Limbic Encephalitis Associated with Antibodies to Cell Membrane Antigens

Hücre Membranı Antijenlerine Karşı Antikorlarla İlişkili Limbik Ensefalit

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SUMMARY
Limbic encephalitis patients usually present with rapidly progressive memory deficit, psychiatric symptoms, seizures, CSF inflammatory findings and EEG or MRI abnormalities in the temporal lobes. While these findings might be caused by viral infections or systemic autoimmune disorders, many patients with limbic encephalitis have an immune-mediated etiology (paraneoplastic or not) characterized with serum or CSF antineuronal antibodies. Once considered rare, non-viral immune mediated limbic encephalitis is now increasingly recognized and new immunophenotypes are identified. With the advent of new diagnostic techniques, novel serum or CSF antibodies have been detected in the majority of limbic encephalitis patients previously regarded as seronegative. These antibodies are mainly directed against the cell membrane antigens such as voltage-gated potassium channels and N-methyl-D-aspartate receptors expressed by the hippocampal and cerebellar neuropil and play a significant pathogenic role. Furthermore, this immunopehonotype associates less frequently with cancer or cytotoxic T cell infiltration than other limbic encephalitis variants and responds significantly better to immunosuppressive treatment methods. *(Nöropsikiyatri Arşivi 2007; 44: 101-7)*
Key words: Limbic encephalitis, paraneoplastic, non-paraneoplastic, antibodies

ÖZET
Limbik ensefalit hastaları genellikle hızlı ilerleyişli bellek kaybı, psikiyatrik semptomlar, nöbetler, inflamatuar BOS bulguları ve temporal loblarda EEG ve MR değişiklikleri ile başvururlar. Bu bulgulara viral enfeksiyonlar ve sistemik otoimmün hastalıklar da sebep olabilmekle beraber, pek çok limbik ensefalit hastasında serum veya BOS'da antinöronal antikorlarla karakterize immun-aracılı bir etiyoloji (paraneoplastik veya non-paraneoplastik) mevcuttur. Bir zamanlar nadir olduğu düşünülen non-viral immun-aracılı limbik ensefalit olgularına giderek daha fazla rastlanmakta ve yeni immünolojik fenotipler tanımlanmaktadır. Yeni tanı tekniklerinin ortaya çıkmasıyla, önceden seronegatif olduğu sanılan limbik ensefalit hastalarının çoğunda yeni serum veya BOS antikorları saptanmıştır. Bu antikorlar, büyük ölçüde, hipokampus ve serebellum nöropillerinde bulunan voltaj bağımlı potasyum kanalları ve N-metil-D-aspartat reseptörleri gibi hücre membranı antijenlerine karşı gelişmekte ve muhtemelen patojenik rol oynamaktadırlar. Ayrıca bu immünolojik fenotip diğer limbik ensefalit varyantlarına kıyasla kanser ve sitotoksik T hücresi infiltrasyonu ile daha az ilişkili olup immün sistemi baskılayıcı tedavi yöntemlerine daha iyi yanıt vermektedir.*(Archives of Neuropsychiatry 2007; 44: 101-7)*
Anahtar kelimeler: Limbik ensefalit, paraneoplastik, non-paraneoplastik, antikorlar

Introduction

Limbic encephalitis was first described by Brierley et al. in 1960 (1). In 1968, Corsellis et al. used the term "limbic encephalitis" and noticed for the first time a relationship between limbic encephalitis and cancer (2). In the following years, several paraneoplastic antineuronal antibodies were discovered and various clinical-immunological associations were established (e.g. anti-Hu and small cell lung cancer (SCLC), anti-Ma2 and testicular cancer) (3-6). These findings have had a substantial impact on clinical neurology. The understanding that limbic symptoms may be induced by immune-mediated mechanisms has not only corroborated the notion that autoimmunity can affect behavior, affection and cognition but also has facilitated the diagnosis and treatment of patients presenting with neuropsychological symptoms.

However, until recently, limbic encephalitis has been inaccurately considered as a rare and untreatable disease that is almost always associated with cancer. In 2001, a limbic encephalitis patient was reported to have antibodies to a cell membrane antigen, voltage-gated potassium channel (VGKC) (7). Notably, this patient had no cancer, was responsive to immunomodulating treatments and the antibody titers correlated with the severity of the clinical symptoms. Further examination of limbic encephalitis patients' samples with novel diagnostic techniques revealed that many patients previously considered as seronegative did in fact have antibodies directed against cell membrane antigens such as N-methyl-D-aspartate receptor (NMDAR), responded significantly better to immunotherapy and were less frequently associated with cancer.

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These reports have shown that limbic encephalitis is more frequent than formerly suggested, is potentially treatable and often presents without a cancer. Detection of well-characterized serum or CSF antineuronal antibodies is generally considered as an indicator of autoimmune origin and warrants immunotherapy. On the other hand, limbic encephalitis patients with no detectable antibodies might be deprived from immunomodulating treatments. Although limbic encephalitis patients associated with antibodies to cell membrane antigens give a significant response to immunotherapy, conventional techniques often do not detect these antibodies. These facts necessitate a better understanding of these recently described limbic encephalitis syndromes. In this review, after briefly browsing the general features of classical limbic encephalitis, we will focus on clinical and diagnostic features of the recently identified immunophenotypes associated with cell membrane antigens.

