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Clinical and Immunological Diversity of Limbic Encephalitis: A Model for Paraneoplastic Neurologic Disorders

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The most important contribution to the understanding and management of paraneoplastic neurologic disorders (PND) is the discovery that many of these disorders are immune mediated. It is believed that cytotoxic T-cell responses and antibodies that target neuronal proteins usually expressed by the underlying tumor cause the neurologic symptoms [1]. The detection of these antibodies has provided diagnostic tests that allow recognition of the disorder as paraneoplastic and direct the search of the tumor to selected organs [2].

Despite the diagnostic usefulness of the paraneoplastic antibodies, their detection does not supersede the importance of the clinical assessment, because some antibodies can be found in patients who have cancer without PND [3] and, conversely, approximately 40% of patients who have PND do not have detectable antibodies [4]. Furthermore, rigorous correlations indicate that in the appropriate clinical setting some antibodies are specific markers of PND (ie, anti-Hu, anti-Yo, anti-CV2, anti-Ma2) [4], whereas others (ANNA3, PCA2) are less specific markers of PND [5].

A better understanding of the function of the paraneoplastic neuronal (or onconeuronal) antigens along with modelling PND in animals results in improved treatment strategies. For the clinician who currently confronts these patients, however, the best chance to affect the neurologic outcome depends on: (1) the prompt diagnosis of the disorder, (2) the early discovery and treatment of the tumor, and (3) the use of immunotherapy. Likewise, any clinical features or tests suggesting that the patient's syndrome is not a PND are also important to prevent delays incurred by unnecessary oncologic evaluations.

In 60% of patients who have PND the neurologic symptoms develop before the presence of cancer is known, so these patients are usually seen first by general practitioners or neurologists [6]. In an attempt to improve the recognition of these syndromes, the authors recently proposed a logical approach to the management of limbic encephalitis and postulated that many patients without well-characterized antibodies harbor novel immune responses [6,7]. This approach takes into consideration the type of syndrome, the neuroimaging and cerebrospinal fluid (CSF) findings, and whether the autoantigens are intracellular or are located in the cell membrane. Disorders associated with intracellular autoantigens usually associate with cytotoxic T-cell mechanisms and are less likely to improve than are disorders that associate with autoantigens in the cell membrane. This review summarizes the authors' findings of limbic encephalitis and postulate that a similar approach can be used for syndromes involving other areas of the nervous system.

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HISTORICAL REMARKS

Limbic encephalitis causes impressive deficits that are characteristically dominated by rapid and severe loss of short-term memory, but recognition of this syndrome did not occur until the 1960s, when most other PNDs were already known. It was Brierley and colleagues [8] who initially reported three patients who had "subacute encephalitis of later adult life, mainly affecting the limbic areas"; two of the patients had evidence of cancer (one confirmed at autopsy), but the investigators considered "most unlikely that this finding was in any way related to the encephalitis although its occurrence should be noted." In 1968 Corsellis and colleagues [9] coined the term "limbic encephalitis" to describe one patient who had severe short-term memory loss and two patients who had memory loss and dementia in association with bronchial carcinoma; the three patients had inflammatory and degenerative changes concentrated in the temporal parts of the limbic gray matter. The same investigators reviewed eight previously reported cases and established for the first time a relationship between limbic encephalitis and systemic cancer.

Once the relationship between cancer and the limbic dysfunction was established, three pathogenic hypotheses were proposed: (1) a degeneration (not further defined) of the nervous system in which inflammatory infiltrates were a secondary "reaction to the tissue breakdown," (2) a viral infection, and (3) an immune-mediated response against the nervous system that is the currently accepted hypothesis.

The first immune response identified in association with limbic encephalitis was the anti-Hu antibody [10]. This antibody associates with small cell lung cancer (SCLC) and paraneoplastic limbic encephalitis that usually affects other areas of the nervous system (encephalomyelitis). Since then, other immune responses have been identified, some of them with more syndrome specificity for limbic dysfunction than the anti-Hu immune response (Table 1) [11-13].

RECOGNIZING THE SYNDROME

Paraneoplastic limbic encephalitis usually presents with irritability, depression, insomnia or hypersomnia, seizures, hallucinations, and short-term memory loss that may progress to frank dementia [14]. Psychomotor or temporal lobe seizures predominate over generalized seizures [15]. Most patients have EEG abnormalities that may include foci of epileptic activity in one or both temporal lobes or focal or generalized slow activity [16]. In patients who have seizures, the memory deficits can be difficult to examine, and the absent history of cancer may complicate even more the recognition of the disorder as paraneoplastic. Conversely, in patients known to have cancer (~30%–40% of cases) the development of similar symptoms may suggest several complications of cancer or its treatment and diverse etiologies that can also occur in noncancer patients (Table 2). The clinical history and identification of inflammatory abnormalities in the CSF rules out some of these etiologies and increases the index of suspicion for paraneoplastic limbic encephalitis, although similar findings can be found in viral infections and autoimmune disorders. Approximately 70% of patients who have limbic encephalitis develop MRI abnormalities in the medial temporal lobes that are best seen with fluid-attenuated inversion recovery (FLAIR) sequences [14,16]. The abnormalities can be asymmetric and occasionally may show contrast enhancement. Brain fluorodeoxyglucose-PET (FDG-PET) is particularly useful in patients without seizures and normal MRI; it usually shows FDG hyperactivity in temporal lobes and may reveal other areas of hypermetabolism, suggesting additional foci of encephalitis (Fig. 1) [6,17,18].

