SMGroup

Limbic Encephalitis

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INTRODUCTION

Limbic encephalitis (**LE**) is a rare disorder that affects the middle temporal lobe of the brain.

It was described in 1960 by Brierley [1] in three adult patients with subacute encephalitis mainly affecting the limbic region. Out of these three patients, two had evidence of neoplasia (left kidney leiomyoma, bronchial carcinoma). In 1968 Corsellis et al [2]. Coined the name LE to define three patients with severe memory impairment and bronchial carcinoma who showed degenerative changes in the gray matter of limbic areas, and characterized it as an autoimmune disease. Currently recognized as a paraneoplastic syndrome, the tumor causes a cross-immunological response against limbic structures.

Currently there are three varieties of LE: viral, idiopathic (non-paraneoplastic autoimmune) and paraneoplastic [3].

In spite of the broad spectrum of viral, bacterial and fungal pathogens that may be responsible for infections of the central nervous system (**CNS**) and especially of LE, viral etiology is the most frequent, being herpes simplex virus type 1 (**HSV-1**)) the germ most commonly implicated as the cause, not only of viral encephalitis but of LE in particular. It can affect up to 70 per cent of immunocompetent patients with infectious LE. On the other hand, immunocompromised patients,

such as those with human immunodeficiency virus infection, patients who have required bone marrow or stem cell transplantation, other etiological agents such as herpes simplex virus type 2 and herpes viruses human 6 and 7 need to be considered [4,5].

Idiopathic or paraneoplastic autoimmune is a potentially reversible and probably antibody-mediated variety [6], among which voltage-gated potassium channel antibodies (**VGKC**) are to be highlighted, has also been associated with neoplasms, especially of the lung and thymoma, but requires five years free of disease. It is caused by an abnormal immune response that damages the neurons of the immune system.

With regard to the neurological paraneoplastic syndromes of the LE, it is noteworthy that they affect several areas of the neuroege, are rare, with an incidence of less than 1 per cent and associated with neoplasms [7]. There is a 75 per cent relationship with small cell bronchial carcinoma [8,9], followed by testicular cancer, breast carcinoma, ovarian teratoma, thymoma, colon, kidney, Hodgkin's disease, immature teratoma (the latter two are the most common in people under 40 years) [9-11], and the rarer, chronic myeloid leukemia, plasma cell dyscrasia, neuroblastoma and prostate cancer. In about 60-75 per cent of patients, neurological symptoms precede the identification of the cancer (regardless of its location) [7,12]. Cases have been described in which a paraneoplastic LE appears preceding, even in years, the patient's own neoplasia. In some cases it may appear later or be present in localized phase, which is why it must be taken into account and make corresponding screening examinations. In the paraneoplastic LE, antibodies that have some degree of specificity with respect to neoplasia are identified (Table 1).

Neurological paraneoplastic syndrome is defined as those dysfunctions of the CNS and the peripheral nervous system in patients with associated neoplasms, which are not caused by metastatic invasion, opportunistic infections, side effects to antineoplastic treatment, metabolic, nutritional and vascular alterations [13].

Many have an immunopathogenic basis mediated by an immune response triggered by the tumor process with expression of onconeuronal proteins. Antineuronal antibodies with high specificity have been described with regard to certain neoplasms [7], which allow to establish the paraneoplastic origin and to direct the search of the primary tumor.

Neurological paraneoplastic syndromes are uncommon: 0'01 per cent of patients with associated neoplasms [14]. The most frequent are Lambert-Eaton myasthenic syndrome consisting of 3 per cent of lung carcinomas, myasthenia gravis that appears in 15 per cent of thymomas, and peripheral neuropathy demyelinating. Finally, a rare variant of plastocytoma is POEMS syndrome that appears in up to 50 per cent of cases and consists of polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes. Paraneoplastic syndromes affecting the CNS are more prevalent in women and persons above 50 years old [15].

The LE cannot establish a real incidence, there are no excessive published cases, and, so far, it is an under diagnosed entity.

