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## Suggested Reference

Anderson, N. E., & Barber, P. A. (2016). Limbic encephalitis – a review. *Journal of Clinical Neuroscience*, 15(9), 961-971. doi: [10.1016/j.jocn.2007.12.003](https://doi.org/10.1016/j.jocn.2007.12.003)

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## **LIMBIC ENCEPHALITIS: FOUR PATIENTS AND REVIEW OF THE LITERATURE**

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Support in the form of grants: Nil

## Abstract

The clinical features of limbic encephalitis are diverse and early diagnosis of the disorder is frequently difficult. Four patients with limbic encephalitis are described. An anti-neuronal antibody was identified in three of these patients. Antibodies directed against voltage-gated potassium channels, the N-methyl-D-aspartate receptor and an unidentified neuropil antigen were each found in one patient. The fourth patient had multifocal paraneoplastic encephalitis associated with small cell lung cancer. The clinical and imaging findings associated with these antibodies and the other anti-neuronal antibodies described in patients with limbic encephalitis are reviewed. An approach to the diagnosis and management of limbic encephalitis is presented.

## Key Words

Limbic encephalitis, autoantibodies, paraneoplastic syndromes

## Introduction

The cardinal sign of limbic encephalitis is a severe impairment of short-term memory.[1-4] Anterograde amnesia is often associated with behavioural and psychiatric symptoms such as anxiety, depression, irritability, personality change, acute confusional state, hallucinations, and complex partial and secondary generalised seizures. The symptoms typically develop over a few weeks or months, but they may evolve over a few days. The neuropathological findings include mononuclear inflammatory cell infiltrates, loss of neurons, and proliferation of astrocytes and microglia in the hippocampus and amygdala.[5,6] In many patients limbic encephalitis is a paraneoplastic syndrome, which is most commonly associated with small cell lung cancer (SCLC), breast cancer, testicular tumours, teratomas, Hodgkin's lymphoma and thymomas.[2] Neurological symptoms precede diagnosis of the malignancy in 60-75% of these patients.[2,4] Limbic encephalitis can also occur in the absence of malignancy.[7,8]

The clinical manifestations of limbic encephalitis are diverse and patients often present with a puzzling clinical picture. Delayed diagnosis is common, but improvements in neuroimaging and identification of anti-neuronal antibodies in patients with limbic encephalitis have facilitated recognition of the disorder. Early diagnosis is important, because limbic encephalitis may improve after immunotherapy or removal of a tumour, if one is present.

We describe four patients with limbic encephalitis. We review the anti-neuronal antibodies associated with limbic encephalitis and describe a clinical approach to patients with suspected limbic encephalitis.

## Patients

### Patient 1

A 41 year-old woman presented following a generalised tonic-clonic seizure. During the previous six months there had been a change in her behaviour and loss of interest in normal activities. In the two weeks prior to admission, she experienced recurrent stereotyped episodes with flashing lights in the right visual field and a left hemicranial headache. One week later she developed focal motor status epilepticus in the right arm. She had a 30 pack-year smoking history. Neurological examination showed impairment of short-term memory, dysphasia and right inferior quadrantanopia.

Antinuclear antibody was positive (titre 1:320), but double-stranded DNA, extractable nuclear antigen, anti-neutrophil cytoplasmic and thyroid microsomal antibodies were absent. Chest radiography was normal. Magnetic resonance imaging (MRI) with T2-weighted and fluid attenuation inversion recovery (FLAIR) sequences showed multiple hyperintense cortical and subcortical lesions in both cerebral hemispheres including the medial temporal lobes (Fig. 1). Contrast-enhanced scans were not obtained. Cerebral angiography was normal. Electroencephalography (EEG) showed epileptiform activity arising independently from both hemispheres and electrographic seizures originating in

the right fronto-temporal and left posterior temporal regions. The cerebrospinal fluid (CSF) had  $9 \times 10^6/l$  lymphocytes, but was otherwise normal. A right frontal lobe brain biopsy was normal except for a focal collection of lymphocytes in the overlying dura. Dural and brain cultures were sterile.