Overall the information provided by the clinical and electrophysiologic findings, routine CSF studies, and MRI and metabolic neuroimaging serves to establish the diagnosis of limbic

encephalitis in 70% to 80% of patients. None of these studies, however, defines a paraneoplastic etiology that should always be considered in patients who have a subacute limbic syndrome.

RECOGNIZING THE PARANEOPLASTIC ETIOLOGY

There are several disorders unrelated to cancer that may cause limbic dysfunction (Table 2). A paraneoplastic etiology can only be established with the demonstration of paraneoplastic antibodies in serum or CSF or with the demonstration of a tumor [4]. Neuropathologic studies do not establish a paraneoplastic etiology, because similar inflammatory infiltrates, neuronal loss, microglial activation, and gliosis can be observed in non-paraneoplastic disorders.

The antibodies that are reliable markers of a paraneoplastic etiology are shown in Table 1. Antibodies to voltage-gated potassium channels (VGKC) are considered markers of non-paraneoplastic limbic encephalitis, but in fact may occur in patients who have cancer, and therefore their detection does not exclude a paraneoplastic etiology [19].

In a study of 50 patients and a review of 176 previously reported cases, the tumors more frequently associated with limbic encephalitis were SCLC, testicular tumors, teratoma of the ovary, Hodgkin lymphoma, and breast cancer [14].

DIAGNOSTIC DILEMMAS

In 40% to 50% of patients who have a clinical syndrome compatible with limbic encephalitis, no paraneoplastic antibodies are identified [14,20]. Additionally there are other patients whose symptoms of limbic dysfunction are atypical or develop in association with clinical and neuroimaging findings, suggesting involvement outside the limbic system [21]. Because the CSF of these patients often demonstrates pleocytosis and intrathecal IgG synthesis, and because symptoms may respond to immunotherapy, a possible immunopathogenesis was considered [22]. The working hypothesis was that many of these patients develop antibody-associated immune responses that were missed using current diagnostic techniques. To test this hypothesis the authors examined patients' sera and CSF with several tissue processing and immunohistochemical techniques and with cultures of rat hippocampal neurons; these studies resulted in the identification of several novel autoantibodies.

NOVEL NEURONAL ANTIBODIES

Encephalitis Associated with Antibodies Against the Neuropil and Dendrites of Hippocampus

Using modified immunohistochemical techniques, Ances and colleagues [6] found that patients who had encephalitis predominantly involving the temporal lobes harbored serum or CSF antibodies to antigens expressed in the cell membrane of neurons and dendritic processes of the neuropil of the hippocampus. These antibodies are detected using paraformaldehyde fixed tissue from non-perfused animals and are missed by immunoblot, immunoprecipitation with dendrotoxin (used to detect VGKC antibodies), and immunohistochemistry with methanol-acetone or acetone-fixed tissue. Because some of these novel antibodies are highly specific for hippocampal proteins, they are also missed by commercial laboratories that only use cerebellum as the tissue substrate for immunologic studies. Two additional features that may complicate the detection of these antibodies are the predominant detection in the CSF rather than serum and a tendency to disappear with the neurologic improvement.

Preliminary characterization of the autoantigens indicated that these are diverse and concentrated in the hippocampus. Some autoantigens partially colocalized with synaptophysin and spinophilin, suggesting an immune-mediated attack on hippocampal dendrites (Fig. 2) [23].

Attempts to characterize each of the neuropil autoantigens and corresponding sub-syndromes have resulted in the identification of a specific immune-mediated phenotype in patients who have ovarian teratoma (see later discussion) [7]. These patients' sera or CSF frequently show immunolabeling of antigens that are expressed at the cytoplasmic membrane of hippocampal neurons and processes (Fig. 3A,B). The immunolabeling also occurs in cultures of live hippocampal neurons to which minimal amounts of antibodies are added briefly to the media, suggesting that the antigens are on the cell surface (Fig. 3C). Immunoprobing of a hippocampal-expression library with patients' antibodies resulted in the isolation of EFA6A, a protein that interacts with a member of the two-pore-domain potassium channel family and is involved in the regulation of the dendritic development of hippocampal neurons. Some members of this ion channel family (ie, TASK-1 and TASK-3) are known to play roles in controlling breathing and arousal [24,25].

