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Limbic Encephalitis and Variants Related to Neuronal Cell Membrane Autoantigens

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Abstract: Limbic encephalitis refers to an inflammatory process involving the hippocampi, amygdala and less frequently frontobasal and insular regions. This disorder used to be considered extremely rare, invariably associated with cancer, and unresponsive to treatment. However, recent studies suggest that limbic encephalitis is more frequent than it was previously thought, and a substantial number of patients may recover. This is due in part to the development of clinical diagnostic criteria and identification of antibodies directed against two broad categories of antigens: 1) intracellular or classical paraneoplastic antigens, including Hu, Ma2, and CV2/CRMP5, among others, and 2) cell surface antigens including, voltage-gated potassium channels (VGKC), N-methyl-D-aspartate receptor (NMDAR), and others expressed in the neuropil of the hippocampus. While the disorders related to the first category of antibodies associate with cancer (lung, testis and other), prominent brain infiltrates of T-cells, and limited response to treatment, the disorders related to the second category of antibodies associate with other tumors (thymoma, teratoma, Hodgkin's lymphoma), appear to be antibody-mediated, and respond better to immunotherapy. Of particular interest in the later group is the disorder that associates with antibodies to extracellular epitopes of NR1/NR2 heteromers of the NMDA receptor. Patients with this syndrome may present as limbic encephalitis but more frequently manifest severe psychiatric symptoms, seizures, dyskinesias, autonomic instability or hypoventilation. In all, the study of these disorders provides a link between immunologic processes and neuronal events involved in memory, cognition, seizures, and neuronal degeneration.

(臨床神経, 48 : 871—874, 2008)

Key words : limbic encephalitis, paraneoplastic, non-paraneoplastic, antibodies

Introduction

The first description of limbic encephalitis is attributed to Brierley and colleagues who in 1960 reported 3 patients with "subacute encephalitis of later adult life, mainly affecting the limbic areas"; two of the patients had evidence of cancer (1 confirmed at autopsy) but the authors 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 used the term "limbic encephalitis" to describe 3 patients with severe short-term memory and dementia in association with bronchial carcinoma; all 3 patients had inflammatory and degenerative changes concentrated in the temporal parts of the limbic grey matter. These authors established for the first time a relationship between systemic cancer and limbic encephalitis. For the next 20 years, limbic encephalitis was considered a rare disorder that almost always occurred in association with cancer. In

the 80s and 90s, advances in neuroimaging and the discovery of several paraneoplastic antibodies facilitated the recognition of this disorder, suggesting that its frequency was underestimated. By the end of this period, several clinical-immunological associations were established (e.g., anti-Hu and small-cell lung cancer [SCLC], or anti-Ma2 and germ-cell tumors of the testis). These studies facilitated the identification of patients with similar syndromes but without paraneoplastic antibodies or tumors, or with "atypical" tumors. Studies have now shown that many of these patients do in fact have antibodies to neuronal cell surface antigens.

Classic Limbic Encephalitis

The classic syndrome of limbic encephalitis includes the rapid development of irritability, depression, sleep disturbances, seizures, hallucinations, and short-term memory loss. The subacute development, in days or weeks, of short-term memory deficits is considered the hallmark of the disorder.

The EEG is almost always abnormal, revealing foci of epileptic activity in one or both temporal lobes or focal or generalized slow activity.

In 80% of patients the CSF shows a mild to moderate lymphocytic pleocytosis, usually less than 100 white blood cells / μ l, increased protein concentration (usually < 150 mg/dl), normal glucose concentration, and frequently elevated IgG index and oligoclonal bands. Some patients, particularly those with antibodies to voltage gated potassium channels (VGKC), may have normal CSF or only mild inflammatory changes.

In 70-80% of patients with a typical syndrome of limbic encephalitis, with or without CSF inflammatory abnormalities, the MRI FLAIR/T2 sequences show unilateral or bilateral hyperintense signal in the medial aspect of the temporal lobes. Overall, the information provided by the combination of clinical, EEG, MRI, and routine CSF studies suggests the diagnosis of limbic encephalitis in most patients with a classic presentation of the syndrome.

