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LATE DIAGNOSIS OF LIMBIC ENCEPHALITIS ASSOCIATED WITH LGI1 ANTIBODIES LEADING TO RELAPSES

DIAGNÓSTICO TARDIO DE ENCEFALITE LÍMBICA ASSOCIADA A ANTICORPOS LGI1 QUE LEVAM A RECIDIVAS

DIAGNÓSTICO TARDÍO DE ENCEFALITIS LÍMBICA ASOCIADA A ANTICUERPOS LGI1 QUE LLEVAN A RECIDIVAS

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ABSTRACT

Autoimmune encephalitis has been a subject of research in the past few years; most of the cases are non-paraneoplastic and associated with an antibody to a surface protein of neurons. Studies have shown that VGKC complex is indeed represented by three proteins, and LGI1 is the most prevalent in limbic encephalitis. This entity is characterized by monophasic presentation with acute or subacute onset, memory loss, confusion, seizures and psychiatric symptoms. The presentation of anti-LGI1 antibodies in serum or CSF confirms the diagnosis. The treatment consists of immunotherapy with good clinical response, which is a criterion for diagnosis. We report a case of a patient with diagnosis confirmed six months after the symptoms onset, improvement after immunotherapy, but with episodes of relapse.

Keywords: Encephalitis/immunology; Limbic encephalitis; Inmunotherapy.

RESUMO

A encefalite autoimune tem sido assunto de pesquisa nos últimos anos, a maioria dos casos é não paraneoplásica e associada ao anticorpo para uma proteína de superfície dos neurônios. Estudos têm mostrado que o complexo VGKC é efetivamente representado por três proteínas, e a LGI1 é a mais prevalente na encefalite límbica. Essa entidade é caracterizada por apresentação monofásica com início agudo ou subagudo, perda de memória, confusão mental, crises convulsivas e sintomas psiquiátricos. A apresentação de anticorpos anti-LGI1 no soro ou no LCE confirma o diagnóstico. O tratamento consiste em imunoterapia com boa resposta clínica, que é um critério diagnóstico. Relatamos o caso de um paciente com diagnóstico confirmado seis meses após o início dos sintomas, com melhora após imunoterapia, porém com episódios de recaídas.

Descritores: *Encefalite/imunologia; Encefalite límbica; Imunoterapia.*

RESUMEN

La encefalitis autoinmune ha sido asunto de investigación en los últimos años; la mayoría de los casos es no paraneoplásica y asociada al anticuerpo para una proteína de superficie de las neuronas. Estudios han mostrado que el complejo VGKC es efectivamente representado por tres proteínas, y la LGI1 es la más prevalente en la encefalitis límbica. Esa entidad es caracterizada por presentación monofásica con inicio agudo o subagudo, pérdida de memoria, confusión mental, crisis convulsivas y síntomas psiquiátricos. La presentación de anticuerpos anti-LGI1 en el suero o en el LCE confirma el diagnóstico. El tratamiento consiste en inmunoterapia con buena respuesta clínica, que es un criterio diagnóstico. Relatamos el caso de un paciente con diagnóstico confirmado seis meses después del inicio de los síntomas, con mejora después de inmunoterapia, aunque con episodios de recaídas.

Descriptores: *Encefalitis/inmunología; Encefalitis límbica; Imunoterapia.*

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INTRODUCTION

Autoimmune encephalitis

Autoimmune encephalitis have been termed autoimmune channelopathies, despite the fact that the antigen is the protein surface and not the channel itself. These proteins can be found anywhere in the nervous system, but can be highly specific (eg limbic encephalitis). Although rare, the entity began to be recognized and treated in recent years, with the expectation of new antibodies discovery in the future.[1]

Affected patients have amnesia, confusion, seizures, psychiatric symptoms and some of them develop encephalopathy with movement disorders, loss of consciousness and hypothalamic disorders. Some patients have this condition related to tumors: ovarian teratoma, thymoma, small cells lung cancer; but the majority do not exhibit association with neoplasia.[1-3] Limbic encephalitis is an inflammatory process affecting predominantly the medial temporal lobe (hippocampus, amygdala) and orbitofrontal cortex. Patients typically present rapid progression of memory deficits, psychiatric disorders and seizure.[4] Autoimmune etiology must be considered if there are abnormalities on MRI, EEG and CSF, including antineuronal antibodies in serum and CSF.[5]

Limbic encephalitis: voltage gated potassium chanel spectrum (VGKC); leucine rich glioma inactivated 1 protein (LGI1)

Limbic encephalitis was initially described as a rare clinic pathological entity, involving amnesia, seizures and psychological disorders associated with neoplasia. However, paraneoplastic limbic encephalitis is a rare complication and a non-neoplastic type, associated with antibodies against neuronal proteins, began to be recognized recently. Several antibodies were identified in these cases, for example, anti-NMDAR, anti-AMPAR, anti-GABA BR type, anti-VGKC.[1]