CLINICAL MANIFESTATION

The clinical presentation consists of recent memory deficits with relative preservation of cognitive functions, depression, personality changes, irritability and seizures (complex temporal lobe seizures with or without motor involvement of the face and limbs are common). Hypothalamic-diencephalon dysfunction, including somnolence, hyperthermia, hyperphagia, and, less frequently, pituitary hormone deficiency [12]. Onset is sub acute in more than 80 per cent of cases, and may precede the diagnosis of cancer by months, even years [16]. With regard to psychiatric disorders, which appear in more than 40 per cent of cases, they may consist of: affective changes (15%), hallucinations (10%), personality changes (5%), memory compromise up to 80% of cases, confusion (40%), cognitive deficit (15%). Hyperthermia and somnolence are also frequent [17-20]. When it comes to a paraneoplastic syndrome, the clinic generally accompanies symptoms associated with pathology outside the hippocampus region, as it produces a more diffuse affectation.

DIAGNOSIS

As it is a disease with low incidence and absence of tumor at the beginning of the disease, the diagnosis requires high clinical suspicion.

Neuroimaging is very useful. Computed tomography (**CT**) is usually normal [21]. In magnetic resonance imaging (**MRI**) about 70 per cent of cases present asymmetric hyperintensity of temporal lobes, especially in the FLAIR and T2 sequences. In T1 sequence it is possible to see hypointense or atrophic lesions in the temporal and limbic regions. After the administration of paramagnetic contrast, capture of contrast is not usually observed in early stages, but there may be gyriform abstraction as the disease gets worse, usually within a week after the onset of symptoms. In diffusion-enhanced sequences restriction thereof by cytotoxic edema can be identified [22] (Figure 1).

The T2 and FLAIR sequences are the most important, since they can more clearly identify unilateral or bilateral hyperintense lesions in the cortex of the temporal lobes, hippocampus and tonsillar nuclei. There may be visible lesions in other parts of the CNS, such as the hypothalamus and the brain stem. 70 per cent of the patients with paraneoplastic LE present alterations in the MRI, of which 90 per cent have similar lesions to those as described [23]. MRI is usually normal in 30 per cent. Rosenfeld et al. found that about 70 per cent of patients with neurological abnormalities of paraneoplastic origin have MRI abnormalities in regions such as the thalamus, midbrain, pons, paraventricular and periaqueductal gray regions, as well as in the medulla [24] (Figure 1).