CLINICAL-IMMUNOLOGIC PHENOTYPES OF PARANEOPLASTIC LIMBIC ENCEPHALITIS

Based on these studies the authors propose three groups of immune-mediated limbic encephalitis, each likely including several sub-phenotypes as outlined here and in Table 3.

Limbic Encephalitis and Antibodies to Well-Characterized Intracellular Onconeuronal Antigens (Hu, Ma, CV2/CRMP5, and Amphiphysin)

Clinical features that preferentially associate with each autoantigen are shown in Table 1 [20, 26-28]. Irrespective of the type of immunity, the CSF of these patients usually shows moderate pleocytosis and increased protein concentration, elevated IgG synthesis, and oligoclonal bands. The corresponding paraneoplastic antibodies are found in the CSF and almost always in the serum. The antibodies are usually detectable in serum for months or years after treatment of the tumor or immunotherapy [29]. Autopsy and biopsy studies suggest that cytotoxic T-cell mechanisms play a prominent pathogenic role [26,30,31]. There are no animal models for any of these immunities except for amphiphysin-associated stiff-person syndrome [32]. The management should focus on the prompt diagnosis and treatment of the tumor. At early stages of the disease, when there is evidence of inflammation suggested by CSF analysis or PET neuroimaging, immunotherapies directed at antibodies and cytotoxic T-cells can be considered [33,34]. The use of corticosteroids, IVIg, or plasma exchange has limited value if the tumor is not treated. Cyclophosphamide has been used in individual cases with mild to moderate effects [35,36].

Some patients who have antibodies to Ma2 proteins have better neurologic outcome than patients who have other antibodies (ie, Hu, CV2/CRMP5). The reason for the different outcomes is unclear but may be related in part to the fact immunity to Ma2 often associates with testicular tumors that are easier to remove and are more responsive to chemotherapy than other neoplasms (ie, SCLC) [26].

Limbic Encephalitis and Antibodies to VGKC (Kv1.1, Kv1.2, and Kv 1.6)

In addition to limbic encephalitis, patients who have these antibodies may develop peripheral nerve hyperexcitability, autonomic dysfunction, hyperhydrosis, seizures (without evidence of limbic encephalopathy), rapid eye movement sleep behavior abnormalities, or a combination of peripheral and central nervous system dysfunction called Morvan syndrome [37-39].

The limbic encephalitis of patients who have VGKC antibodies frequently associates with hyponatremia and infrequently with cancer. Hyponatremia cannot be used as a distinctive feature of this immunity, however, because it also occurs in 11% of patients who have SCLC as part of the paraneoplastic syndrome of inappropriate secretion of antidiuretic hormone

(SIADH) [40]. The brain MRI findings of patients who have VGKC antibodies are similar to other types of immune-mediated limbic encephalitis [41], although some paraneoplastic immunities (ie, anti-Ma2) often show additional abnormalities in the hypothalamus and upper brainstem that may enhance with contrast [42].

When compared with any other type of limbic encephalitis, patients who have VGKC antibodies are less likely to develop CSF pleocytosis or intrathecal synthesis of IgG and usually do not have intrathecal synthesis of VGKC antibodies [6,38,41].

There is no single distinctive feature of limbic encephalitis associated with VGKC antibodies; this disorder therefore should be considered in patients who have no smoking history and develop subacute symptoms of limbic dysfunction in association with hyponatremia with or without autonomic dysfunction or peripheral nerve excitability. Supportive laboratory studies include symmetric or asymmetric medial temporal lobe MRI FLAIR hyperintensities and normal or mild CSF abnormalities. For this group of patients, in particular those who are young, a thymoma may be present [43]. Similar findings can occur in older individuals and smokers, and in these patients a paraneoplastic manifestation of SCLC should be strongly considered [19,37].

The treatment of limbic encephalitis with VGKC antibodies is based on IgG-depleting strategies, such as plasma exchange or IVIg, in combination with corticosteroids. In the authors' experience, tapering prednisone over 3 to 4 weeks after intravenous methylprednisolone may result in neurologic relapse. It is therefore reasonable to use daily prednisone for 3 to 4 weeks and then convert to an every-other-day regimen for several months. Significant neurologic improvement or recovery occurs in 70% of the patients [38,41]. At early stages of the disorder some patients develop life-threatening hyponatremia and status epilepticus; the long-term outcome is usually good, although short-term memory deficits may persist.

Limbic Encephalitis of Patients Who Have Antibodies to Novel Neuronal Membrane Antigens

This is a heterogeneous group of disorders that may encompass a larger number of patients than those who have antibodies to VGKC (Kv1.1, Kv1.2, and Kv 1.6). The common clinical phenotype includes predominant behavioral and psychiatric symptoms (that may obscure short-term memory deficits), seizures, and brain MRI abnormalities that are less frequently restricted to the hippocampus than in classic limbic encephalitis. FDG-PET may reveal foci of hypermetabolism in the frontotemporal lobes, brainstem, or cerebellum. Combining MRI and FDG-PET studies, the temporal lobes are preferentially affected. Patients harboring these novel antibodies are more likely to have intrathecal IgG synthesis, CSF pleocytosis, and systemic tumors (thymoma, teratoma) than those who have VGKC antibodies and do not develop hyponatremia [6].