Prednisone 60 mg/day and azathioprine 200mg/day were started, but there was no improvement in the dysphasia or cognitive impairment. Focal motor status, complex partial seizures and occasional generalised seizures continued despite treatment with multiple anti-epileptic drugs. MRI six months later did not show any change. Fifteen months after her original presentation she was readmitted with generalised status epilepticus. A chest radiograph showed opacification of the left upper lobe. She died four days later.

Post-mortem examination revealed a SCLC arising in the left main bronchus and disseminated systemic metastases with one small metastasis in the right frontal lobe of the brain. There were patchy perivascular lymphocytic infiltrates, astrocytic proliferation and loss of neurons in the cerebral cortex including the amygdala and parahippocampal gyri. Serum and CSF were not available to search for anti-neuronal antibodies.

## Patient 2

A 67 year-old woman with type II diabetes mellitus and treated hypothyroidism presented with a three month history of progressive anterograde amnesia, fluctuating confusion, anxiety, delusions, hallucinations, and complex partial and tonic-clonic seizures. She had

had persistent hyponatraemia for nine months prior to presentation. She was afebrile, drowsy, restless and disorientated. Short-term memory was impaired, verbal and motor responses were slow and her mini-mental state examination (MMSE) score was 16/30. The rest of the neurological examination was normal. Thyroid function tests, thyroid antibodies, MRI, CSF and computed tomography (CT) of the chest, abdomen and pelvis were normal. The EEG showed widespread irregular slow wave activity. Voltage-gated potassium channel (VGKC) antibodies (Dr. Angela Vincent) were present at a level of 5441 pM (normal < 100 pM). She was treated with methylprednisolone 1g per day over 5 days, but no other immunosuppressive treatment was used. Three months after treatment her mental state had improved (MMSE 26/30), the EEG had normalised and the VGKC antibody level had dropped to 311 pM. Twelve months later the MMSE was 28/30.

### Patient 3

A 58 year-old woman developed a prodromal illness with arthralgias, rash and headache. Two weeks later there was a rapid change in her behaviour with elevated mood, poor concentration, hallucinations, insomnia, disinhibited social and sexual behaviour, and coprophagia. At times she was restless and agitated, but for long periods she was catatonic, mute and akinetic with severe rigidity and dystonia in the limbs. These periods were accompanied by apnoeic episodes causing respiratory acidosis. There were no focal neurological signs. Psychotropic medications and electroconvulsive therapy did not produce any improvement. She developed recurrent seizures and hypoventilation requiring admission to the intensive care unit. Thyroid function tests, thyroid microsomal antibodies, MRI and CSF were normal. The EEG showed a severe generalised

abnormality of the background activity. Antibodies to the N-methyl-D-aspartate receptor (NMDAR) were identified, but anti-Hu and anti-Ma2 antibodies were not present. CT of the chest, abdomen and pelvis, and intravaginal ultrasound were normal. She had a bilateral oophorectomy, but no ovarian abnormality was found. She was treated with high dose steroids, two courses of intravenous immunoglobulin and pulsed intravenous cyclophosphamide. There was a gradual improvement in her behavioural symptoms over the next six months, but there was a persistent deficit of immediate and delayed recall on memory tests.

#### Patient 4

A 58 year-old woman presented with a six-month history of severe anxiety, panic attacks, depression, dysphasia and partial motor seizures involving the right face. The neurological examination showed anterograde amnesia, non-fluent dysphasia and minor upper motor neuron signs in the right arm. The serum sodium was 128 mmol/L. MRI revealed multiple non-enhancing cortical lesions including abnormalities in both medial temporal lobes (Fig. 2a-d). The CSF protein was 0.79 g/L, but the leukocyte count and glucose concentration were normal and there were no oligoclonal bands. There was generalised slowing of the background EEG activity, but there was no focal or epileptiform abnormality. Anterior mediastinal and pleural masses were identified on CT. Biopsy of the pleural mass showed metastatic thymoma. She was treated with cyclophosphamide, adriamycin, cisplatin and prednisone followed by surgical debulking of the tumour. Her symptoms resolved and the neurological examination returned to normal during chemotherapy. After six months MRI showed complete resolution of the



cortical lesions. An antibody that recognised an antigen expressed on neuronal cell membranes and dendrites in the hippocampus and the molecular layer of the cerebellum was found in the patient's serum (Dr. Josep Dalmau). Anti-Hu, CRMP-5 and VGKC antibodies were absent.