Clinical Features and Diagnosis

The diagnosis of limbic encephalitis is based on core clinical symptoms of acute or subacute onset short-term memory loss, seizures and behavioral changes, neuroimaging evidence for unilateral or bilateral medial temporal lobe involvement and exclusion of other disorders that may affect the limbic system. The most characteristic clinical feature of limbic encephalitis is the short-term memory loss, which might be masked by seizures, confusion or abnormal behaviour. In a clinical study conducted with 50 limbic encephalitis patients, 46% of the patients had acute confusional state, 14% had cognitive decline and 42% had psychiatric symptoms (4). In another study of 24 patients, 92% had cognitive dysfunction and 50% psychiatric symptoms (8). Seizures occur in approximately 60% of patients with limbic encephalitis. Complex partial seizures (40%), generalized seizures (24%) or a combination of seizure types (36%) have been reported (4). EEG often demonstrates uni- or bilateral temporal lobe epileptic discharges or slow background activity. EEG monitoring is important in patients with confusion or low level of consciousness for the diagnosis of non-convulsive status epilepticus (8,9).

CSF examination typically shows mild to moderate lymphocytic pleocytosis (usually less than 100 white blood cells/ml), increased protein (usually <150 mg/dl) and normal glucose concentration. Increased IgG production, oligoclonal bands and intrathecal synthesis of paraneoplastic antibodies are also frequently encountered. Alternatively, CSF of patients with anti-VGKC antibody is often normal (Table 1). CSF analysis is also required to rule out leptomeningeal metastasis (4,8,10-12). MRI is the best technique to exclude metastatic lesions and other cancer associated complications. Uni- or bilateral medial temporal lobe enhancement demonstrated by T2 and fluid-attenuated inversion recovery (FLAIR) sequences is the hallmark of limbic encephalitis. MRI abnormalities can be asymmetrical and may occasionally show contrast enhancement. More often than MRI examination, (18F) Fluorodeoxyglucose positron emission to-

Table 1. Comparison of clinical features of limbic encephalitis immunophenotypes

	Antibodies to intracellular antigens (e.g. Hu, Ma2, CV2)	Antibodies to VGKC (cell membrane antigen)	Antibodies to NMDAR (cell membrane antigen)	Antibodies to other cell membrane antigens
CSF inflammatory changes	Frequent	Infrequent or mild	Frequent	Frequent
Intrathecal synthesis of antibodies	Frequent	Infrequent or absent	Frequent. Antibodies may only be detected in CSF	Not studied
Symptoms different from classic limbic encephalitis	Several according to the type of antibody	Neuromyotonia, REM sleep disorders, epilepsy, Morvan's syndrome	Psychiatric symptoms, decreased level of consciousness, autonomic instability, hypoventilation, dyskinesias	Infrequent. The clinical picture is typical of limbic encephalitisencephalitis
MRI findings	Frequent typical findings*	Frequent typical findings	Normal or FLAIR increased signal in cerebral or cerebellar cortex, transient meningeal enhancement. In about 25% of cases: typical findings	Typical findings and/or FLAIR increased signal in focal cortical regions.
Frequently associated tumors	Depends on the antibody type (e.g. lung, testis, breast, thymoma)	Usually no tumor, in 20% of cases: thymoma, less frequently SCLC	Ovarian teratoma, rarely no tumor	Tumors of the thymus, Hodgkin's lymphoma, SCLC, no tumor.
Response to treatment (tumor removal and/or immunotherapy)	Infrequent, except 30% of patients with anti-Ma2 antibodies and testicular tumors.	Frequent; corticosteroids and/or plasma exchange, IVIg	Frequent; ICU, tumor resection, corticosteroids, plasma exchange, IVIg, other	Frequent; tumor resection, corticosteroids plasma exchange, IVIg
Pathological examination of the CNS	Microgliosis, intense lymphocytic infiltrates	Not studied	Intense microgliosis, IgG deposits, rare lymphocytic infiltrates	Not studied

*Typical findings- T2/FLAIR hyperintensity in medial temporal lobes.
IVIg- intravenous immunoglobulins, REM- rapid eye movement, ICU- intensive care unit.

mography (FDG-PET) studies may show hypermetabolism in frontotemporal lobes, brainstem and cerebellum in addition to medial temporal lobes (4,8,13,14) (Figure 1). Overall, clinical, electrophysiological, CSF, MRI and metabolic neuroimaging studies establish the diagnosis of limbic encephalitis in 70-80% of patients (4,13,14).

Following the diagnosis of limbic encephalitis, the possible paraneoplastic etiology is corroborated with demonstration of the tumor and paraneoplastic antibodies in serum, CSF or the tumor. In most instances tumor is shown by CT of the chest, abdomen and pelvis. FDG-PET is useful in demonstrating occult neoplasms or small metastatic lesions. Type of the syndrome and the paraneoplastic antibody may suggest a specific test such as ultrasound of the testes in anti-Ma2 positive patients (15).