In contrast to patients who have paraneoplastic antibodies to intracellular antigens, the encephalitis of patients who have any of these collectively termed “neuropil antibodies” improves with immunotherapy and, if present, treatment of the associated tumor. This clinical improvement usually associates with improvement of MRI and FDG-PET abnormalities and a decrease of antibody titers [6].

The Encephalitic Syndrome Associated with Ovarian Teratoma and Antibodies to Antigens That Co-Localize with EFA6A

A subgroup of patients who have antibodies to neuronal cell membrane antigens have ovarian teratoma. These patients harbor antibodies to antigens that co-localize with EFA6A, which is a hippocampal protein upregulated by N-Methyl-D-Aspartate (NMDA) receptors. The clinical and immunologic similarities of these patients suggest that they are affected by a distinct

syndrome. This includes subacute psychiatric symptoms, short-term memory deficits, seizures, rapid decrease of level of consciousness, and frequent central hypoventilation [44,45]. The clinical picture, young age of the patients, and absent history of cancer may lead to a diagnosis of acute psychosis, malingering, or drug abuse. A similar encephalitic syndrome had been previously reported in several patients who have ovarian teratoma; in most instances an immunopathogenesis was suspected but not identified [22,46-49].

The CSF of these patients usually shows pleocytosis and elevated protein concentration and IgG index. In some patients the EFA6A-like reactive antibodies can only be demonstrated in the CSF.

Because EFA6A interacts with a member of the two-pore domain potassium channel, and some members of this potassium channel family seem to be important for control of breathing and arousal, it is tempting to speculate that the patients' antibodies disrupt the function of these channels [24,25].

Despite the severity of the clinical features, most patients who have teratoma-associated encephalitis improve with treatment of the tumor, plasma exchange, IVIg, and corticosteroids [7]. The limited number of cases prevents firm treatment recommendations, but removal of the teratoma seems important. Some of these patients require intensive and prolonged care because of ventilatory problems, and the recovery is usually slow (weeks or months). In a recent review of nine patients who had encephalitis associated with ovarian teratoma, one of the patients died as a result of neurologic complications and the other patients significantly improved or totally recovered. Since then, the authors have identified four additional patients who have the same syndrome and recovered after combining these treatments; one patient did not improve after tumor removal but had a dramatic response to corticosteroids and cyclophosphamide.

Limbic Encephalitis: A Model for Other Paraneoplastic Disorders

A question raised by these studies is whether a similar diversity of phenotypes and immune responses against intracellular and cell membrane antigens occurs in other paraneoplastic disorders. For syndromes involving the peripheral nervous system, several immune mechanisms mediated by humoral or cytotoxic T-cell responses have been demonstrated. For example, antibodies to ion channels or receptors are involved in the dysfunction of the neuromuscular junction and nerves, resulting in the Lambert-Eaton myasthenic syndrome (LEMS), neuromyotonia, and myasthenia gravis [50,51]. Humoral immune mechanisms also seem to play critical roles in dermatomyositis and several neuropathies associated with monoclonal gammopathies [52-54], whereas predominant cytotoxic T-cell responses are involved in polymyositis, vasculitis of the nerve and muscle, and several subacute predominantly axonal neuropathies [55-58].

In the paraneoplastic disorders of the CNS, the study of novel immune responses is limited by the difficulty in obtaining tissue and in demonstrating antibodies against cell membrane antigens. In limbic encephalitis, an observation that led the authors to reassess the presence of immune responses was that some patients improve with immunosuppressants. For other paraneoplastic disorders, however, such as cerebellar or brainstem encephalopathies, the potential for recovery or improvement is more limited. This has been noted in patients who have disorders mediated by antibodies, such as LEMS and cerebellar degeneration in association with antibodies to voltage-gated calcium channels (VGCC). Although immunomodulation and immunosuppression improve the symptoms of LEMS, the concomitant cerebellar deficits are much less responsive to treatment [59-61]. Despite this low potential for recovery, there are reports of patients who have paraneoplastic cerebellar dysfunction whose symptoms improved after treatment of the tumor or immunosuppression [62-65]. In some of these patients, as in approximately 40% of patients who have cancer and

subacute cerebellar degeneration without paraneoplastic antibodies, the CSF showed inflammatory abnormalities identical to those found in patients who have paraneoplastic antibodies, suggesting an immune-mediated pathogenesis. These findings and recent evidence that patients may harbor antibodies that spare neuronal cell bodies but react intensively with the neuropil and dendrites of the molecular layer of the cerebellum (Fig. 4) (Josep Dalmau, MD, unpublished data, 2005) suggests that the antigen diversity described in limbic encephalitis may also occur in other syndromes. The authors anticipate that analysis of the CSF at symptom presentation with techniques that allow detection of antibodies to cell membrane antigens will reveal novel immune responses. Characterization of these immune responses hastens diagnosis, improves treatment of the associated disorders, indicates the relative risk for an underlying tumor (paraneoplasia), and suggests the type of tumor more frequently involved.