## Discussion

These four patients illustrate several points about autoimmune limbic encephalitis: the clinical manifestations are diverse, paraneoplastic and non-paraneoplastic forms of the disease exist, and improvement may occur with treatment. An anti-neuronal antibody was identified in three of our patients: VGKC antibody in Patient 2, NMDAR antibody in Patient 3 and an anti-neuropil antibody in Patient 4. Serum and CSF from Patient 1 were not available to search for an anti-neuronal antibody, but we suspect this patient had the anti-Hu antibody. A SCLC was discovered at autopsy and the post-mortem abnormalities were typical of paraneoplastic encephalomyelitis. Anti-Hu is a marker of paraneoplastic encephalomyelitis associated with SCLC and epilepsy partialis continua can be the presenting manifestation of anti-Hu-associated encephalomyelitis.[9,10]

The clinical manifestations of limbic encephalitis are protean, but investigations can assist in the diagnosis. A lymphocytic pleocytosis, an increased protein concentration and oligoclonal bands in the CSF provide support for a diagnosis of limbic encephalitis. However, similar CSF abnormalities can occur with other inflammatory disorders or infections, and the CSF may be normal in limbic encephalitis. The EEG typically shows

focal or generalised slow wave abnormalities, and epileptiform activity, electrographic seizures, or periodic lateralised epileptiform discharges in the temporal regions.[4] T2-weighted and FLAIR MRI sequences often show hyperintense signal and mild swelling of the medial temporal lobes.[11,12] These changes may eventually be replaced by medial temporal lobe atrophy. Fluorodeoxyglucose positron emission tomography (PET) may reveal hypermetabolism in the medial temporal lobes, even when MRI is normal.[13]

Several anti-neuronal antibodies have been described in patients with limbic encephalitis. These antibodies are helpful diagnostic markers in a patient presenting with an unusual constellation of clinical and imaging abnormalities (Table 1).

#### Anti-Hu (anti-neuronal nuclear antibody, type I)

Anti-Hu recognises a family of RNA-binding proteins expressed in neuronal nuclei. One of these proteins, HuD, is expressed in SCLC cells and has a major role in triggering the immune response.[14] The most common clinical presentation of anti-Hu-associated paraneoplastic disease is sensory neuronopathy. Limbic encephalitis is the main presenting manifestation in 10% of patients.[15] Other manifestations may include brainstem encephalitis, cerebellar ataxia, motor neuronopathy, autonomic neuropathy, and symptoms of multifocal cortical disease including epilepsy partialis continua, aphasia and visual field abnormalities.[15,16] Three-quarters of the patients with anti-Hu have SCLC,[15,16] but only 50% of patients with limbic encephalitis and SCLC have anti-Hu.[17] Anti-Hu-negative patients with limbic encephalitis and SCLC do not usually

develop symptoms beyond the limbic system and are more likely to improve after treatment of the cancer than anti-Hu-positive patients.[17]

Anti-Hu-associated paraneoplastic encephalomyelitis typically has a poor prognosis. Treatment of the tumour may be associated with stabilisation of the neurological symptoms, but a dramatic improvement is rare.[15] Limbic encephalitis is more likely to respond to treatment than the other neurological manifestations of anti-Hu.[2]

### Anti-Ma2

Ma proteins have a role in the biogenesis of mRNA.[18] They are expressed in neurons, tumours of patients with anti-Ma-associated paraneoplastic disease and testicular germ cells.[18-20] Ma2 is the major autoantigen, but additional antibodies to Ma1 or Ma3 occur in 40% of patients.[18]

Anti-Ma2 is mainly found in young men with a testicular germ cell tumour, but it can occur with non-small cell lung cancer, breast cancer and other tumours.[18,21] A classical syndrome of limbic encephalitis is seen in 20% of anti-Ma2 patients, but more commonly limbic encephalitis is associated with hypothalamic and brain stem dysfunction. Symptoms of hypothalamic disease may include hypersomnia, cataplexy, rapid eye movement (REM) sleep behaviour disorder, hypnagogic hallucinations, gelastic seizures, weight gain, hyperthermia and diabetes insipidus.[21,22] Vertical gaze paresis and mild cerebellar ataxia are the most common signs of brain stem disease. Atypical Parkinsonism is an uncommon manifestation.

