5 mg/dl, urea levels of 95 mg/dl, C-reactive protein (CRP) levels of 15.6 mg/dl, the rest being normal. Doctors proceeded with orotracheal intubation and lumbar puncture (LP) followed by secretion of cerebrospinal fluid (CSF) colourless at normal-pressure without cells, glucose levels of 68 mg/gl and protein levels of 64 mg/dl (plasma proteins 5.2 g/dl). Doctors proceeded with sedoanalgesia, fluid therapy, levetiracetam, and broad-spectrum IV antimicrobial treatment including acyclovir. They were isolated in bronchoaspiration and one hemoculture of the extended-spectrum-beta-lactamase-producing *Klebsiella pneumonia* without condensation in the chest X-ray was collected; both the urine culture and the CSF culture tested negative. CSF with polymerase chain reaction (PCR) for herpes simplex virus (HSV), cytomegalovirus (CMV), varicella zoster virus (VZV) and Epstein-Barr virus (EBV) all tested negative, and the cytology to rule out malignant cells tested negative too. Serologies for human immunodeficiency virus (HIV), hepatitis, HSV, CMV and VZV tested negative for active infections. Elevated CA 125 level (180.3 U/ml); remaining tumour markers normal. Negative

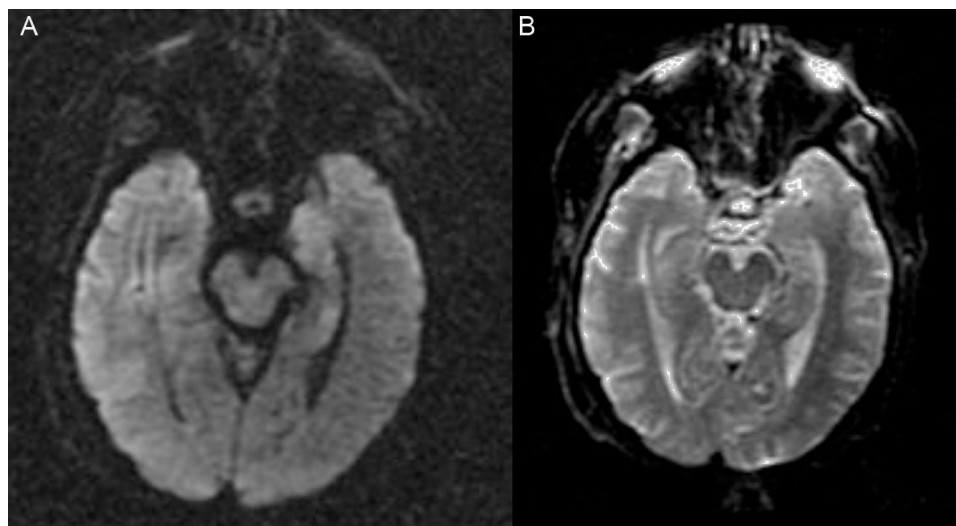


**Figure 1** NMR of the brain, FLAIR sequence. Signal hyperintensity in the hippocampic region of both temporal lobes of left predominance.

test results for the anti-DNA antibodies, antinuclear antibodies, c-ANCA and p-ANCA. Thyroid hormones in normal ranges with replacement therapy and negative test results for the antiperoxidase and antithyroglobulin antibodies. One second CT scan with the administration contrast is performed and it rules out structural disease, and also another control LP with secretion of colourless fluid at normal pressure with normal biochemical profile without cells, and negative for malignancy. Given the low level of consciousness, one electroencephalogram (EEG) is performed that is consistent with the effects of sedation and the nuclear magnetic resonance (NMR) of the brain with the following results: in the T2-weighted sequence of the hippocampic region, there is hyperintensity of left predominance, in the diffusion-weighted sequence, there is hyperintensity and a mild decrease of the apparent diffusion coefficient (ADC) in the hippocampic region of the left temporal lobe. After the administration of paramagnetic contrast there is no presence of any uptakes (Figs. 1 and 2A and B).

Given the clinical data and the characteristic neuroimaging obtained, a diagnosis of LE was suggested; onconeurological

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**Figure 2** NMR of the brain ([A]: diffusion study, and [B]: ADC coefficient). The diffusion study shows hyperintensity with discrete decrease of the ADC coefficient in the hippocampic region of the left temporal lobe.

antibodies tests in blood and CSF (against NMDA, IA-2, GAD, Hu, Yo, Ri, PNMA2, CV2, antiphysine, titin, recoverin and SOX1) were conducted and they tested negative. Treatment with 1 mg/kg/d of IV methylprednisolone was initiated that resulted in a slow but favourable neurological recovery. The patient was discharged from the ICM unit after 35 days, then from the hospital after 20 days, and then administered 1 mg/kg/d of oral prednisone for the next three<sup>3</sup> months after which she achieved ad integrum neurological recovery.

The clinical manifestations of LE are the subacute<sup>2</sup> appearance of several neuropsychiatric alterations including, among others, cognitive impairment, seizures, depression, irritability, hallucinations, and loss of short term memory.<sup>3,4</sup> In most cases, the CSF<sup>5</sup> shows inflammatory changes with discrete proteinorrachia and/or pleocytosis without pathognomonic findings. The CT scan<sup>5</sup> is usually normal, without contrast uptake, while in 70% of the cases, the NMR of the brain<sup>5</sup> is asymmetrically hyperintense in both temporal lobes, especially the T2 and the FLAIR-weighted sequences, while remains unenhanced after the administration of contrast. The EEG can show temporal or diffuse slowness, temporal spikes, and temporal or generalized focal seizure activity.