Limbic encephalitis associated with antibodies to VGKC complex was the first one with well described response to immunotherapy.[3] Six main findings characterize these autoimmune responses: extracellular epitopes, binding of antibody and antigen is evident in affected cells, the antibody alters the structure or function of neuronal antigen, the effect of the antibody is usually reversible, the clinical presentation is similar to pharmacological or genetic models in which the antigen is disrupted, and the immune-mediated symptoms are responsive to immunotherapy in most cases.[6] Recent studies show antibodies to VGKC complex have affinity for other proteins identified in extracts of mammalian cortical neuronal membrane. The most common proteins are LGI1 and CASPER2, the less frequent is contactin 2.[1, 7]

Anti-LGI1 antibodies were initially identified by immunoprecipitation and spectroscopy, representing 70% of VGKC complex that was extracted from rabbit brain and identified using 125Ialfa – dendrotoxin, an ophidian toxin for VGKC subtypes Kv1.1, 1.2 and 1.6.[1]

LGI1 is a presynaptic protein associated with Kv1 VGKCs synaptic and other neuronal proteins. The two specific receptors for LGI1 are disintegrin and metalloproteinase domain-containing proteins 22:33 (ADAM22, 23), which is expressed post and presynaptically. It is also found in large quantities in the hippocampus and neocortex.[1] The probable physiopathology of limbic encephalitis anti-LGI1 is supported by the epileptogenic effects of purified IgG from a patient who has limbic encephalitis and anti-LGI1 causing neuronal excitability in hippocampus samples.[8]

Mutations in the gene that encondes the protein LGI1 are associated with autosomal dominant temporal lobe epilepsy, also defined as autosomal dominant lateral partial epilepsy with auditory aura.[6] In experiments using mices with transgenic expression of the protein, abnormal neurons were found and seizures occurred. Moreover, the protein deletion results in lethal phenotype characterized by myoclonic and tonic seizures.[9] Antibodies to LGI1 have been found mainly in patients with limbic encephalitis and epilepsy, but there are some cases with Morvan's syndrome.[1]

In a study conducted in the UK, high titers of antibodies to VGKC complex (> 400pmol by L - Normal: <100pmol per L) were found in 1-2 persons per million per year, and 67% of these patients had limbic encephalitis. The rest had neuromyotomia (11%), Morvan's syndrome (5%), isolated epilepsy (4%) or CSF findings that could not be fitted into any categoria.[1, 9] In another study in which the cohort was represented by a large number of paraneoplastic syndromes (51%), LGI1 were detected in 77% of the cases.[1]

This article aims to review the literature available on limbic encephalitis associated with antibodies to LGI1 and report an illustrative case, which is followed in our service.

MATERIAL AND METHODS

We performed an extensive investigation, including EEG, MRI, whole-body FDG-PET, and a full panel of auto-antibodies, including indirect immunofluorescence test for protein LGI1.

Case report (results)

Male patient, 64 years old, was found in his home during an episode of generalized tonic clonic seizure in June of 2013. The patient had a medical history of insulin-dependent diabetes refractory to treatment. At the emergency room, hyperglycemia was identified and reversed with insulin. After this episode, he began to present rapidly progressive dementia, with loss of recent memory, disorientation and later psychotic symptoms (aggression, irritability, persecutory thoughts). In January 2014, the patient was admitted for evaluation in our hospital. The family denied new episodes of seizures but reported episodes of exacerbation of the other symptoms described above. General physical exam was normal. On neurological exam, he was disoriented in time and space and he had difficulties in the exam of recent memory (recall); he also had symmetric diminished vibratory sensitivity in both legs up to the knees and bilateral intentional tremor. On further investigation, MRI showed mild atrophy of the hippocampi, more pronounced on the left. Three routine EEGs performed on occasion demonstrated no changes. CSF presented increase of IgG (10.5mg/dl) and protein (84mg/dl). He scored 14/30 on MOCA (Montreal Cognitive Assessment) (visual space and executive function 3/5, naming 3/3, attention 5/6, language 0/3, abstraction 0/2, recall 0/5, orientation 3/6). Whole-body PET and oncology antibodies were negative. Indirect immunofluorescence test for protein LGI1 was positive in blood and in CSF. The patients received intravenous immunoglobulin with improvement of the symptoms (MOCA after-visual space and executive function 5/5, naming 3/3, attention 5/6, language 2/3, abstraction 2/2, recall 1/5, orientation 4/6-22/30). He was discharged with prednisone 60 mg per day and orientation to decrease the dose slowly, carbamazepine 200 mg three times daily and maintenance of insulin. In February 2014, the patient returns to the emergency due to a status epilepticus. After seizure control, further investigation showed worsening of the CSF pattern