Most Ma2-positive patients have MRI abnormalities in the hypothalamus, thalamus, midbrain and medial temporal lobes. Some lesions show contrast enhancement and mimic a tumour.[18,21] CSF hypocretin levels are low or undetectable.[23]

Neuropathological examination demonstrates perivascular and interstitial infiltrates of T and B lymphocytes, and plasma cells.[18,24]

The neurological symptoms of Ma2-encephalitis improve following immunotherapy or treatment of the tumour in one-third of the patients.[21] Men below the age of 50 with Ma2-encephalitis usually have a microscopic intratubular germ cell tumour, even when tumour markers and imaging show no evidence of cancer.[25] Orchidectomy is recommended if there is no other type of tumour and there is new testicular enlargement, a history of cryptorchidism or ultrasound evidence of testicular microcalcification. The neurological disorder often improves after an orchidectomy.

#### Collapsin response-mediator protein (CRMP-5) antibody

The CRMP-5 antibody is associated with a wide variety of clinical syndromes including cerebellar ataxia, encephalomyelitis, parkinsonism, uveitis, retinopathy, optic neuropathy, polyradiculopathy, and sensory, sensorimotor, autonomic, or cranial neuropathy.[26,27]

An association between limbic encephalitis and chorea is a clue to the presence of the CRMP-5 antibody.[28] Some patients with the CRMP-5 antibody have clinical, MRI and neuropathological findings that are indistinguishable from other forms of paraneoplastic

limbic encephalitis.[29,30] Limbic encephalitis may be associated with multifocal cortical disease.[30,31]

The CRMP-5 antibody has been found in patients with SCLC, malignant thymoma and other neoplasms, but 10% of patients do not have an identifiable neoplasm.[26] This antibody has been identified in a few patients with SCLC or thymoma without paraneoplastic disease.[26] Neurological improvement may follow treatment of an underlying thymoma.[29] The CRMP-5 antibody is probably identical to the anti-CV2 antibody.[29,32,33]

#### Amphiphysin antibodies

Amphiphysin antibodies were first discovered in women with breast cancer and stiff person syndrome, but these antibodies are associated with a broad spectrum of neurological disorders including encephalopathy, cerebellar ataxia, myelopathy and neuropathy.[34] Three-quarters of patients with amphiphysin antibodies have coexisting autoantibodies, which may account for the diverse clinical manifestations. Rarely, amphiphysin antibodies have been found in patients with limbic encephalitis and SCLC.[34,35] Some of these patients have coexisting anti-Hu and VGKC antibodies, which may be independently associated with limbic encephalitis.

#### Voltage-gated potassium channel (VGKC) antibodies

Most patients with VGKC-associated limbic encephalitis present with a subacute amnesic syndrome, like Patient 2. Simple motor and complex partial seizures, and REM sleep

behaviour disorder are common, but headache, drowsiness and loss of consciousness are not usually present.[36-39] Hyponatraemia is common. The CSF leukocyte count is often normal, but there may be a mild lymphocytic pleocytosis.[38] MRI abnormalities are usually confined to the hippocampus and amygdala,[37,38] but occasionally there also is signal change in the basal ganglia.[40] Most patients with VGKC antibodies do not have an underlying malignancy, but patients with SCLC, malignant thymoma and prostate adenocarcinoma have been found.[36,37,41,42] A co-existing anti-glial nuclear antibody may indicate an underlying SCLC.[43]

VGKC-associated limbic encephalitis should be treated with high-dose intravenous methylprednisolone.[37] Patients also may respond to intravenous immunoglobulins or plasmapheresis followed by high dose prednisone.[41] Although patients often improve following treatment, residual medial temporal lobe atrophy and memory deficits are common.[37,38] Improvement is more likely with early treatment. Clinical improvement is associated with a reduction in the antibody level.