Today we can distinguish three<sup>3</sup> types of LE:<sup>6</sup> paraneoplastic, viral and idiopathic (non-paraneoplastic autoimmune).

Our patient shows clinical data associated with additional tests that are highly suggestive of LE. In the context of immunosuppression and since the most common cause of LE is viral, we ruled out a diagnosis of viral LE since the CRP in the CSF tested negative for HSV, CMV, VZV, and EBV (sensitivity and specificity over 95%).<sup>7</sup> Differential diagnosis was conducted with other causes of encephalopathy with affectionation of the temporal lobe such as mesial sclerosis, ischaemic stroke, cerebral neoplasm, Hashimoto encephalopathy and lupus encephalopathy.

Taking these data into consideration, the most probable clinical diagnosis is paraneoplastic LE<sup>8</sup> (PLE). This is

a rare entity (occurring in <1% of patients with cancer) and in between 60 and 70% of the cases, the neurological clinical manifestations can occur even years before the identification of the neoplasm; the tumours more commonly associated with PLE are small cell lung carcinomas (50%), testicular cancers (20%), and breast cancers (8%).

The diagnosis of this entity requires meeting the four<sup>4</sup> following criteria:<sup>9</sup> a compatible clinical picture, absence of neuro-oncological complications, <4 years-interval between symptom onset and the diagnosis of the tumour, and at least, one of the following: (a) inflammatory changes in the CSF with a negative cytology, (b) one NMR of the brain with changes in the temporal lobe, (c) the identification of onconeural antibodies<sup>6,10</sup> in blood or the CSF—present in between 50 and 60% of cases whose specificity is over 90%.

Our patient meets all diagnostic criteria except for testing positive for onconeural antibodies.

The LE is a rare and misdiagnosed clinical entity that should be taken into consideration when conducting the differential diagnosis of confusional state of subacute onset. In medical literature there are very few cases of PLE reported, and it is an exceptional diagnosis after the neoplastic process.

Management of PLE is based on symptom control and the initiation of oncospecific and/or immunomodulating therapy. Up to 50% of the patients do not respond to first line immunomodulating therapies (corticoids, IV immunoglobulins or plasma exchange—alone or combined). In the management of refractory cases, the administration of second-line therapies (rituximab and cyclophosphamide—alone or combined)<sup>10</sup> enables full recoveries or with minimal deficits in 80% of the cases.

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## Usefulness of etomidate in patients with Cushing syndrome with severe arterial hypertension and hypopotassemia<sup>☆</sup>



## Utilidad de etomidato en paciente con síndrome de Cushing con hipertensión arterial e hipopotasemia graves

Cushing syndrome (CS) has a low prevalence in children and is rarely a cause for admission to the Pediatric Intensive Care Unit (PICU). However, it may manifest with severe and potentially life-threatening electrolytic disorders and arterial hypertension. We present the case of a nursing infant with CS admitted to the PICU due to severe arterial hypertension and hypopotassemia, in which etomidate was used to counter cortisol synthesis.

A 14-month-old infant girl was referred to our hospital due to suspected CS. The parents described hypotonus from 8 months of age, weight gain in the last four months, and recent rejection of food intake. The patient presented physical features consistent with CS, hypotonus, irritability and disconnection from the surroundings. The blood pressure was above percentile 99 for her age and size (200/120 mmHg). The brain CT and MRI scans revealed alteration of the supratentorial white matter in relation to edema. In the context of severe arterial hypertension, this was consistent with posterior reversible encephalopathy syndrome (PRES), with left thalamic hemorrhage. Echocar-

diography showed left ventricular hypertrophy. Maximum dose labetalol (3 mg/kg/h) was administered to control the blood pressure, followed by the combination of captopril, amlodipine and diuretics. Severe hypopotassemia was recorded (2.3 mEq/l) and was seen to persist despite high intravenous replacement doses (12 mEq/kg/day).

The endocrine study confirmed the suspicion of primary CS (urinary free cortisol 7578  $\mu\text{g}/\text{m}^2/24\text{h}$ , plasma cortisol 1665 ng/ml). The measurement of ACTH (<5 pg/ml) showed CS to be independent of the hormone. The abdominal ultrasound and brain and adrenal gland CT and MRI studies revealed no tumor disease. Somatostatin receptor scintigraphic assessment revealed no pathological uptake. In view of the persistence of arterial hypertension and hypopotassemia, we introduced ketoconazole at increasing doses (200 mg/24 h), with scant clinical and laboratory test response (plasma cortisol 1548 ng/ml after 72 h of treatment). No liver toxicity was observed. We then added etomidate 0.03 mg/kg/h, which resulted in partial adrenal axis suppression, with a reduction of the cortisol levels to 309 ng/ml as determined 24 hours after the start of perfusion. Improved blood pressure control was thus achieved, allowing the suspension of labetalol. The potassium values also normalized, making it possible to reduce intravenous administration. Etomidate was continued during 5 days, with plasma cortisol control values maintained between 331 and 300 ng/ml. However, in the last 48 hours the patient developed septic shock secondary to central venous catheter-related *E. coli* bacteremia that proved refractory to vasoactive support and corticosteroid replacement therapy, leading to the death of the patient.

The necropsy study revealed cortical nodular hyperplasia of both adrenal glands. The PRKAR1A gene, associated to pigmented nodular adrenocortical disease,<sup>1</sup> and the only known gene associated to infant CS, proved negative.

Cushing syndrome is infrequent in infancy. Once plasma cortisol elevation is confirmed, the underlying cause must be investigated. The determination of plasma ACTH allows differentiation between ACTH-independent CS (<5 pg/ml) and ACTH-dependent CS (>15 pg/ml). Computed

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