Detection of specific antibodies does not only uncover the paraneoplastic etiology but also provides hints about the underlying cancer, response to treatment, prognosis and possible serious clinical problems that may be encountered during the course of the disease (e.g. severe hyponatremia in anti-VGKC limbic encephalitis or hypoventilation in anti-NMDAR limbic encephalitis). Serum/CSF antibodies are detected by a range of immunological techniques including immunohistochemistry, western blot, immunocytochemistry and radioimmunoassay. Pathological examination of the brain usually demonstrates inflammatory infiltrates, neuronal loss, microglial activation and gliosis, which are non-specific and can be observed in any immune-mediated limbic encephalitis (16,17).

Differential Diagnosis

Viral encephalitis, autoimmune limbic encephalitis (paraneoplastic or not) and central nervous system (CNS) involvement of a systemic autoimmune disease (e.g. Hashimoto's thyroiditis, Sjögren's syndrome and systemic lupus erythematosus) are three major groups of disorders that should be considered in diagnosis of limbic encephalitis. Particularly, herpes simplex virus (HSV) and human herpesvirus 6 (HHV-6) encephalitis may almost perfectly mimic typical autoimmune limbic encephalitis.

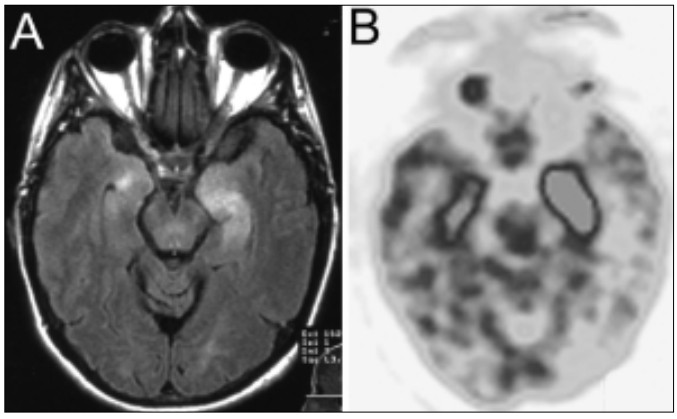


Figure 1. Medial temporal lobe involvement in the brain MRI (A) and FDG-PET (B) of a patient with limbic encephalitis, carcinoma of the thymus and serum/CSF antibodies to hippocampal neuropil antigens. Axial MRI FLAIR and FDG-PET sequences were matched to show the area of maximal involvement

HSV encephalitis is diagnosed by demonstration of HSV DNA in CSF by PCR. This assay has 94% sensitivity and 98% specificity but it can be negative within the first 72 hours of symptom onset (18,19). HHV-6 encephalitis is often observed in immunosuppressed patients (e.g. after bone marrow or hematopoietic stem cell transplantation) and is diagnosed by CSF HHV-6 PCR (20). It is very unlikely for other viral agents such as varicella-zoster virus and cytomegalovirus to cause symptoms and MRI findings compatible with limbic encephalitis. Likewise, immune-mediated systemic autoimmune diseases rarely present with isolated and typical limbic encephalitis. Usually, these patients have a wide array of neurological symptoms and multiple MRI lesions in widespread CNS regions. Nevertheless, there are a few Hashimoto's thyroiditis, systemic lupus erythematosus and CNS angiitis patients reported to present with classical limbic encephalitis findings (21-23). A list of immune-mediated or infectious disorders presenting with complete or partial limbic symptoms is provided in Figure 2.

Immunophenotypes of Autoimmune Limbic Encephalitis

Recent studies have demonstrated that antibodies of limbic encephalitis patients are directed against two broad categories of antigens: intracellular paraneoplastic antigens and cell membrane antigens (paraneoplastic or not) (10). Well-characterized intracellular antigens are Hu (ANNA1), CV2/CRMP5 and Ma2 (Ta) (9,15) and cell membrane antigens are VGKC and NMDAR (7,11,12,24,25). The second group was established recently by the introduction of new tissue processing and immunohistochemistry techniques, which enabled characterization of several novel antibodies. Analysis of serum/CSF samples of limbic encephalitis patients with these new techniques gave way to detection of antibodies in 93% of 39 limbic encephalitis patients prospectively identified on clinical grounds. Notably, antibodies to known antigens (Hu, Ma2, VGKC) were detected only in 49% of the patients (36% anti-Hu or anti-Ma2, 13% anti-VGKC), whereas antibodies to novel cell membrane antigens were detected in 44% of the patients (26), who would formerly be considered as seronegative. Some of these novel antigens were later found out to be NMDAR (24).