After excluding a viral etiology, a problem that the physician confronts when initially examining a patient with suspected limbic encephalitis is to determine if the disorder is paraneoplastic or not. This difficulty stems from the fact that in 60-70% of paraneoplastic cases, the neurologic disorder precedes the detection of the tumor and conversely, a similar clinical picture, CSF, and MRI findings also occur without cancer association.

Cancer screening with CT of the chest, abdomen and pelvis, or body FDG-PET and paraneoplastic antibody testing are useful when they are positive, but in at least 40% of patients these tests are negative. Recent experience indicates that a substantial number of patients considered "antibody negative" do in fact have antibodies against novel autoantigens that are usually on the neuronal cell membrane.

Limbic encephalitis with antibodies to intracellular antigens

The main intracellular autoantigens related to immune mediated limbic encephalitis are Hu, Ma2, and less frequently CV2/CRMP5 and amphiphysin. Antibodies to these antigens may associate with a classic syndrome of limbic encephalitis, but each antibody has other characteristic neurologic associations and different underlying tumors. These antibodies associate with cytotoxic T cell mechanisms that are considered the main pathogenic effectors.

Anti-Hu: Patients with these antibodies may present with symptoms suggesting involvement of any part of the nervous system, including cerebral cortex (epilepsia partialis continua), limbic system, brainstem, cerebellum, spinal cord, dor-

sal root ganglia, autonomic ganglia and nerves. For those who present with symptoms of classic limbic encephalitis, the examination often reveals signs or symptoms related to dysfunction of other areas of the nervous system, mainly the dorsal root ganglia. Most patients have a history of smoking, and the associated tumor is a SCLC. About 50% of all patients with SCLC and limbic encephalitis develop anti-Hu antibodies. A study suggested that the neurologic prognosis is better for those who do not have anti-Hu antibodies.

In patients with anti-Hu antibodies, treatment of the tumor and immunotherapy targeting the T-cell response may result in symptom stabilization (or lack of progression to encephalomyelitis), but rarely improvement.

Anti-Ma2: These antibodies associate with an encephalitis that predominantly involves the limbic system, hypothalamus and brainstem. Symptoms include clinical features of classic limbic encephalitis, but some patients present with prominent excessive daytime sleepiness, narcolepsy, cataplexy, hyperphagia, and hypothalamic-pituitary hormonal deficits. Other patients develop a prominent hypokinetic syndrome and supranuclear gaze palsy that initially involves vertical gaze, but may evolve to extensive deficits, including horizontal gaze and nuclei of cranial nerves. Cerebellar dysfunction is not prominent in patients with antibodies limited to Ma2, but patients with both Ma1 and Ma2 antibodies may have cerebellar and brainstem dysfunction. The above constellation of symptoms may suggest the diagnosis of Whipple's disease.

In men younger than 50 years, anti-Ma2 encephalitis almost always associates with germ-cell tumors of the testis; in older men and women the most frequent tumors are non-SCLC and breast cancer.

Patients with germ-cell tumors of the testis and anti-Ma2 associated encephalitis often benefit from orchiectomy and immunotherapy that may include corticosteroids and IVIg. Overall, 35% of patients with anti-Ma2 encephalitis have neurologic improvement, most of them patients with testicular tumors.

Anti-CV2 or CRMP5: These antibodies occur in patients with paraneoplastic encephalitis associated with SCLC, thymoma, or less frequently other tumors. The development of isolated or classic limbic encephalitis is less frequent in these patients than in those with anti-Hu antibodies. The repertoire of symptoms associated with CV2 antibodies is ample and includes encephalomyelopathy, axonal sensorimotor neuropathy, and more distinctively chorea, uveitis and optic neuritis. Accordingly, the brain MRI findings are rarely limited to the medial temporal lobes. The involvement of frontostriatal and basal ganglia circuitry may result in personality change, obsessive-compulsive behavior, and cognitive defi-

cits.