VGKC antibodies also are found in patients with isolated neuromyotonia and Morvan's syndrome.[44-47] Morvan's syndrome resembles limbic encephalitis with hallucinations, delirium, memory impairment, insomnia, REM sleep behaviour disorder and autonomic hyperactivity accompanied by myokymia.[45,46] The CSF and MRI are often normal. There usually is no underlying malignancy, but Morvan's syndrome may occur in patients with thymoma and other malignancies. Autonomic hyperactivity and neuromyotonia occasionally occur with VGKC-associated limbic encephalitis.[36-39]

VGKC antibodies are detected with a radioimmunoprecipitation assay using  $\alpha$ -dendrotoxin, which binds to Kv1.1, Kv1.2 and Kv1.6 ion channel subunits.[48]

Hippocampal Kv1.1 potassium channels have a role in neuronal excitability and memory. Sera from patients with limbic encephalitis bind preferentially to Kv1.1 channels, while sera from patients with neuromyotonia or Morvan's syndrome bind relatively more strongly to Kv1.2 and Kv1.6 channels.[48] This may explain why some patients develop central nervous system symptoms without peripheral nerve involvement. VGKC antibody titres are lower in patients with neuromyotonia and Morvan's syndrome than in patients with limbic encephalitis.

#### N-methyl-D-aspartate receptor antibodies

Antibodies directed against the NMDAR have been identified in young women with an ovarian teratoma and a severe but treatment-responsive encephalitis.[49-55] Most of these patients have a prodromal flu-like illness, which is followed by acute, severe psychiatric symptoms including personality change, paranoia and delusional thought processes. Agitation and confusion alternate with periods of staring, dystonia and catatonic posturing. These symptoms are often wrongly attributed to acute schizophrenia, neuroleptic malignant syndrome, or lethal catatonia and the patients are initially referred to a psychiatrist.[54] Severe anterograde amnesia is often present, but it may be masked by the psychiatric manifestations. Other clinical features may include generalised and complex partial seizures, choreoathetosis, myoclonus, dyskinesias, decreased level of

consciousness, central hypoventilation and signs of autonomic instability.[49,52]

Hyponatraemia does not usually occur.[55]

Most patients with an NMDAR antibody have an ovarian teratoma, of which 70% are benign. In some patients a teratoma has been found in the mediastinum and other patients have no underlying tumour.[52] The ovarian tumour may be detected with CT or intravaginal ultrasound. PET may be negative if the tumour is benign.

A CSF lymphocytic pleocytosis and oligoclonal bands are found in most of these patients.[52] MRI of the brain is often normal, but may show T2 and FLAIR abnormalities in the medial temporal lobes, other areas of the cerebral cortex, cerebellum and brain stem. Neuropathological abnormalities include microglial proliferation and neuronal degeneration in the hippocampus, but the changes may be more widespread.[52,56] Unlike the other forms of autoimmune limbic encephalitis, perivascular and interstitial T cell infiltrates are uncommon.

Serum and CSF contain antibodies directed against an antigen expressed on the cell membranes of hippocampal neurons. The antibody may be barely detectable in the serum.[52] These antibodies react with glutamate-binding NR1/NR2B-containing heteromers of the NMDAR. The tumours in these patients contain nervous tissue that express NR1/NR2 subunits and react with the patient's antibody. Ectopic expression of NR1/NR2 subunits by nervous tissue in a teratoma may cause failure of immune



tolerance and trigger the immune response. The prodromal viral-like illness may facilitate the abnormal immune response.[52]

There often is a dramatic clinical improvement following tumour resection, plasmapheresis, intravenous immunoglobulin, or immunosuppressive therapy.[52]

Immunotherapy alone may produce a transient improvement, but resection of the tumour appears to be essential for maintenance of the response. The encephalitis may recur if the tumour recurs.[52]

An NMDAR antibody was found in Patient 3. Her clinical presentation was typical of the clinical syndrome associated with this antibody, but our patient was unusual in that a tumour was not found and there was no CSF pleocytosis.