(white cells 13 red cells 52 proteins 309 IgG 47,5 glucose 223) and he underwent a pulse therapy with methylprednisolone 1 g daily for 3 days, with improvement of the symptoms. In March 2014, he returned to the hospital due to progressive worsening of the periods of fluctuations of humor (threatened his son, ran away from home), which improved after plasmapheresis. In April 2014, he came back to the hospital because of viral diarrhea and decompensation of diabetes, periods of mood fluctuation and disorientation. New cycle of immunoglobulin was prescribed and he remains as an outpatient in our epilepsy clinic. As future therapy, we decided to maintain treatment with cyclophosphamide and repeated plasmapheresis in order to avoid new relapses.

DISCUSSION

Clinical presentation

Patients with anti-LGI1 enchephalitis present acute or subacute onset, memory loss, confusion, seizures, agitation and psychiatric symptoms for days or weeks. There may be a history of infection. Some patients presented in the onset psychosis episode[10] or cryptogenic epilepsy.[11] Most common after 40 years of age and in men (2:1).[1] In the case reported above, the patient initially presented with secondary generalized seizure that was attributed to hyperglycemia, followed by loss of recent memory, exacerbation episodes with confusion and agitation.

REM sleep behavior disorder is commom,[12] other sleep disorders , startle syndrome,[13] ataxia and hypothermia in some cases.[14] Intestinal pseudo-obstruction can also be found, probably due to the action of antibodies in myenteric plexus.[15]

Patients may present brief dystonic movements, mainly of the face and upper extremities, which is called brachiofacial dystonic seizure, progressing to symptoms of encephalitis.[16,17] In some cases, these movements may occur 60-100 times per day and can be misdiagnosed as myoclonus or startle disease.[16]

Investigation

Serum sodium: Low concentrations of sodium (115-130mmol per L) before the start of antiepileptic drugs or any other treatment has been a clue to the diagnosis of limbic encephalitis associated with antibodies against the VGKC complex.[18] In a study conducted in the United States, 60% of the patients experienced hyponatremia, which can be related to syndrome of inappropriate secretion of antidiuretic hormone by the LGI1 expression in the hypothalamus and kidney.[9] Unfortunately, we do not have this information about our patient.

Antibody to LGI1: In patients who have limbic encephalitis, levels are normally high (> 400 pmol/L) and it can be higher than 1000 pmol/L. The test conducted was qualitative and patient was positive in blood and CSF. However, low titers can be found, especially in children[19, 20] in the recovery period or in patients who improved espontaneously.[21] In addition, lower titers are found in patients who have epilepsy, in elderly patients[22] and neoplastic patients, particularly those with timoma[23, 24] or lung and others carcinomas.[24-26]

Neoplastic screening: Although most cases of autoimmune encephalitis anti LGI1 are unrelated to cancer, it is important to exclude this possibility. Thymoma is the most common tumor related to this limbic encephalitis[1]. Oncogenic antibodies, whole body PET and CT thoraco-abdominal presented no evidence of cancer in the case reported.

Magnetic resonance image (MRI): T2 or FLAIR hyperintense signal in unilateral or bilateral mesial temporal lobe is common, as described in our patient. However, 45% of patients with limbic encephalitis with anti LGI1 have a normal MRI at the beginning or during the course of disease.[16]The amygdala is affected in some cases, even without changes in temporal lobe.[27,28] Despite the treatment and fluctuation of symptoms presented by the patient, there was no significant change in the follow-up MRI.

PET: PET may be more sensitive than MRI to assess hippocampal dysfunction. It shows hypermetabolism in the early stage of the disease and hypometabolism in later stages.[27, 28]

Electroencephalogram (EEG): The EEG shows interictal foci of epileptiform activity or slow activity in the anterior and mesial temporal region, it may also be detected in the frontal region, as well as ictal activity in the same areas.[1] For brachiofacial dystonia, electrodecrement may precede events, which is typical of tonic seizures.[6] During hospitalization, our patient showed no seizures and his EEG was normal.

Cerebrospinal fluid (CSF): IgG and oligloconal bands (OCB) can help identify an autoimmune change, as in our patient, before confirmation by antibodies. However, OCB cannot be detected early in the disease and even during its evolution.[18, 29]

Classification and pathogenesis

Vincent et al. brings important questions in their review on the subject discussed above, for example, questions such as how these diseases are classified - based on clinical presentation or in antibody? Whereas it is still restricted the access to antibodies, perhaps the clinical classification prevails until the tests are commercially more accessible to institutions with less purchasing power. Furthermore, the therapeutic procedure is the same, regardless of the antibody that is causing, and the importance of this fact lies in the better understanding of the physiopathology, in response to immunotherapy and prognosis of the condition.