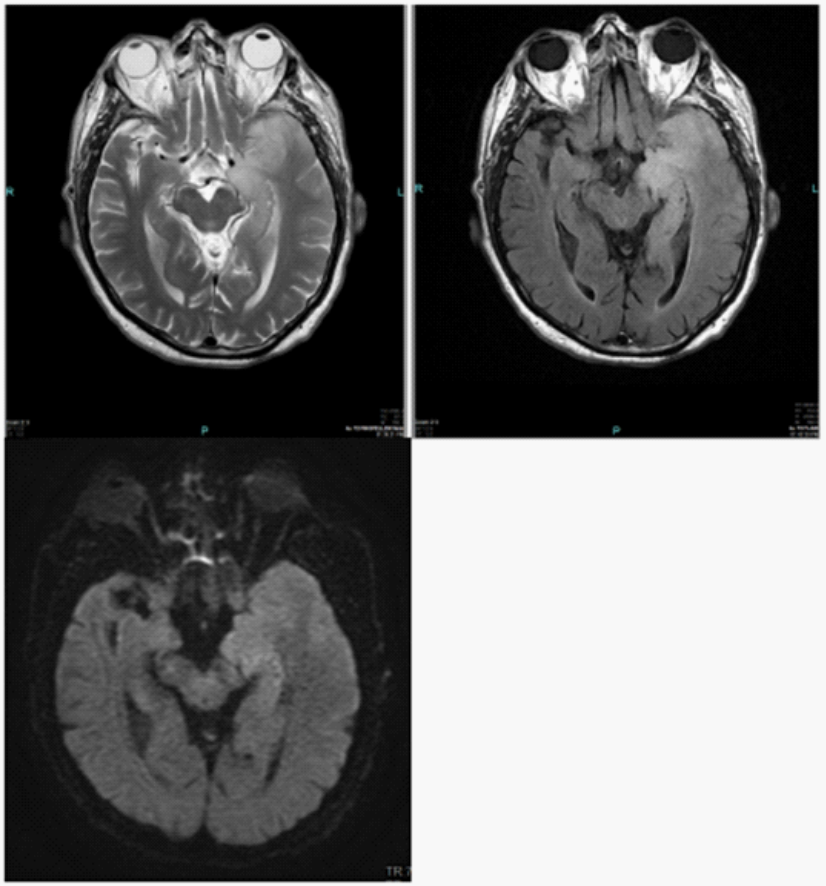

Figure 1: MRI. The sequences Axial T2 [A], FLAIR [B], and potentiated in diffusion (b 1000) [C] of a patient diagnosed of autoimmune non-paraneoplastic limbic encephalitis (without detecting positive antibodies) with clinical manifestations of seizures, confusion and dysphagia associated with marked cortical thickening and diffuse hyperintensity of the medial and inferior region of the left temporal lobe with extensive hippocampal commitment. In the diffusion sequence, restriction is observed in the zone.

In cases where MRI is normal, fluorodeoxy glucose-positron emission tomography may show hyper metabolism in the hippocampus21, it has a higher sensitivity than CT for the detection of hidden neoplasm, but the greater utility of this image study is its high negative predictive value, which is near 90 per cent, which has weight to determine that it does not have a neoplasms at the time of the study [25].

The electroencephalogram is useful in cases of presentation in the form of a confusional syndrome or altered level of consciousness. About 50 per cent of cases may show temporary or diffuse slowness, temporal spikes, electrical crises or status epilepticus, focal, temporal or generalized.

Cerebrospinal fluid (**CSF**) examination is useful to rule out meningeal carcinomatosis. Non-pathognomonic discrete inflammatory elements suggestive of an infectious or immune cause are identified. Mild pleocytosis may appear 30-40 leukocytes/mm3 with a predominance of T cells, which may be up to 75 per cent, a slight elevation of proteins

(50-100mg/dL) typically at the expense of IgG. This test is abnormal in up to 80 per cent of cases [23,26,27].

30 per cent of cases show an associated syndrome of inappropiate secretion of antidiuretic hormone.

Histopathology shows CD8 (+) T lymphocytic infiltrates in perivascular and parenchymal tissue, microglial nodules, gliosis and neuronal loss in the gray matter of the hippocampus, cingulate cortex, piriform cortex and frontal orbit, insular cortex and tonsillar nuclei.

The presence of onconeuronal antibodies is one of the most effective tests for diagnosis [24,28-30]. About 60 per cent of patients with a neurological paraneoplastic syndrome have detectable levels of auto antibodies in the serum or in the CSF. Its detection provides specificity greater than 90 percent, it is the best diagnostic method [28]. In certain paraneoplastic syndromes auto antibodies can be detected in the CSF, without being found in serum, so that whenever possible it should be sought to be present in both body spaces [31]. The absence of antibodies, 30 per cent, or atypical antibodies, between 5-10 per cent, does not rule out the diagnosis, as well as their only presence does not confirm it either [28]. Its presence is a predictive factor of good prognosis, related to the limited stage of the neoplasms, a complete response to treatment and an increased survival [32] (Table 1).

Table 1: Association between antibodies, limbic encephalitis and cancer.