Limbic encephalitis with antibodies to intracellular antigens

The main autoantigens related to this group are Hu, CV2/CRMP5 and Ma2. These antigens have been characterized by different laboratories and reported in large cohorts of limbic encephalitis patients. Detection of these antibodies suggests paraneoplastic etiology and demands extensive clinical, CSF and neuroimaging evaluation to find out the cancer (lung, testis, breast, thymus cancer and others), even if no tumor is found at initial evaluation. This immunophenotype is usually resistant to IgG depleting treatment strategies and CNS specimens of the patients contain T, B and plasma cell infiltrates that are possibly responsible from neuronal damage (16,17) (Table 1).

Less frequently encountered antigens include amphiphysin (27), serine/threonine kinase 2 (28) and anti-glial nuclear anti-

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body (AGNA) (29). These antigens are primarily associated with an underlying lung cancer (SCLC or non-SCLC), with the exception of anti-amphiphysin antibody, which is also frequently associated with breast cancer (30). An extensive review on limbic encephalitis associated with antibodies to intracellular antigens can be found elsewhere (10).

Limbic encephalitis with antibodies to cell membrane antigens

Well-characterized cell membrane antigens related with limbic encephalitis are VGKC and NMDAR, both of which are ubiquitously expressed in the nervous system but particularly concentrated in the hippocampus (7,11,14,24). Furthermore, some patients present with antibodies to cell membrane antigens expressed by hippocampal or cerebellar neuropil. Although these antigens (will be referred from hereafter as novel neuropil antigens) have not yet been characterized, the clinical features of the patients have been reported (14). In this group of limbic encephalitis, frequency of an accompanying cancer is much lower (Table 1). While most anti-VGKC limbic encephalitis patients have no detectable tumors, almost all anti-NMDAR limbic encephalitis patients present with an underlying teratoma (24). The frequency of cancer in the patients with antibodies to novel neuropil antigens needs to be further clarified. In a recent report, 2 out of 5 patients with anti-novel neuropil antigen antibodies were free of any detectable tumors (14).

Patients with antibodies to cell membrane antigens often respond to IgG depleting treatment methods and there is usually correlation with the clinical status and antibody titers (Table 1). Therefore, IgG appears to be the major pathogenic factor in this category. Pathological examination of the brain specimen of a single anti-NMDAR encephalitis patient has shown intense IgG deposits but rare lymphocytic infiltrates corroborating this assumption (24).

The relative frequencies of limbic encephalitis patients related with these three groups of cell membrane antigens remain to be determined. However, a review of the database of a single institution showed that around 30% of patients with cell membrane antibodies present with anti-VGKC antibodies and 70% have antibodies against NMDAR (55%) or novel neuropil antigens (15%) (personal communication with J Dalmau).

Identification of these immunophenotypes is mainly established by immunohistochemistry and immunocytochemistry assays. Antibodies to cell membrane antigens intensely immunolabel the neuropil of the hippocampus or cerebellum, with highly characteristic patterns that depend on the target antigen. The best immunohistochemistry results are obtained using paraformaldehyde fixed brain tissue from non-perfused rats (Figure 3). Following the demonstration of the neuropil staining, further characterization of the antibody type is required. For this purpose, live rat neurons or cells transfected with specific cell membrane antigens of interest (e.g. NR1 subunit of the NMDAR) are tested by immunocytochemistry for antibody binding. Anti-VGKC, anti-NMDAR and anti-novel neuropil antigen antibodies all show distinctive staining patterns (Figure 3) (14,24,25).

Anti-VGKC antibodies can also be detected by a radioimmunoassay method based on the labeling of the antibodies by radioactive α-dendrotoxin, which binds to the VGKC subunits Kv1.1, Kv1.2 and Kv1.6 (7). In contrast with antibodies to intracellular antigens, antibodies to cell membrane antigens usually do not yi-