Most cases of autoimmune encephalitis associated with anti - LGI1 are not related to cancer, and the mechanism leading to the production of these antibodies is unknown. In the case reported above, patient had refractory diabetes, but the test for anti –GAD antibodies was negative.

Diagnosis

Antibodies are identified by indirect immunohistochemistry. Immunopreciptation of protein extracts of neurons and subsequent spectroscopy can identify the antigen. For this, the patient serum is used, which contains the basal cells to be analyzed. The radioimmunoassay has become commercially avaliable.[1] Antibody concentrations are generally higher in serum than in CSF, which could be negative.[22, 25] The test available at our institution, is the indirect immunofluorescence in HEK293 cells transinfected with the LGI1 protein gene.

Definitive diagnosis is characterized by the presence of specific antibody in serum or CSF and responding to immunotherapy. Probable diagnosis is defined by the presence of antibody or presence of another neuronal marker of immune process discussed above or a related clinical finding, and response to immunotherapy. Possible diagnosis is described as a clinical diagnosis, and other neuronal marker of immune process (anti - GAD antibodies of unknown neuronal surface) or response to immunotherapy.[30] Our patient had a late diagnosis, six months after symptoms onset, and obtained response to immunotherapy, but he showed relapse of the condition after 3 weeks. The same occurred with other therapeutic options used.

Differential diagnosis

Other diagnoses should be considered in clinical conditions like this: Wernick's encephalopathy, encephalopathy induced by drugs or toxins, and viral encephalitis. Under the relatively recent knowledge of these antibodies, the question about the diagnosis arises on similar cases that have been diagnosed in the past as unproved viral encephalitis. In a study of encephalitis in the UK, 3% of patients had antibodies against complex VGKC.[31]

Studies in non-prion rapidly progressive dementia have found anti VGKC complex antibody, even in patients who fit in the criteria including for Creutzfed-Jakob disease with good response to immunotherapy.[32]

Treatment

The role of antibodies in neuromuscular diseases is well known since the 1970s. Affected patients have rapid improvement with plasma exchange, which removes antibodies from the circulation. Over the past 10 years, various diseases of the central nervous system, mediated by antibodies against surface proteins expressed in neurons, with significant improvement after immunotherapies have been discovered, although the recovery is slower compared to the peripheral diseases.[1]

This slow improvement could be due to a long time needed to recover the CSF changes and slow reduction of antibodies concentration.[1] In addition, the improvement after plasmapheresis is discussed, since the probable pathophysiology of these encephalitis involves intrathecal production of antibodies. The use of cyclophosphamide and rituximab are also debatable, but with few case reports referring good response.[33]

Some studies indicate the use of intravenous immunoglobulin, associated or not with plasmapheresis, followed by high doses of oral corticosteroids. For those who do not respond to first-line treatment and have negative screening for cancer, second-line immunotherapy with rituximab, cyclophosphamide, or both should be used.[30] There are no studies about prolonged immunotherapy to prevent relapse, and there is not known correlation between a high risk of relapse in patients who were not properly treated in the first event.[34] However, it was clear, in our experience with this case, the refractoriness after a delayed treatment, even using first-line drugs, such as described in the literature. As described above, after intravenous immunoglobulin, pulse steroids, plasmapheresis and new cycle of immunoglobulin, we opted for the use of cyclophosphamide and plasma exchange in case of exacerbations, which have been frequent in this patient.

Focal or generalized seizures related to LGI1 encephalitis do not respond well to anti-epileptic drugs; however, respond to immunotherapy such as steroids, plasmapheresis and intravenous immunoglobulin.[16, 18, 22] This was experienced by our team in conducting this case.[18]

Follow-up and Prognosis

Non-neoplastic immune-mediated limbic encephalitis has a better prognosis than paraneoplastic limbic encephalitis.[1] The majority responds to treatment in weeks.[30] However, the prognosis is unclear in cases with late diagnosis.

Serum sodium returns to normal and anti-LGI1 antibodies become undetectable within a few months after the start of treatment, increasing the hypothesis of a monophasic illness in many patients. A small number of patients may present with persistently detectable serum antibodies or reappearance of the same level, showing slow improvement clinically or relapse.[16,22] The need to repeat the following antibodies is questionable because the true utility is unknown.[1]

FINAL CONSIDERATIONS

Limbic encephalitis associated with anti-LGI1, as well as other encephalitis associated with antibodies against neuronal surface proteins, needs further studies on is pathophysiology in order to improve the understanding of the course of the disease and to provide better treatment.

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