ANTIBODIES	RELATED NEOPLASIA
Anti-Hu	Small cell carcinoma of the lung, ovary, lymphomas, gastrointestinal tract, kidneys, bladders and prostate
Anti-Yo	Neoplasm of ovary, breast and uterus
Anti-CV2	Small cell lung carcinoma, thymoma, testicular germ cell tumor
Anti-Ma (1-2)	Testicular neoplasm, lung neoplasm, breast neoplasm
Anti-amphiphysin	Small cell lung carcinoma, breast neoplasm
Anti-ANNA-3, anit-PCA-2	Small cell lung carcinoma
Anti-VGKC	Thymoma, small cell lung carcinoma
Anti-neuropil	Thymoma, mediastinal tumor of germinal cells, thyroid neoplasia
Anti-NMDAR	Teratoma, thymomatimoma
Anti-Ri	Neoplasia of breast, cervical, lung, stomach and bladder

These antibodies are directed against two classes of antigens that give rise to the autoimmune response:

- **Intracellular or paraneoplastic classical antigens (Anti-Hu, Anti-Ma2 and Anti-CV2/CRMP-5 and amphiphysin)**: That are mediated by cytotoxic responses (T lymphocytes), suggesting a cellular immune response. The response to treatment is limited, except for LE associated with anti-Ma2 in testicular tumors.
- **Cell membrane antigens:** VGKC and the N-methyl-D-aspartate receptor (**NMDAR**). They are often found in association with a thymoma (especially in the presence of anti-VGKC, usually not detectable in CSF) or a teratoma (usually anti-NMDAR, which can be detected only in CSF and not in serum). Up to 20 per cent of paraneoplastic syndromes related to VGKC antibodies may be caused by small cell lung carcinoma. The response to immunotherapy is generally good [33].

More than half of the tumors associated with paraneoplastic EL are small cell lung carcinomas, and half of them have antibodies against the Hu family of messenger ribonucleic acid (**mRNA**) binding proteins. Onconeuronal proteins Ma1, Ma2 and Ma3 have also been identified as antigens of paraneoplastic EL. Under normal conditions, anti-Ma antibodies react only against neurons and testicular germ cells, since the expression of their mRNA is restricted to brain and testicular tissue. In certain neo plastic tissues such as the breast, colon or parotid, Ma1, Ma2 and Ma3 mRNAs are also expressed. In some cases the anti-neuronal nuclear antibody (**ANNA-3**) is expressed and it does not produce encephalitis, which also influences the individual immunoreactivity (Table 1).

One study found that 100 per cent of the small cell lung tumors analyzed expressed the Hu antigen, but in spite of this, only 15 per cent of these patients had low titers of anti-Hu antibody [34]. This 15 per cent has at least antitumor immune response, while the remaining 85% does not make an effective antitumor immune response, which speaks of a tolerance of T cells towards the tumor. This distinction between activation or tolerance of CD8 (+) T cells is determined by the presence or absence of CD4 (+) T cells respectively [27]. This finding is relevant, since the activation of CD8 (+) T cells could be modulated through medication, which would allow immunotherapy for the treatment of certain neoplasms [3,35].

DIFFERENTIAL DIAGNOSIS

The most important moment in patients with neurological disorders, in which the causes of vascular, infectious, toxic and metabolic origin have been ruled out, is to assess LE as one of the differential diagnoses.

In the case of EL, a differential diagnosis has to be made with Wernicke-Korsakoff syndrome, Alzheimer's disease, cerebrovascular disease, mesial sclerosis, neoplasms, CNS infections, *status epilepticus* and Hashimoto's encephalopathy.

WERNICKE-KORSAKOFF SYNDROME: as a result of thiamine deficiency, common in chronic alcoholism, it also compromises the temporal area and is associated with malnutrition, mal absorption or increase in metabolic needs. Chronic diarrhea, oculomotor alterations or ataxia, is classic of Wernicke's encephalopathy. In addition the typical alterations in the neuroimagen are the changes in periaqueductal gray substance and of the third ventricle.

ALZHEMIMER'S DISEASE: The medial temporal structures, the hippocampus and the entorhinal cortex are the first affected areas, which would explain the commitment of memory, thinking and behavior; however, in this disease the onset and course are insidious.