SUMMARY

The authors recently proposed a logical approach to the management of limbic encephalitis and postulated that many patients who do not have well-characterized antineuronal antibodies harbor novel immune responses. This approach takes into consideration the type of syndrome, the neuroimaging and CSF findings, and whether the autoantigens are intracellular or located in the cell membrane. Disorders related with the first class of autoantigens usually associate with antibodies and cytotoxic T-cell mechanisms and are less likely to improve than are disorders associated with the second class of autoantigens. The latter comprises a diverse group of encephalitides with emerging sub-phenotypes in which humoral mechanisms seem to play a pathogenic role. This article summarizes the authors' experience with limbic encephalitis and postulate that a similar approach can be used for other paraneoplastic disorders.

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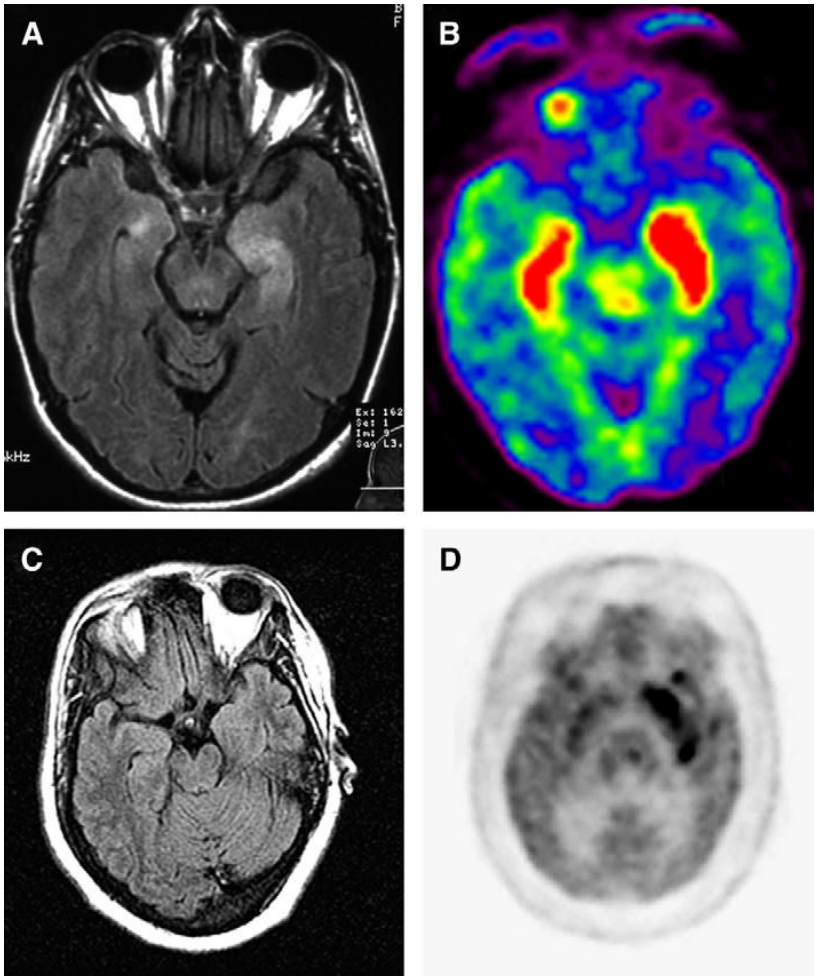

Fig 1.

MRI and FDG-PET in patients who have paraneoplastic limbic encephalitis (*A*) (brain MRI) and (*B*) (FDG-PET) of a patient who had SCLC and anti-Hu associated paraneoplastic limbic encephalitis; note that there is bilateral medial temporal lobe FLAIR hyperintensity that correlates with FDG hyperactivity (*red*) in the PET study. (*C*) Brain MRI and (*D*) FDG-PET of a patient who had paraneoplastic encephalitis associated with carcinoma of the thymus; in this patient the PET study revealed an extensive area of FDG hyperactivity (dark signal in the medial left temporal lobe) that was not noted in the MRI.