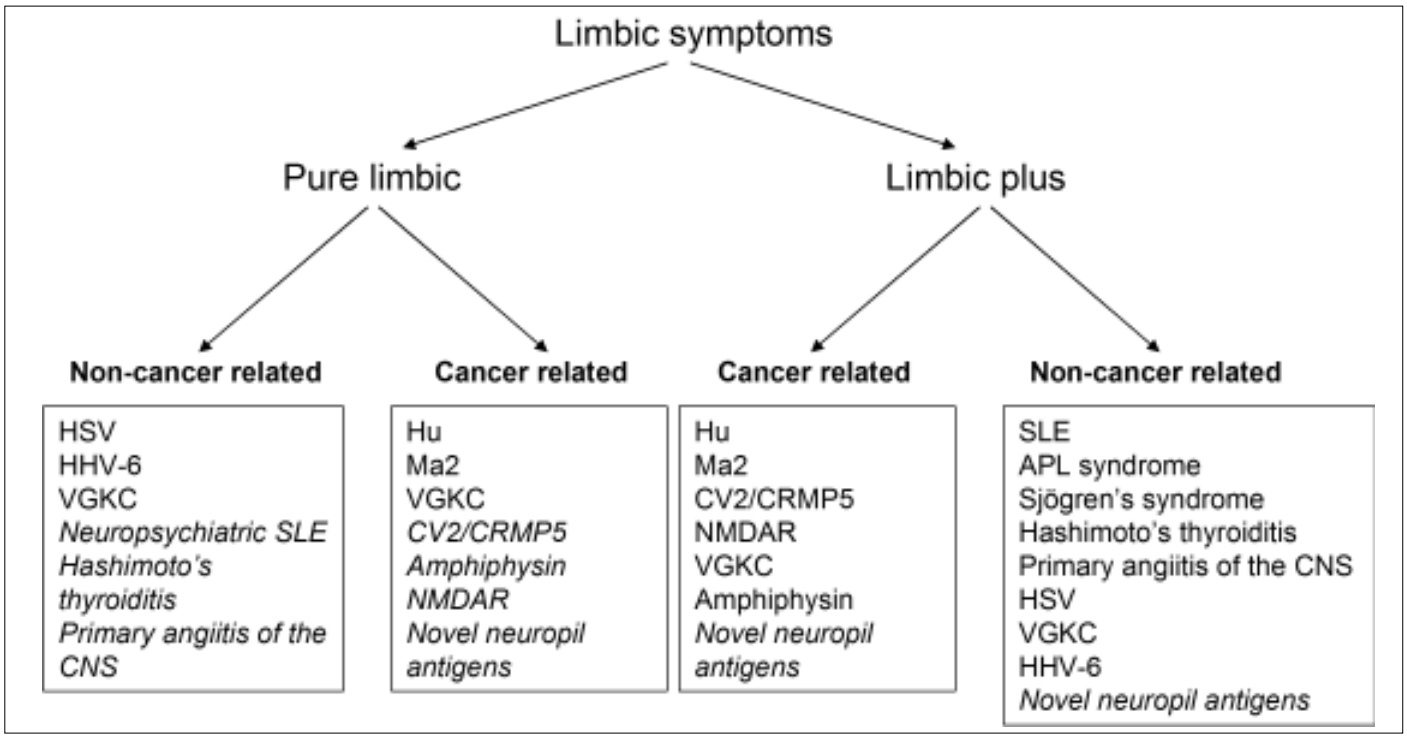


Figure 2. Immune-mediated or infectious disorders presenting with complete or partial limbic symptoms classified according to cancer association. Diseases with less than five patients reported in English literature are written in italics (HSV: herpes simplex virus; HHV6: human herpesvirus-6; VGKC: voltage-gated potassium channel; SLE: systemic lupus erythematosus; CNS: central nervous system; NMDAR: N-methyl-D-aspartate receptor; APL: anti-phospholipid)

eld specific bands in western blot assays. This suggests that these antibodies bind to conformational epitopes, which are lost by the denaturing conditions of the western blot procedure.

Encephalitis associated with VGKC antibodies

Anti-VGKC antibody is associated with neuromyotonia, classical limbic encephalitis and limbic encephalitis with additional symptoms of neuromyotonia, autonomic dysfunction, hyperhydrosis and rapid eye movement sleep behavior abnormalities, also known as Morvan's syndrome (31). Anti-VGKC antibody has also been detected in patients with epilepsy (32), pilomotor seizures (33) and intestinal pseudo-obstruction (34).

Although the cancer frequency is relatively low, there are still various cancer types associated with anti-VGKC limbic encephalitis (mainly thymoma and SCLC) (29,35). A review of all reported VGKC limbic encephalitis patients shows that around 30% of the patients present with a tumor and therefore cancer screening is necessary. Due to relatively low cancer association VGKC-associated limbic encephalitis should be considered in young patients and patients with no smoking history. Brain MRI usually shows FLAIR hyperintensity in the medial temporal lobes (asymmetrical or not). As compared to other limbic encephalitis types, the CSF is frequently normal or shows minimal pleocytosis and elevated proteins (7,10-12).