CEREBRAL VASCULAR DISEASE: The acute presentation of neurological alterations, with abrupt onset and the presence of seizures may suggest an embolic or thrombotic origin of the symptomatology, where 80 per cent of the cases are secondary to ischemic etiology, constituting one of the causes of greater morbidity and mortality in developed countries. However, the absence of focality, as well as the symptomatology of a rather psychiatric appearance, discard this diagnosis [36].

Temporal lobe affectation occurs when the middle cerebral or posterior cerebral arteries are affected. Strokes with temporary affection constitute more than 50 per cent of cases of recent diagnosed seizures in adults, especially in cases of hemorrhagic infarctions.

MESIAL SCLEROSIS: It is one of the known causes of epilepsy of the temporal lobe refractory to treatment, and consists of neuronal loss, hippocampal gliosis and adjacent structures.

NEOPLASMS: The main tumor affectation of the temporal lobe is usually secondary to low grade gliomas. They appear more frequently in young adults and there is a slight male predominance. Seizures are frequent as an early symptom of low grade gliomas.

INFECTION OF THE CENTRAL NERVOUS SYSTEM: Infection of the CNS, especially of viral origin, should be considered as one of the initial diagnoses that should be discarded when a patient presents with the characteristic symptomatology of LE. HSV infection has a predilection for the temporal lobes and the limbic system, which could be in agreement with the clinical course of both entities. CNS infection can be ruled out by means of CSF analysis and imaging methods [36]. Neurosyphilis can also occur with an atypical presentation such as LE.

STATUS EPILEPTICUS: *Status epileptic* is defined as seizures of more than 5 minutes in duration or the presence of two or more seizures without recovery between episodes. In the critical and post-critical period, we can see lesions in the MRI consisting of focal signal hyperintensities in T2-weighted sequences, FLAIR and apparent diffusion coefficient (**ADC**) restriction diffusion in cortical regions and in the hippocampus, all secondary to edema or hypoxia due to energy expenditure during the seizure.

HASHIMOTO'S ENCEPHALOPATHY: Consists of a corticosteroid-responsive encephalopathy associated with autoimmune thyroiditis. Its epidemiology consists of presenting a prevalence of

2.1/100.000, an average age of 45-55 years, female predominance over male (5:1). Hashimoto's encephalopathy may associate other autoimmune diseases (such as diabetes mellitus, systemic lupus erythematosus and/or all variants thereof, etc.). It may appear in euthyroid, hypothyroid or hyperthyroid patients. Regarding the clinic, some authors classify the presentation form into 2 types. It may be a form of vasculitic presentation or a form of progressive presentation. The vasculitic presentation, which presents more incidence of recurrences and remissions, consists of stroke-like episodes. And the progressive presentation is characterized by transient aphasia, tremor, ataxia, sleep disorders, headache, psychosis, paranoia, visual hallucinations, epileptic seizures and myoclonus.

Patients have high titers (with levels > 100 times normal) of antiperoxidase, usually> 200 u/ml. Anti-peroxidase antibodies are present in 100 per cent of Hashimoto's encephalopathies, and antithyroglobulin antibodies in 70 per cent. Antibody levels are not related to the severity of the symptoms. The treatment is corticoid and if it does not improve the clinical, plasmapheresis.

DIAGNOSTIC CRITERIA

The diagnostic criteria of paraneoplastic LE require the presence of four of the following points:

- Compatible clinical picture.
- Exclude other neuro-oncological complications.
- An interval of less than 4 years between the development of neuropsychiatric symptoms and the diagnosis of the tumor.

At least one of the following:

- Inflammatory changes in CSF with negative cytology.
- MRI with changes in the temporal lobe (65% uni or bilateral).
- Identification of antibodies against onconeuronal antigens [37] (Table 1). The suspicion of LE without the evidence of a tumor requires an exhaustive research.

TREATMENT

The treatment consists in controlling the symptoms, especially the epileptic seizures, and in treating the cause: a specific oncospecific and/or immunomodulatory treatment must be administered [7].