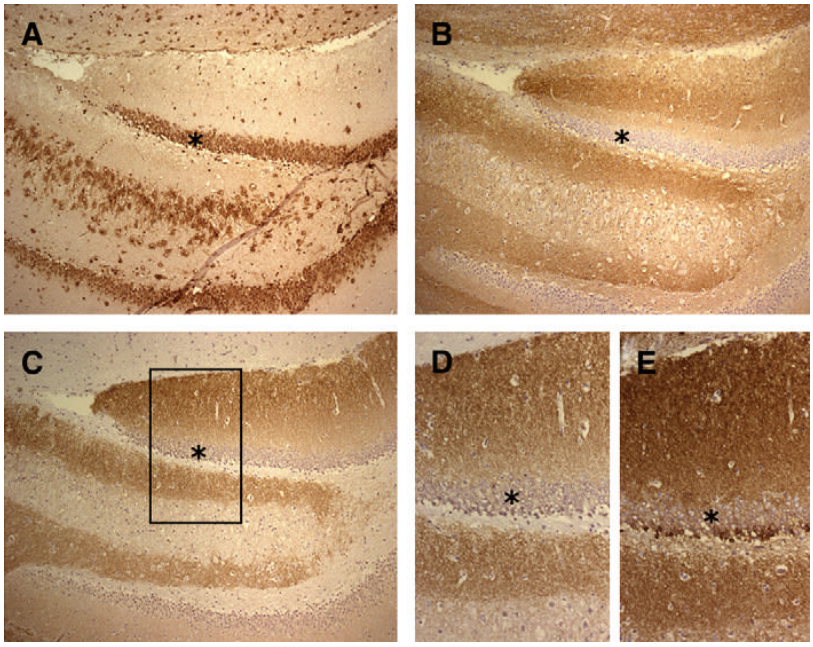

Fig 2.

Antibodies to intracellular and cell-membrane antigens in patients who had limbic encephalitis. (*A*) Coronal section of rat hippocampus immunolabeled with anti-Hu antibodies. (*B*) and (*C*) Consecutive sections of hippocampus immunolabeled with Kv 1.2 VGKC antibodies (*B*) and a novel neuropil antibody (*C*). (*D*) The same antibody reactivity demonstrated in (*C*) at a higher magnification (*rectangular region*). (*E*) Reactivity of another neuropil antibody in a consecutive section of the same region. Note the difference between (*A*) and the rest of the panels; the anti-Hu antibody (*A*) reacts with intracellular antigens (Hu), whereas the other antibodies react with areas of the neuropil that are rich in dendrites and synapses but spare the neuronal cell bodies. In all panels (*) are placed in the same region (neurons of the dentate gyrus) to allow comparison between reactivities. (*A*, *B*, and *C*) ×100; (*D* and *E*) ×200. Sections counterstained with hematoxylin.

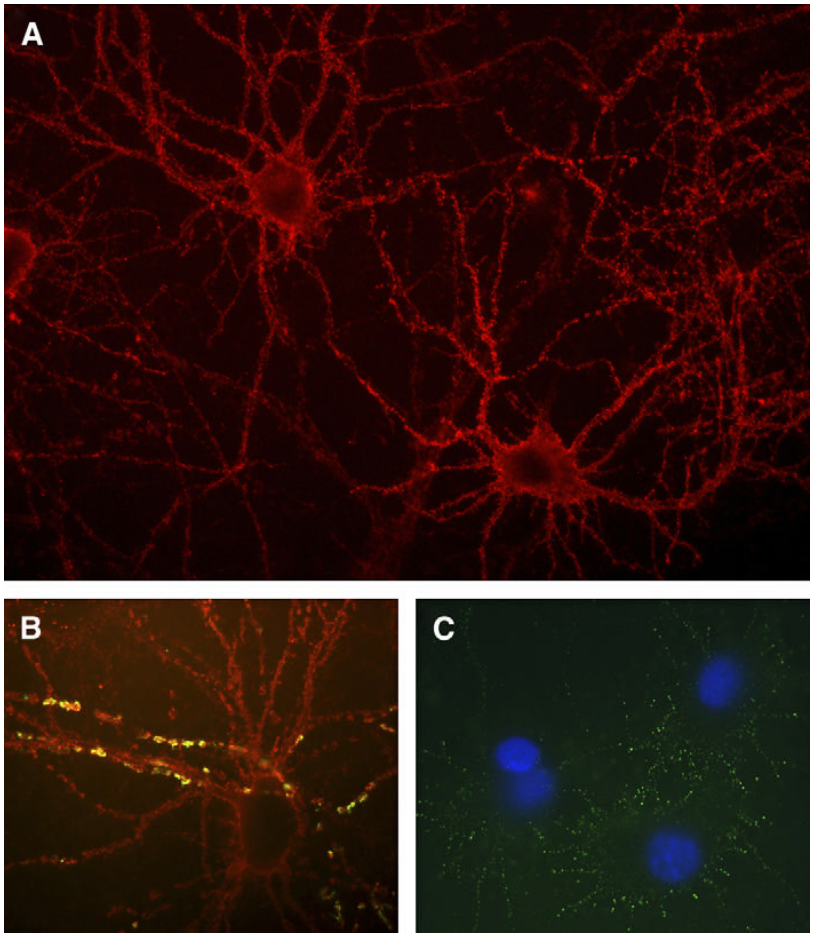

Fig 3.