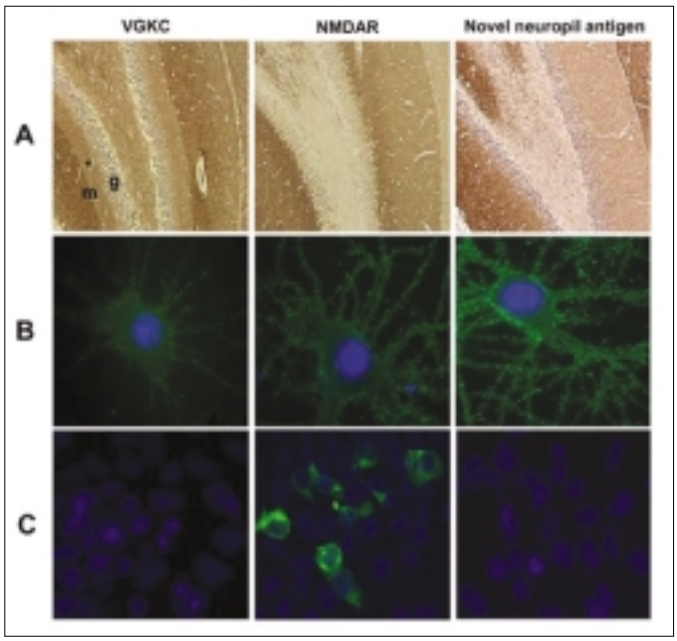


Figure 3. Comparison of staining patterns of CSF samples of limbic encephalitis patients with antibodies to cell membrane antigens. (A) Sagittal sections of rat brain immunoreacting with CSF of patients with antibodies against VGKC (determined with the α-dendrotoxin radioimmunoassay), NMDAR and novel neuropil antigens. Note different patterns of hippocampal reactivity. NMDAR and novel neuropil antigen antibodies react with the entire molecular layer (m, dark brown) adjacent to the granular cells of the dentate gyrus (g, light blue counterstaining), while the VGKC antibodies primarily react with the outer portion of the molecular layer distant from the granular cells and relatively spare the inner portion (*, light brown). Panel B: CSF antibodies from the same patients recognize membrane antigens of cultured live rat hippocampal neurons. Panel C: Confirmation that the CSF antibodies selectively react with NMDARs is achieved using human embryonic kidney (HEK293) cells expressing NR1/NR2B heteromers of the NMDAR. The antibody reactivity is shown with green. In Panels B and C, cell nuclei are labeled with 4,6-diamidino-2-phenylindole-2-HCl (DAPI). Magnification: Panel A x100; Panel B x800; Panel C x400.

Around 70-80% of patients with VGKC antibody-associated disorders respond clinically and radiologically to corticosteroids, intravenous IgG (IVIg) or plasma exchange (11,12). Hyponatremia is frequently encountered in this immunophenotype and may be life-threatening (14,35).

Encephalitis associated with NDMAR antibodies

Recent studies have demonstrated that currently uncharacterized antigens predominantly expressed by the hippocampal and cerebellar neuropil are associated with a phenotype of limbic encephalitis that is often accompanied by an underlying teratoma or thymoma and is responsive to IgG depleting treatments (Table I). The notable clinical feature of this type of limbic encephalitis is the predominance of behavioral and psychiatric symptoms. Different from anti-VGKC associated patients, this immunophenotype presents with CSF pleocytosis, increased protein concentration and elevated IgG index (Table 1) (14).

A subgroup of patients with anti-neuropil antibodies develops a specific syndrome characterized with subacute psychiatric symptoms, seizures, short-term memory deficits, decreased level of consciousness and central hypoventilation often requiring assisted ventilation (24,25). Notably, majority of the patients develop a flu-like illness (fever, headache, malaise or fatigue) a few days before initial symptoms. Psychiatric symptoms often dominate the clinical picture and include extreme agitation, delusions, disorientation and confusion. Because of these symptoms, young age (median age 27 years) and absence of cancer history, these patients are usually first admitted in psychiatric wards, where malingering and drug abuse are frequently considered. Some patients develop choreic or dystonic movements, dyskinesias, sleep dysfunction and autonomic instability. The autonomic instability may include intense fluctuation of blood pressure and temperature, tachycardia, bradycardia, cardiac pauses and diaphoresis. Most patients eventually develop a catatonic state with eyes open, unresponsive to visual threats, mute or mumbling unintelligible words, with increased muscle tone and dystonic postures.

CSF usually shows pleocytosis, increased protein concentration, oligoclonal bands and elevated IgG index. Brain MRI is usually normal or shows non-specific cortical FLAIR abnormalities. Only 1/4 of the patients present with a classical medial temporal lobe hyperintensity. An immature or mature ovarian teratoma or a mediastinal teratoma (1 case) is often found and may be missed with FDG-PET examination. In most patients, imaging studies show a pelvic cyst, which is mistakenly considered unrelated to the neurological symptoms. EEG monitoring usually reveals diffuse delta-theta activity (24,25).

Prompt recognition of the syndrome, removal of the underlying teratoma and immunotherapy appear to shorten the time spent in intensive care unit. Symptoms usually resolve in weeks following removal of the tumor and treatment with corticosteroids, IVIg or plasma exchange (24,25). In a few cases, cyclophosphamide and rituximab have been effectively used (personal communication with J Dalmau).

The target antigen in this syndrome has recently been identified as the NR1/NR2 heteromers of the NMDAR (24). All of the

patients' CSF and/or serum antibodies react with NR1/NR2B co-transfected human embryonic kidney 93 (HEK93) cells and 67% of the patients' antibodies react with NR1/NR2A co-transfected HEK93 cells. These findings suggest that antibodies mainly react with conformational epitopes located on homodimerized NR1/NR2 subunits of the NMDAR. Furthermore, the requirement of NR1 for antibody binding differs this syndrome from others related to antibodies that only bind to NR2 subunits of the NMDAR (e.g. epilepsia partialis continua, Rasmussen's encephalitis, stroke) (36,37).