Encephalitis with antibodies to cell membrane antigens

This is an increasingly recognized group of disorders, in which the associated antibodies likely have a pathogenic role. The main cell membrane antigens include VGKC, NMDAR, and unknown antigens predominantly expressed on the cell surface of neurons and their processes. When assessed by immunohistochemistry, these antibodies intensely immunolabel the neuropil of the hippocampus or cerebellum, with highly characteristic patterns that depend on the target antigen.

Encephalitis associated with VGKC antibodies

In our experience, the encephalitis associated with VGKC antibodies constitutes approximately 30% of all autoimmune encephalitis with antibodies to cell membrane antigens. The two main syndromes include a classic picture of limbic encephalitis, and a less focal encephalitis that associates with psychiatric symptoms, hallucinations, sleep dysfunction, and symptoms of peripheral nerve hyperexcitability (Morvan's syndrome). Hyponatremia is common in both of these syndromes. A review of the literature shows that about 30% of patients with encephalitis associated with VGKC antibodies had an underlying tumor; this frequency decreases to 20% if only thymomas and SCLC are considered.

Brain MRI usually shows FLAIR hyperintensity in the medial temporal lobes; these findings can be asymmetric and rarely enhance with contrast. Compared with other types of limbic encephalitis, the CSF of patients with VGKC antibodies is frequently normal or shows minimal pleocytosis and elevated proteins; in some patients only oligoclonal bands are identified.

The treatment of encephalitis associated with VGKC antibodies includes corticosteroids, removal of antibodies with plasma exchange, and immunomodulation with IVIg. About 80% of patients respond to these treatments. The REM sleep disorders that some patients develop usually resolve along with the improvement of other symptoms.

Encephalitis associated with antibodies to NMDAR

This disorder predominantly affects young women and presents as a complex syndrome that evolves through several stages: prodromal symptoms, psychotic stage, unresponsiveness with hypoventilation, autonomic instability and dyskinesias, and eventual recovery or death. About 60% of patients have a pelvic cyst (dermoid or teratoma of the ovary) that may initially be overlooked or considered unrelated to the neurological symptoms.

The most frequent clinical scenario is a young woman who a few days after a flu-like illness (fever, headache, malaise, or

fatigue), develops anxiety, and mood and affective disorders progressing to severe behavioral and personality disturbances, delusional or disorganized thinking, paranoid ideation, and hallucinations. Patients are usually first seen by psychiatrists or admitted to psychiatric wards with the diagnosis of acute psychosis or schizophrenia. At this stage or later, patients may remain with eyes open, unresponsive to visual threats, mute or mumbling unintelligible words, with increased muscle tone, and dystonic or cataleptic postures resembling a catatonic state. This clinical picture often associates with seizures and decline of the level of consciousness, central hypoventilation, autonomic instability, and dyskinesias. The autonomic instability may include intense fluctuation of blood pressure and temperature, tachycardia, bradycardia, cardiac pauses, and diaphoresis. The dyskinesias almost always start in the face and mouth, manifesting as orofacial movements, clenching of the teeth, dystonia, and may associate with rhythmic contractions of abdominal muscles, and complex movements of the extremities. These dyskinesias do not have epileptic correlates in EEG monitoring, which usually shows diffuse delta-theta activity.

MRI of the brain is usually normal or shows non-focal abnormalities at the initial stages of the disorder. These may include cerebral or cerebellar cortical FLAIR abnormalities, sometimes with subtle or transient meningeal enhancement. About 25% of patients have medial temporal lobe abnormalities similar to those of classic limbic encephalitis. The CSF frequently shows lymphocytic pleocytosis and increased protein concentration.