Immunolabeling of cultured hippocampal neurons. (*A*) Immunolabeling of neurons with CSF of a patient who had carcinoma of the thymus and paraneoplastic limbic encephalitis associated with antibodies to the neuropil of the hippocampus (antigen unknown). Note the intense immunolabeling of the neuronal cell membrane. (*B*) Immunolabeling of neurons with antibodies (*red*) from serum of a patient who had limbic encephalitis without a known cancer. The segments of dendrites in yellow demonstrate co-localization of the autoantigen (unknown) with spinophilin, a marker of dendritic spines. (*C*) Immunolabeling of the surface of live hippocampal neurons with antibodies from a patient who had encephalitis associated with ovarian teratoma; the autoantigen co-localizes with EFA6A. (*A*) ×400; (*B* and *C*) ×800 with oil.

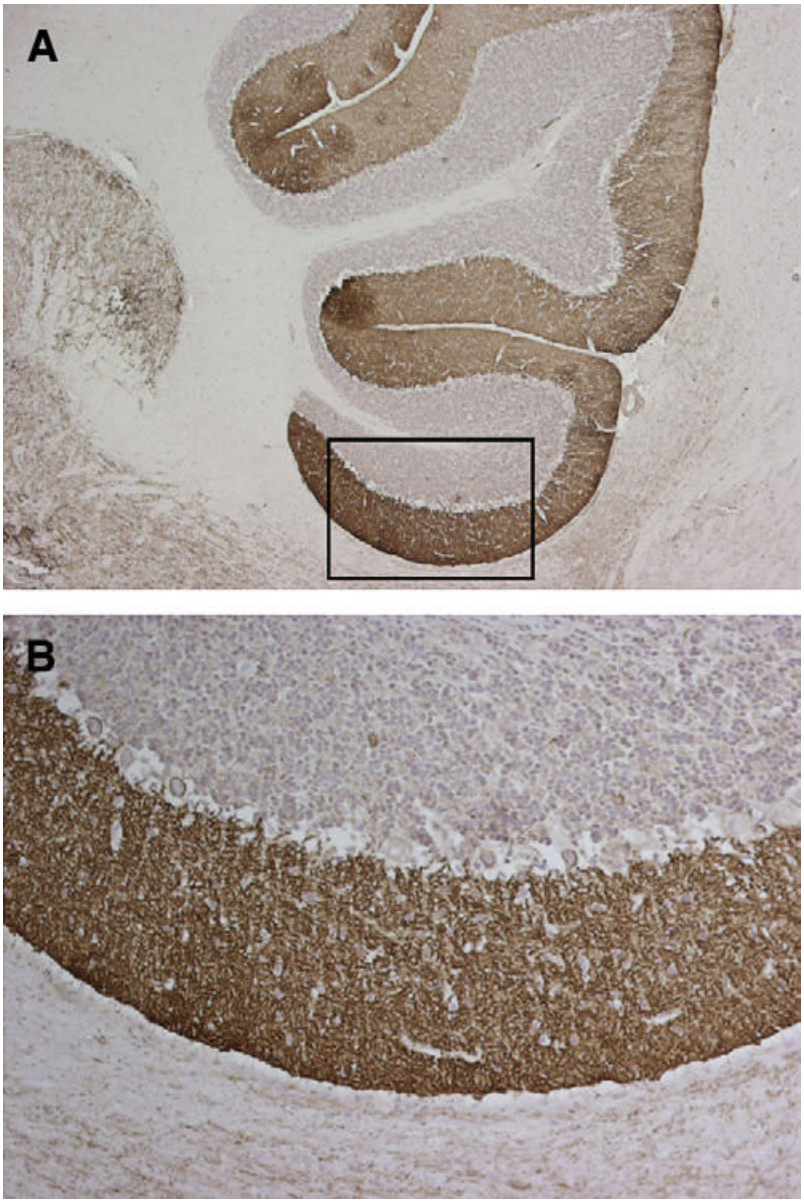

Fig 4.

Patient who had subacute cerebellar dysfunction and CSF antibodies against the molecular layer of the cerebellum. (*A*) A section of rat cerebellum immunostained with the antibodies from the CSF of a patient who had predominant subacute cerebellar degeneration and mild memory deficits without a known cancer. (*B*) Higher magnification of the area indicated in (*A*). Note that there is selective and intense immunolabeling of the neuronal processes running in the molecular layer of the cerebellum; the neuronal cell bodies of the granular layer, Purkinje cells, and cells of the molecular layer are spared. The dendrotoxin immunoprecipitation assay was negative, indicating that the autoantigen (unknown) is not a Kv1.1, 1,2, or 1,6 VGKC. (*A*) ×200; (*B*) ×400. Sections mildly counterstained with hematoxylin.

