AUTOIMMUNE ENCEPHALITIS – THE CELL SURFACE AND SYNAPTIC ANTIBODIES

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Encephalitis
The term encephalitis refers to an inflammatory disorder of the brain of many possible etiologies and a complex differential diagnosis. The manifestations are multiple, including alterations of memory, behavior, cognition, decreased level of consciousness, focal deficits, seizures and dementia. In centers dedicated to the study of the etiology and epidemiology of encephalitis, about 65% of patients remain without a specific diagnosis after all studies are completed. The implications are important because irreversible deficits and mortality are high. In recent years, the discovery that neuronal antibody-associated encephalitis do not only occur in patients with cancer, but also in patients without cancer and that some of these patients have antibodies against cell surface proteins has had multiple implications. First, it has led to a rapid discovery of new forms of encephalitis that have different manifestations and were previously not even suspected to be immune-mediated. Indeed, deficits of memory, behavior, cognition, catatonia, psychosis, abnormal movements, or seizures previously considered “idiopathic” or suspected to be “post-infectious” are now known to be immune-mediated. Second, it has resulted in the identification of antibodies against an expanding group of neuronal cell surface proteins and synaptic receptors, some of which define new syndromes, and third, it has shown that these forms of encephalitis affect children and adults, may occur with or without cancer, and are responsive to treatment.

Anti-NMDA receptor and other autoimmune encephalitis
The incidence of anti-NMDAR encephalitis is not well known (estimated ~2-3/10^6 habitants) although recent studies indicate that it is the second most common autoimmune encephalitis after ADEM, and in centers focused on encephalitis, it has been found to be more frequent than any single type of viral encephalitis. The frequency of an underlying tumor (usually a teratoma) varies according to age, gender and ethnicity. The younger the patient the less likely to have an underlying tumor; however, in women 12-45 year-old the frequency of ovarian teratoma is close to 50%. In a recent study of 577 patients only 12 men were older than 45 years; 3 of them had an underlying tumor (25%). Boys and young men rarely have an associated tumor. Based in the same series, the median age is 21 years: the youngest patient so far identified is 2 months old. Patients develop a highly predictable syndrome that usually presents with prodromal symptoms, such as headache and hyperthermia, and progresses in a few days to change of behavior and psychosis, anxiety, sleep dysfunction (usually insomnia), memory deficit, seizures, decreased level of consciousness, abnormal movements and autonomic instability, often requiring ventilator support. The syndrome usually responds to immunotherapy and removal of the tumor when appropriate (see below). The recovery is slow; it may take more than 18 months to fully recover. Complete recovery or substantial improvement occurs in 80% of the patients. In rare instances, anti-NMDAR encephalitis overlaps with demyelinating disorders, representing a co-existence of two independent disorders rather than a change or widening of the spectrum of symptoms.

In anti-NMDAR encephalitis, the clinical presentation varies according to age. In children, the predominant initial symptoms include, seizures, abnormal movements, or altered behavior; in teenagers and young adults, abnormal behavior and psychosis, and in patients older than 45 years, memory deficits and abnormal behavior. A study showed that young male patients often have seizures as first symptom presentation. Other disorders related to antibodies against neuronal cell-surface proteins do not define new clinical syndromes, but represent different immune responses causing known or poorly defined syndromes. As an example of a well-defined syndrome, antibodies to LGI1, GABA(B) receptor, and AMPA receptor all associate with limbic encephalitis, but they differ in one or more of the following: patients’ age, sex, frequency and type of tumor association, and other co-morbidities (e.g., patients with LGI1 antibodies often develop prodromal faciobrachial dystonic seizures, hyponatremia, and rarely have an underlying tumor, whereas patients with GABA(B) receptor antibodies develop early and refractory seizures and approximately 50% have small-cell lung cancer.

Table 1 summarizes all autoimmune encephalitis (including cerebellar disorders) that occur in association with antibodies against neuronal cell-surface and synaptic proteins. We have included amphiphysin-associated...
disorders because there is some evidence that the antibodies can directly interact with amphiphysin during synaptic vesicle endocytosis.\textsuperscript{12}