In a large majority of cases, pacients improve after tumor resection; surgical treatment within the first 4 months after onset of neurological symptoms has proved to be the best predictor of recovery [38,39].

Up to 50 per cent of patients do not respond to the first-line immunomodulatory treatment, consisting of the administration of corticosteroids (methylprednisolone 1g/day intravenous, for 3-5 days), intravenous immunoglobulins (0.4 g/kg/day, for 3 -5 days) or plasma exchange, separately or in combination. In refractory cases, administration of second-line treatment, consisting of administration of rituximab (375 mg/m^2 weekly, for 4 weeks) and administration of cyclophosphamide (bolus of 600 mg/m^2) alone or in combination allows complete recovery or with minimal deficits in 80 per cent of the cases [40]. In addition, this treatment decreases the likelihood of recurrences.

There are really no guidelines for choosing one treatment or another, the duration of treatment or indications for switching to a second line, its use varies widely among professionals, so there are several studies on this topic. In a retrospective study, an initial treatment was proposed with daily infusions of methylprednisolone 1g/kg/day or of immunoglobulins 0.4g/kg/day for 3-5 days, followed by weekly infusions for 4 to 6 weeks. Data from this study show that 62 per cent of patients had a good response to the first treatment regimen. Of the group of non-responders, half of them improved with a second immunosuppressive agent [41].

Patients with immunosuppressive therapy respond to treatment more slowly than those treated surgically. The response to immunotherapy is variable and largely depends on whether neurological damage is mediated by antibodies or by cells. As previously said, when autoantibodies are detected against an intracellular antigen (neurological damage mediated primarily by cells), management with immunomodulators has no effect on the pathology (except in the paraneoplastic syndrome of testicular tumors associated with Ma2, where response may be seen until in 30 per cent of the cases in which immunosuppressive treatment and surgical treatment of neoplasia are combined). On the other hand, the detection of autoantibodies against a membrane antigen indicates a good response to treatment with immunomodulators [42].

It is unknown whether the evolution of neurological syndromes of paraneoplastic origin is due to an adequate response to the treatment or if the cessation of progression or even resolution of the clinical picture is due to the natural history of the pathology. In patients who respond to immunotherapy, immunosuppression should be considered on a prolonged basis, since recurrences occur in 20-25 per cent of patients38, and at intervals of months or years, usually with a substantial recovery between recurrences [43].

The prognosis is given by an early etiological diagnosis, and if it is paraneoplastic, by the diagnosis and treatment of the tumor. Regarding the factors associated with the response to immunotherapeutics there are predictors of positive response and predictors of negative response. The predictors of positive response are: a sub acute course, a fluctuating course, symptoms of headache and/or tremor, less aggressiveness or severity of the disease, early initiation of treatment and tumor resection (in the case of paraneoplastic agents). The predictors of negative response are: a family history of dementia and the delay in starting treatment.

After treatment improves hyponatremia, seizures and neuropsychiatric disorder, but amnestic disorders may remain as an aftermath.

To sum up, paraneoplastic LE is a clinical picture which affects the temporal lobe of the brain, a clinical condition that is probably underdiagnosed and rare, although in recent years it has manifested itself with some frequency and it is usually confused with neuropsychiatric disorders, so it should be kept in mind in the differential diagnosis of confusional pictures of subacute establisment. In the medical literature there are few reported cases of paraneoplastic LE, being exceptional after diagnosis of the neoplastic process [44]. The knowledge of this entity is of paramount importance for all health personnel, especially for emergency and critical care physicians, as well as knowledge of the imaging characteristics of LE for radiology specialists. The participation of a multidisciplinary team is essential. Considering this entity, the high index of suspicion, exhaustively conducting paraclinical examinations and the search for the oncological disease determinant of it, will allow a timely diagnosis and treatment, improving the quality of life in the survival of these patients, which as it has been seen, is a subsidiary of a specific and potentially reversible treatment.

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