If the disorder is not recognized, patients may remain ventilated for several months in a state resembling catatonia. Prompt identification of the disorder, associated with tumor removal and immunotherapy appear to substantially shorten the time of intensive care support. Immunotherapy may include corticosteroids, plasma exchange, IVIg, and sometimes cyclophosphamide and rituximab. In our experience, patients usually start to gradually improve within 2-3 weeks of tumor removal and immunotherapy. Patients that require intensive care support may start to improve while receiving immunotherapy, allowing removal of the tumor. In other instances, corticosteroids, plasma exchange or IVIg do not appear to have any effect until the tumor is removed. Recent studies show that the disorder can also affect men and children.

The diagnosis of this disorder has been facilitated by the demonstration of antibodies to NMDAR in patients' sera and CSF. These antibodies target extracellular epitopes contained in NR1/NR2 heteromers of the NMDAR; antibody reactivity is totally dependant on the presence of NR1. Therefore, these antibodies are different from those reported against the GluR ϵ 2 or NR2B subunit of the NMDAR that

have been described in several other disorders, including epilepsy partialis continua, Rasmussen's encephalitis, and stroke.

Encephalitis associated with antibodies to other cell membrane antigens

In addition to antibodies against VGKC and NMDAR, there is an emerging group of patients who develop classic limbic encephalitis, but are negative for all known antibodies. A substantial number of these patients have in fact antibodies to unknown antigens that are highly expressed in the neuropil of the hippocampus and cerebellum, targeting epitopes that appear to be extracellular. At this time it is unclear whether the number of antigens is limited to a few or many. The detection of this class of neuronal cell surface-reacting antibodies supports the use of immunotherapy, and carries a better prognosis for neurological improvement than when antibodies to intracellular antigens are detected.

Among 16 patients with limbic encephalitis associated with these antibodies, 7 had no tumors and 9 had tumors including 2 carcinoma of the thymus, 3 lung cancer (2 SCLC), 1 thymoma, 1 ovarian fibrothecoma, 1 melanoma, and 1 Hodgkin's lymphoma. Treatment of the tumor, corticosteroids, plasma exchange or IVIg often resulted in neurologic improvement.

General considerations and treatment implications

For all autoimmune encephalitides, paraneoplastic or not, the exact mechanisms of neuronal dysfunction are unknown. However, clinical experience, neuropathological studies, and analysis of the response to treatment suggest two groups of immune mediated mechanisms that segregate according to the location of the antigens: 1) The encephalitides predominantly mediated by cytotoxic T-cell mechanisms, that include those related to intracellular antigens (Hu, CV2/CRMP5, Ma2, amphiphysin, Ri), and 2) the encephalitides predominantly mediated by antibodies, that include those related to cell membrane or extracellular antigens (NMDAR, unknown neuropil antigens, and VGKC). While disorders of the first group associate with cancer (lung, testis, breast), brain infiltrates of cytotoxic T-cells, and limited response to treatment, the disorders of the second group associate less frequently with cancer (teratoma, thymoma), have less frequent brain inflammatory infiltrates, and respond significantly better to immunotherapy.

When a tumor is found in association with a possible paraneoplastic disorder, removal of the tumor is critical for neurological improvement or stabilization of symptoms. However, most limbic encephalitides related to intracellular antigens do not improve, and at best stabilize, after tumor removal and immunotherapy. For these disorders the optimal immunotherapy is unknown. There are anecdotal cases of patients that improved with tumor removal, corticosteroids, IVIg or plasma exchange, but the effects of these treatments on the cytotoxic T-cell immune response are limited. Our experience and that of others suggest that cyclophosphamide may be effective in some patients. Although theoretically other T-cell immunotherapies could be effective, there is no experience of treating autoimmune limbic encephalitis with tacrolimus, cyclosporine, or mycophenolate mofetil. A recent study assessing the effects of rituximab showed limited efficacy for paraneoplastic syndromes related to intracellular autoantigens.

In contrast, the encephalitides related to cell membrane antigens are significantly more responsive to immunotherapy (IVIg, plasma exchange, corticosteroids, cyclophosphamide, rituximab). Some of these patients may respond to immunotherapy even before the tumor is treated; however, control of the tumor appears to be required for faster improvement or to attain full recovery.

Recommended Readings

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