Table 1

Paraneoplastic antibodies that may associate with limbic encephalitis

Antibody	Syndrome	Cancer
Hu	Limbic encephalitis, encephalomyelitis	SCLC, other
Ma proteins	Limbic, hypothalamic,[a] and brainstem encephalitis	Testis, lung, other
CV2/CRMP5	Limbic, striatal encephalitis (chorea), cerebellar ataxia, peripheral neuropathy, uveitis	SCLC, thymoma
Amphiphysin	Limbic encephalitis, stiff-person syndrome	Breast, SCLC

[a] Hypothalamic pituitary hormonal deficits; decreased CSF hypocretin (associated with hypersomnia, narcolepsy).

Table 2

Differential diagnosis of limbic encephalopathy

Disorder	Distinctive features or tests
Disorders that selectively involve the limbic system	
Herpes simplex encephalitis	HSV DNA in CSF (sensitivity 94%, specificity 98%)
Paraneoplastic limbic encephalitis	Paraneoplastic antibodies detectable in serum and CSF of 60% of patients (see subtypes in Table 1)
Autoimmune non-paraneoplastic limbic encephalitis	VGKC (may also occur as paraneoplastic manifestation of thymoma, SCLC)
Disorders that predominantly involve the limbic system	
Degenerative disorders (Alzheimer disease, fronto-temporal dementia, mild cognitive impairment)	Amnestic syndrome may predominate at early stages
Severe hypoxia	History of cardiac arrest, carbon monoxide poisoning, or drug overdose
Transient global amnesia	Bitemporal hypoperfusion as shown by SPECT or abnormal diffusion-weighted MRI
Temporal lobe seizures	Abnormal FLAIR and diffusion-weighted MRI in temporal lobes following status epilepticus; hippocampal atrophy in mesial temporal sclerosis
Endocrine dysfunction (Cushing disease, corticosteroid treatment, post-traumatic stress disorder)	Decreased hippocampal volume may be found in chronic hypercortisolism
Wernicke-Korsakoff encephalopathy	Deficit of B1: poor nutrition, consumption by tumor Doxifluridine
Disorders that may involve the limbic system	
Head trauma	Contusion affecting inferomedial or anterior temporal lobes (“contre-coup” lesion)
Systemic autoimmune disorders	
Lupus erythematosus	Ribosomal-P antibodies
Hashimoto encephalitis	Thyroperoxidase and thyroglobulin antibodies
Sjögren syndrome	Anti-Ro(SSA)/La(SSB); salivary gland biopsy
Infections	HHV6 (usually after stem cell transplantation) Neurosyphilis
Tumors (gliomatosis cerebri)	Diagnostic brain biopsy
Stroke with bilateral posterior cerebral artery involvement	Amnestic syndrome often coexists with cortical blindness, prosopagnosia, apraxia of ocular movements, and other

Abbreviations: Anti-Ro(SSA)/La(SSB), Sjögren's syndrome serology; CSF, cerebrospinal fluid; HSV, herpes simplex virus; VGKC, voltage-gated potassium channels.

Table 3

Clinical features, response to treatment, and prognosis related to type of antibody and location of antigens

	Neuronal antibodies: Hu, Ma2, CV2/CRMP5, amphiphysin, atypical (intracellular antigens)	**VGKC antibodies (cell membrane antigens)**	**Novel neuropil antibodies (cell membrane antigens)**
Hippocampal specificity of antibodies	No; antibodies react with neurons of any part of the neuraxis	Mild; all patients with similar pattern of antibody reactivity	Intense; different patterns (some with pure limbic reactivity)
CSF inflammatory abnormalities[a]	Frequent	Infrequent (normal CSF or with mild abnormalities)	Frequent
Intrathecal synthesis of antibodies	Frequent	Infrequent/absent	Frequent
Hyponatremia	No (except some patients with SCLC)	Frequent	No
Clinical phenotypes other than limbic encephalitis	Several according to type of antibody [66]	Neuromyotonia; Morvan syndrome [38]	Prominent behavioral and psychiatric symptoms and seizures; central hypoventilation may occur [6,7]
Brain MRI	Frequent medial temporal lobe FLAIR/T2 hyperintensities (classic findings)	Frequent classic findings	Infrequent classic findings but frequent temporal lobe involvement
Tumor association	SCLC, non-SCLC, testicular tumors, thymoma, other	Infrequent: SCLC, thymoma	Frequent: teratoma, thymoma
Response to treatment (tumor and/or immunosuppression)	Rare; except for patients with testicular tumors and Ma2 encephalitis	Frequent (corticosteroids, IVIg, plasma exchange)	Frequent (tumor and/or corticosteroids, IVIg, plasma exchange)
Clinical course	Progressive until stabilization or death (Hu, CV2/CRMP5); relapses are rare	Relapses may occur and are treatable	Relapses may occur and are treatable
Antibody titers	Usually detectable for months or years	Decrease or disappear in months	Decrease or disappear in months

[a] Pleocytosis, increased protein concentration, elevated IgG index, oligoclonal bands.