Pathological examination of a brain sample obtained from an anti-NMDAR encephalitis patient has shown extensive microgliosis, neuronal degeneration and intense IgG deposits predominantly involving but not restricted to hippocampus (24). In contrast with limbic encephalitis associated with antibodies to intracellular antigens (16,17), there were rare T cell, B cell and plasma cell infiltrates in a few sections (e.g hippocampus, frontal lobe) and there was no lymphocytic infiltration in most CNS regions (24). Using antibodies to anti-microtubule-associated protein-2 (MAP-2), all examined tumor specimens of anti-NMDAR encephalitis patients were shown to bear mature or non-mature appearing nerve cells with a dense network of neuropils. Some of these nerve cells expressed NR2A and NR2B subunits of NMDAR, which co-localized with patients' antibodies. Additionally, intense T cell, B cell and plasma cell infiltrates were observed in all the examined tumor sections (24). It is well known that the tumor tissue associated with a paraneoplastic disorder might express neuronal antigens and this expression might trigger an autoimmune response to CNS, eventually generating neurological symptoms. Notably, ovarian teratoma samples associated with anti-NMDAR encephalitis is unique in possessing not only the neuronal target autoantigens but also the entire neuronal cells. All these data suggest that the teratoma tissue might be directly involved in generation of an autoimmune response against hippocampal neurons, which abundantly express NMDARs and thus induce limbic encephalitis.

Encephalitis associated with novel neuropil antigen antibodies

In addition to patients with anti-VGKC and anti-NMDAR antibodies, there is an emerging group of limbic encephalitis cases that are negative for all known antibodies. In these patients, the target antigens are expressed by hippocampal and cerebellar neuropil. By both immunohistochemistry and immunocytochemistry, these patients' antibodies produce a staining pattern that is very similar to that of anti-NMDAR antibody. However, they do not react with NR1/NR2 expressing HEK93 cells (Figure 3). Identical to anti-VGKC and anti-NMDAR encephalitis, patients with these antibodies significantly respond to immunotherapy and they have a better prognosis than that of patients with antibodies to intracellular antigens (14).

Conclusion

The accumulating data on limbic encephalitis suggest that there are two types of pathogenic immune mechanisms depending on whether the target antigen is located within the cell or on the cell membrane. While, limbic encephalitis associated with intracellular antigens is mainly mediated by cytotoxic T cells, encephalitis related to cell membrane or extracellular antigens appears to be mainly mediated by antibodies. Furthermore, the first group associates with cancer, resistance to immunotherapy and cytotoxic T cell infiltrates in the brain and the second group associates less frequently with cancer, have less frequent brain inflammatory infiltrates and respond significantly better to immunotherapy. Patients with antibodies to cell membrane antigens usually recover promptly following tumor removal and immunotherapy, which might include cyclophosphamide and rituximab. The good treatment response and recovery rate obligate the recognition of these recently described syndromes. However, except anti-VGKC antibodies, commercial testing is not available for antibodies related to this group of limbic encephalitis. Due to the conformational nature of the target epitopes, recognition of these antibodies might require novel techniques summarized above and depicted in Figure 3. Therefore, the patient's serum and CSF should be examined in research laboratories, when any of these disorders is suspected.

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References

1. Brierley JB, Corsellis JAN, Hierons R, et al. Subacute encephalitis of later adult life. Mainly affecting the limbic areas. Brain 1960; 83:357-68.
2. Corsellis JA, Goldberg GJ, Norton AR. "Limbic encephalitis" and its association with carcinoma. Brain 1968; 91:481-96.
3. Bakheit AM, Kennedy PG, Behan PO. Paraneoplastic limbic encephalitis: clinico-pathological correlations. J Neurol Neurosurg Psychiatry 1990;53:1084-8.
4. Gultekin SH, Rosenfeld MR, Voltz R, et al. Paraneoplastic limbic encephalitis: neurological symptoms, immunological findings and tumour association in 50 patients. Brain 2000;123:1481-94.
5. Alamowitch S, Graus F, Uchuya M, et al. Limbic encephalitis and small cell lung cancer. Clinical and immunological features. Brain 1997;120:923-8.
6. Voltz R, Gultekin SH, Rosenfeld MR, et al. A serologic marker of paraneoplastic limbic and brain-stem encephalitis in patients with testicular cancer. N Engl J Med 1999;340:1788-95.
7. Buckley C, Oger J, Clover L, et al. Potassium channel antibodies in two patients with reversible limbic encephalitis. Ann Neurol 2001;50:73-8.
8. Lawn ND, Westmoreland BF, Kiely MJ, et al. Clinical, magnetic resonance imaging, and electroencephalographic findings in paraneoplastic limbic encephalitis. Mayo Clin Proc 2003;78:1363-8.
9. Espay AJ, Kumar V, Sarpel G. Anti-Hu-associated paraneoplastic limbic encephalitis presenting as rapidly progressive non-convulsive status epilepticus. J Neurol Sci 2006;246:149-52.
10. Dalmau J, Bataller L. Clinical and immunological diversity of limbic encephalitis: a model for paraneoplastic neurologic disorders. Hematol Oncol Clin North Am 2006;20:1319-35.
11. Vincent A, Buckley C, Schott JM, et al. Potassium channel antibody-associated encephalopathy: a potentially immunotherapy-responsive form of limbic encephalitis. Brain 2004;127:701-12.
12. Thieben MJ, Lennon VA, Boeve BF, et al. Potentially reversible autoimmune limbic encephalitis with neuronal potassium channel antibody. Neurology 2004;62:1177-82.