#### Antibodies against novel cell membrane antigen

An antibody to an unknown antigen expressed in the cell membrane of hippocampal neurons has been found in patients with limbic or multifocal encephalitis, as seen with Patient 4.[55,57] The clinical and imaging features are similar to NMDAR antibody-associated encephalitis. These patients have either a teratoma or thymoma.[55] Patient 4 illustrates the dramatic improvement that follows treatment of the tumour.[55]

#### Other paraneoplastic anti-neuronal antibodies

An antibody to adenylate kinase 5 was found in two men with non-paraneoplastic limbic encephalitis that was refractory to immunotherapy, while an antibody to BR

serine/threonine kinase 2 was detected in a patient with limbic encephalitis and SCLC.[58,59] Anti-neuronal nuclear antibody types II (anti-Ri) and III may be associated with an encephalopathy or dementia, but the clinical features and neuropathology suggest disease extending beyond the limbic system.[60,61]

#### Pathogenetic significance of anti-neuronal antibodies

Ectopic expression of a neuronal protein within a tumour appears to trigger an anti-tumour immune response. If there is a breakdown of immune tolerance in the brain, antibodies and cytotoxic T cells generated by this immune response may react with neurons expressing these onconeural antigens.[62] However, it is not known if these anti-neuronal antibodies are involved in the pathogenesis of neurological disease. Antibodies directed against ion channels and receptors in cell membranes, dendrites and synapses (VGKC and NMDAR antibodies) may interfere with neural transmission.

Limbic encephalitis associated with antibodies against cell membrane antigens often improves after removal of the antibody, or treatment of the tumour.[57] Except for patients with anti-Ma2 and a testicular tumour, patients who have antibodies against intracellular antigens do not respond as well to immunotherapy or treatment of the cancer.[15,67]

#### Diagnostic approach

Based on recent studies, an approach to the investigation and acute management of patients with limbic encephalitis has been proposed.[63] The first step is to obtain MRI of

the brain and CSF examination. MRI abnormalities in the medial temporal lobes are helpful in confirming a diagnosis of limbic encephalitis,[11,12] but normal imaging does not exclude the diagnosis. Medial temporal lobe abnormalities also occur with herpes simplex encephalitis and other disorders. Once an infectious cause has been excluded, the second step is to search for a tumour and an anti-neuronal antibody. There are no clinical, imaging or CSF abnormalities that are specific to any particular immune phenotype, but there may be clues to which tumour and antibody is present (Fig. 3). Many of the appropriate antibody tests are not available in commercial laboratories and, depending on the clinical situation, CSF and serum may need to be sent to a research laboratory (Table 2).[57] Patients with autoimmune limbic encephalitis can deteriorate rapidly and treatment with intravenous immunoglobulin or high-dose intravenous methylprednisolone should be commenced while awaiting the results of the antibody tests.[57,63]

### Differential Diagnosis

One of the difficulties in the diagnosis of limbic encephalitis is that other neurological disorders can have a similar clinical presentation (Table 3). It may be difficult distinguishing between limbic encephalitis and an acute confusional state secondary to a metabolic or toxic encephalopathy. Impairment of attention and global cognitive impairment are typical of an acute confusional state, but these features may be present in limbic encephalitis. Anterograde amnesia is the dominant early manifestation of Alzheimer's disease, but degenerative neurological disorders have a more insidious onset of symptoms than limbic encephalitis. Behavioural and psychiatric symptoms are

common in limbic encephalitis and these patients are frequently misdiagnosed as having a psychiatric disorder.[52] The psychiatric symptoms may obscure short-term memory impairment. Inflammatory changes in the CSF, signal abnormalities in the medial temporal lobes, a focal EEG abnormality, and detection of an anti-neuronal antibody help to distinguish limbic encephalitis from a metabolic encephalopathy, Alzheimer's disease, or a primary psychiatric disorder.

Some infections of the central nervous system may be difficult to distinguish from autoimmune limbic encephalitis. Herpes simplex virus (HSV) has a predilection to involve the temporal lobes, but distinguishing between herpes simplex encephalitis and autoimmune limbic encephalitis is usually straightforward. Herpes simplex encephalitis usually presents with a rapid deterioration over a few days with fever, headache, seizures and confusion.[64] Medial temporal lobe lesions are usually seen on MRI, but more widespread abnormalities and haemorrhagic changes also may be present.[65,66] The polymerase chain reaction (PCR) assay for HSV DNA in the CSF has a high specificity and sensitivity for herpes simplex encephalitis.[67] Acute limbic encephalitis can develop in the first few weeks after allogeneic haemopoietic stem cell or solid organ transplantation.[68,69] Most of these patients are afebrile, but they have a lymphocytic pleocytosis and bilateral MRI signal abnormalities in the uncus, amygdala, entorhinal cortex and anterior hippocampus with sparing of the parahippocampal gyrus. The PCR assay for human herpes virus type 6 (HHV6) in the CSF is positive in two-thirds of these patients, but an identical syndrome occurs in patients with a negative PCR assay. HHV6 has been identified in a few immunocompetent patients with focal encephalitis.[70]

Unilateral or bilateral hippocampal abnormalities are observed in one-fifth of patients with Japanese encephalitis, but most patients also have MR abnormalities in the thalami, substantia nigra and basal ganglia.[71] Other flavivirus infections can present in a similar fashion. Viruses that usually cause diffuse encephalitis occasionally present with focal limbic encephalitis.[72,73] Patients with Creutzfeldt Jakob disease have more widespread cortical dysfunction. The MRI abnormalities and the absence of inflammatory CSF changes distinguish Creutzfeldt Jakob disease from limbic encephalitis.[74] The clinical and MRI findings in neurosyphilis occasionally resemble limbic encephalitis.[75]

Hashimoto's encephalopathy is a steroid-responsive encephalopathy associated with high concentrations of anti-thyroid antibodies in the serum and CSF.[76,77] The typical clinical features, which include drowsiness, confusion, coma, tremor and myoclonus, suggest diffuse cortical dysfunction rather than a limbic encephalopathy.[76] The CSF is usually acellular, but the CSF protein concentration is often elevated and oligoclonal bands may be present. Non-specific MRI abnormalities, including diffuse atrophy, white matter abnormalities and focal cortical lesions, occur in 50% of patients. Hashimoto's encephalopathy falls within the spectrum non-vasculitic autoimmune inflammatory meningoencephalitis, which occurs with other systemic autoimmune disorders including Sjögren's syndrome and systemic lupus erythematosus (SLE).[78,79] The neuropathological abnormalities are not usually restricted to the medial temporal lobes, but the clinical and imaging findings may resemble limbic encephalitis.[80-82] Limbic encephalitis has been reported in other inflammatory diseases including relapsing polychondritis [83,84] and Behçet's disease.[85]

Brain tumours, especially primary central nervous system lymphoma and gliomatosis cerebri, can have a clinical presentation and MRI appearance that resemble limbic encephalitis.[63,86] Anterograde amnesia is a classical finding in Wernicke Korsakoff syndrome, but these patients usually have a more severe retrograde amnesia than occurs with bilateral medial temporal lobe lesions and there is a distinctive distribution of MRI lesions.[87]

Although autoimmune limbic encephalitis is rare, it probably is under-recognised. MRI abnormalities in the medial temporal lobes after prolonged or multiple seizures often have been attributed to seizure-induced cytotoxic oedema and gliosis,[88] but some of these patients may have had limbic encephalitis. It may be difficult to differentiate limbic encephalitis from an acute confusional state or a psychiatric disorder. MRI and CSF examination are often, but not always, helpful indicators of an inflammatory process. Identification of an anti-neuronal antibody helps in the diagnosis of limbic encephalitis. Rapid diagnosis of limbic encephalitis is important, because the neurological disorder associated with antibodies to antigens in neuronal cell membranes or the anti-Ma2 antibody often responds dramatically to immunotherapy and treatment of the underlying tumour.

### Acknowledgements

The authors gratefully acknowledge the assistance of Drs. Josep Dalmau, Francesc Graus and Angela Vincent for performing tests for anti-neuronal antibodies and Drs. Barry Snow, Gail Riccitelli and Campbell White for information about their patients. Dr. Dalmau reviewed a draft of the manuscript.

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Table 1: Anti-neuronal antibodies associated with limbic encephalitis

Antibody	Main tumours	Additional clinical features	Response to treatment <sup>1</sup>
Anti-Hu	SCLC	Sensory neuronopathy Brain stem, cerebellar signs Motor neuronopathy Autonomic neuropathy Multifocal encephalomyelitis	Poor
Anti-Ma2	Testis	Hypothalamic dysfunction Rostral brain stem dysfunction Atypical Parkinsonism	30% improve
CRMP-5	SCLC, thymoma	Cerebellar ataxia Encephalomyelitis Chorea, parkinsonism Uveitis, retinopathy	Poor