13. Kassubek J, Juengling FD, Nitzsche EU, et al. Limbic encephalitis investigated by 18FDG-PET and 3D MRI. J Neuroimaging 2001; 11:55-9.
14. Ances BM, Vitaliani R, Taylor RA, et al. Treatment-responsive limbic encephalitis identified by neuropil antibodies: MRI and PET correlates. Brain 2005;128:1764-77.
15. Mathew RM, Vandenberghe R, Garcia-Merino A, et al. Orchiectomy for suspected microscopic tumor in patients with anti-Ma2-associated encephalitis. Neurology 2007;68:900-5.
16. Bernal F, Graus F, Pifarre A, et al. Immunohistochemical analysis of anti-Hu-associated paraneoplastic encephalomyelitis. Acta Neuropathol (Berl) 2002;103:509-15.
17. Blumenthal DT, Salzman KL, Digre KB, et al. Early pathologic findings and long-term improvement in anti-Ma2-associated encephalitis. Neurology 2006;67:146-9.
18. Tyler KL. Update on herpes simplex encephalitis. Rev Neurol Dis 2004;1:169-78.
19. Whitley RJ. Herpes simplex encephalitis: adolescents and adults. Antiviral Res 2006;71:141-8.
20. Zerr DM. Human herpesvirus 6: a clinical update. Herpes 2006; 13:20-4.
21. Stubgen JP. Nervous system lupus mimics limbic encephalitis. Lupus 1998;7:557-60.
22. McCabe DJ, Burke T, Connolly S, et al. Amnesic syndrome with bilateral mesial temporal lobe involvement in Hashimoto's encephalopathy. Neurology 2000;54:737-9.
23. Schwab P, Lidov HG, Schwartz RB, et al. Cerebral amyloid angiopathy associated with primary angiitis of the central nervous system: report of 2 cases and review of the literature. Arthritis Rheum 2003;49:421-7.
24. Dalmau J, Tuzun E, Wu HY, et al. Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. Ann Neurol 2007;61:25-36.
25. Vitaliani R, Mason W, Ances B, et al. Paraneoplastic encephalitis, psychiatric symptoms, and hypoventilation in ovarian teratoma. Ann Neurol 2005;58:594-604.
26. Bataller L, Kleopa KA, Wu GF, et al. Autoimmune limbic encephalitis in 39 patients: immunophenotypes and outcomes. J Neurol Neurosurg Psychiatry 2007;78:381-5.
27. Dorresteijn LD, Kappelle AC, Renier WO, et al. Anti-amphiphysin associated limbic encephalitis: a paraneoplastic presentation of small-cell lung carcinoma. J Neurol 2002;249:1307-8.
28. Sabater L, Gomez-Choco M, Saiz A, et al. BR serine/threonine kinase 2: a new autoantigen in paraneoplastic limbic encephalitis. J Neuroimmunol 2005;170:186-90.
29. Zuliani L, Saiz A, Tavolato B, et al. Paraneoplastic limbic encephalitis associated with potassium channel antibodies: value of anti-glial nuclear antibodies in identifying the tumour. J Neurol Neurosurg Psychiatry 2007;78:204-5.
30. Pittock SJ, Lucchinetti CF, Parisi JE, et al. Amphiphysin autoimmunity: paraneoplastic accompaniments. Ann Neurol 2005;58:96-107.
31. Liguori R, Vincent A, Clover L, et al. Morvan's syndrome: peripheral and central nervous system and cardiac involvement with antibodies to voltage-gated potassium channels. Brain 2001;124:2417-26.
32. Majoie HJ, de Baets M, Renier W, et al. Antibodies to voltage-gated potassium and calcium channels in epilepsy. Epilepsy Res 2006;71:135-41.
33. Wieser S, Kelemen A, Barsi P, et al. Pilomotor seizures and status in non-paraneoplastic limbic encephalitis. Epileptic Disord 2005;7:205-11.
34. Viallard JF, Vincent A, Moreau JF, et al. Thymoma-associated neuromyotonia with antibodies against voltage-gated potassium channels presenting as chronic intestinal pseudo-obstruction. Eur Neurol 2005;53:60-3.
35. Ohshita T, Kawakami H, Maruyama H, et al. Voltage-gated potassium channel antibodies associated limbic encephalitis in a patient with invasive thymoma. J Neurol Sci 2006;250:167-9.
36. Takahashi Y, Mori H, Mishina M, et al. Autoantibodies and cell-mediated autoimmunity to NMDA-type GluRepsilon2 in patients with Rasmussen's encephalitis and chronic progressive epilepsia partialis continua. Epilepsia 2005;46(Suppl 5):152-8.
37. Bokesch PM, Izykenova GA, Justice JB, et al. NMDA receptor antibodies predict adverse neurological outcome after cardiac surgery in high-risk patients. Stroke 2006;37:1432-6.