		Neuropathy	
Amphiphysin	Breast, SCLC	Stiff person syndrome	Poor
		Multifocal disease	
VGKC	Nil	REM sleep behaviour disorder	Good
		Hyponatraemia	
NMDAR	Ovarian teratoma	Psychiatric symptoms	Good
		Dystonia	
		Depressed consciousness	
		Hypoventilation	
Neuropil	SCLC, thymoma	Multiple	Good

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SCLC = small cell lung carcinoma; CRMP-5 = collapsin response-mediator protein-5; VGKC = voltage-gated potassium channel;

REM = rapid eye movement; NMDAR = N-methyl D-aspartate receptor

<sup>1</sup>Treatment of tumour, immunotherapy, or both

Table 2: Anti-neuronal antibodies: Research laboratories

Antibody	Laboratory	Specimen	Cost	Time	Additional information
VGKC	Professor Angela Vincent, Weatherall Institute of Molecular Medicine, John Radcliffe Hospital, Oxford OX3 96DS, England	Serum (1 mL)	£40	≤ 1 month	Brief clinical information with serum
NMDAR	Dr. Josep Dalmau, Department of Neurology, 3 W. Gates, University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19104, U.S.A. <a href="mailto:josep.dalmau@uphs.upenn.edu">josep.dalmau@uphs.upenn.edu</a>	CSF ± serum	Nil	≤ 2 weeks	E mail Dr. Dalmau first Detailed clinical information CSF essential

VGKC = voltage-gated potassium channel antibodies; NMDAR = N-methyl D-aspartate receptor antibodies; CSF = cerebrospinal fluid

Table 3: Differential diagnosis of limbic encephalitis

Cause	Distinguishing Clinical Features	MRI lesion	CSF	Diagnostic Tests
Metabolic encephalopathy	Drowsiness, inattention, confusion	Normal	Normal	Blood tests
Alzheimer's disease	Slow onset, other cognitive abnormalities	Hippocampal atrophy	Normal	Nil
Psychiatric disorders	Normal short-term memory	Normal	Normal	Nil
HSV encephalitis	Acute onset, fever, headache, coma	Temporal lobe	↑white cells ↑ protein	CSF HSV PCR
Post-transplant	Transplantation	Medial temporal lobe	↑white cells	CSF HHV6 PCR
PML	HIV infection Immunosuppression	White matter	Normal	CSF JCV PCR ± Brain biopsy
Creutzfeldt Jakob disease	Myoclonus, dementia, cerebellar ataxia	Cortex, basal ganglia	14-3-3 protein	Brain biopsy
Hashimoto's encephalopathy	Drowsiness, confusion, coma, myoclonus	Non-specific	↑protein	Anti-thyroid abs
NAIM	Drowsiness, confusion, coma	Non-specific	Normal	Serum antibodies

CNS vasculitis	Diffuse or multifocal brain disease	Multiple infarcts	± ↑white cells	Angiography Brain biopsy
“Top of basilar” stroke	Abrupt onset, visual field deficits, abnormal eye movements	Medial thalamic infarcts	Normal	MRI/MRA
Brain tumour	± headache	Contrast-enhancing lesion	±malignant cells	Brain biopsy
Wernicke-Korsakoff	Anterograde and retrograde amnesia Eye movement abnormalities Ataxia	Periventricular lesions	Normal	Response to thiamine

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MRI = magnetic resonance imaging; CSF = cerebrospinal fluid; HSV = herpes simplex virus; PCR = polymerase chain reaction;

HHV6 = human herpes virus type 6; PML = progressive multifocal leukoencephalopathy; JCV = JC virus; NAIM = non-vasculitic autoimmune inflammatory meningoencephalitis; MRA = magnetic resonance angiography

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## Figures

### Figure 1

Patient 1: FLAIR MRI showing increased signal in both medial temporal lobes and the left occipital lobe (a) and the left lateral temporal lobe (b).

### Figure 2

Patient 4: FLAIR MRI at presentation showing areas of increased signal in the (a) right anterior temporal and medial temporal lobes; (b) both medial temporal lobes; (c) insular cortex bilaterally, right medial frontal lobe and left occipital lobe and (d) left parietal lobe.

### Figure 3

Guide to the investigation of autoimmune limbic encephalitis