Table 1: Main antigens and syndromes in autoimmune encephalitis

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Presenting symptoms</th>
<th>Main Syndrome, other features</th>
<th>Cancer frequency</th>
<th>Cancer type</th>
</tr>
</thead>
<tbody>
<tr>
<td>NMDA receptor</td>
<td>Psychiatric (adults); seizures, dyskinesias (children)</td>
<td>NMDA receptor encephalitis\textsuperscript{10-12}</td>
<td>Overall 40%; up to 58% in women 18-45 years</td>
<td>Teratoma*</td>
</tr>
<tr>
<td>AMPA receptor</td>
<td>Memory loss, confusion</td>
<td>Limbic encephalitis\textsuperscript{13-14}</td>
<td>65%</td>
<td>Thymoma, SCLC, other</td>
</tr>
<tr>
<td>GABAb receptor</td>
<td>Memory loss, seizures</td>
<td>Limbic encephalitis with early and prominent seizures\textsuperscript{15-17}</td>
<td>50%</td>
<td>SCLC</td>
</tr>
<tr>
<td>LGI1</td>
<td>FBD seizures, memory deficits</td>
<td>Limbic encephalitis, frequent hiponatremia, HLA susceptibility\textsuperscript{18,19}</td>
<td>5-10%</td>
<td>Thymoma</td>
</tr>
<tr>
<td>CASPR2</td>
<td>Cognitive dysfunction, seizures, neuropathic pain, neumyotonia, cerebellar</td>
<td>Morvan; limbic encephalitis\textsuperscript{20-22}</td>
<td>Overall 20%. In Morvan (20-50%)</td>
<td>Thymoma**</td>
</tr>
<tr>
<td>GABAa receptor</td>
<td>Seizures, confusion</td>
<td>Encephalitis with refractory seizures, status epilepticus. Multifocal cortical-subcortical FLAIR-MRI abnormalities\textsuperscript{23,24}</td>
<td>25%</td>
<td>Thymoma, other</td>
</tr>
<tr>
<td>DPPX</td>
<td>Diarrhea, GI symptoms, loss of weight.</td>
<td>Encephalitis, hyperekplexia\textsuperscript{25-27}</td>
<td>&lt;10%</td>
<td>Lymphoma</td>
</tr>
<tr>
<td>Dopamine-2 receptor</td>
<td>lethargy, movement disorder, psychosis, agitation, ataxia</td>
<td>Basal ganglia encephalitis (dystonia, parkinsonism, chorea, oculogyric crisis)\textsuperscript{28}</td>
<td>0%</td>
<td>n/a.</td>
</tr>
<tr>
<td>mGluR5</td>
<td>Memory loss, confusion</td>
<td>Encephalitis\textsuperscript{29}</td>
<td>A few cases described</td>
<td>Hodgkin disease</td>
</tr>
<tr>
<td>Neurexin-3α</td>
<td>Confusion, seizures</td>
<td>Encephalitis\textsuperscript{30}</td>
<td>0%</td>
<td>n/a.</td>
</tr>
<tr>
<td>IgLON5</td>
<td>Parasomnia, sleep breathing difficulty; bulbar syndrome, PSP-like; cognitive decline, chorea</td>
<td>NREM and REM sleep disorder, and brainstem dysfunction; HLA susceptibility\textsuperscript{31,32}</td>
<td>0%</td>
<td>n/a.</td>
</tr>
<tr>
<td>DNER (Tr)</td>
<td>Gait instability</td>
<td>Cerebellar ataxia\textsuperscript{33,34}</td>
<td>&gt;90%</td>
<td>Hodgkin</td>
</tr>
<tr>
<td>mGluR1</td>
<td>Gait instability</td>
<td>Cerebellar ataxia\textsuperscript{35,36}</td>
<td>n/a</td>
<td>Hodgkin</td>
</tr>
<tr>
<td>Glycine receptor</td>
<td>Muscle rigidity, spasms</td>
<td>PERM, stiff-person syndrome, encephalitis\textsuperscript{37,38}</td>
<td>&lt;5%</td>
<td>Thymoma, lung, Hodgkin</td>
</tr>
<tr>
<td>Amphiphysin</td>
<td>Rigidity, spasms</td>
<td>Stiff-person, encephalitis\textsuperscript{39}</td>
<td>&gt;90%</td>
<td>Breast, SCLC</td>
</tr>
</tbody>
</table>

*The association with teratoma is sex and age-dependent. While young adult females frequently have an ovarian teratoma, the presence of a tumor is uncommon in children or young adult males.\textsuperscript{8}

**Patients with Caspr2 antibodies and Morvan syndrome are more likely to have thymoma than those without Morvan syndrome.\textsuperscript{21,40}

NMDA, N-methyl-D-aspartate; AMPA, alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid; GABAb, gamma-aminobutyric acid type B; LGI1, leucine-rich glioma inactivated 1; CASPR2, connectin-associated protein 2; GABAa, gamma-aminobutyric acid type A; DPPX, dipeptidyl-peptidase-like protein; mGluR, metabotropic glutamate receptor; DNER, delta/notch-like epidermal growth factor-related receptor; VGCC, voltage-gated calcium channel; Gly, glycine; REM, rapid-eye movement; NREM, non rapid-eye movement; PERM, progressive encephalomyelitis with myoclonus; GI: gastrointestinal; SCLC: small-cell lung cancer.
The identification of these disorders has helped to establish the immune etiology of previously ill-defined disorders, such as some forms of “encephalitis lethargica”, “choreathetosis post-HSV encephalitis” in children, and cognitive and psychiatric alterations post-HSV encephalitis in adults. For additional information on the clinical recognition and differential diagnosis of autoimmune encephalitis see

New pathogenic mechanisms

The syndromes associated to most autoantibodies against cell surface or synaptic antigens show close similarity to the phenotypes of animal models in which the antigens have been altered genetically or pharmacologically. This and the fact that patients often improve after immunotherapy suggest that the antibodies play an important pathogenic role. Moreover, in some disorders such as anti-NMDA receptor, AMPA receptor, GABAA receptor, DPPX, or neurexin 3α encephalitis, the antibodies alter the levels or function of the corresponding target in *in vitro* or *in vivo* models; this effect correlates with the titer of antibodies, and is reversible upon removing the antibodies (Table 1). Although the IgG subtypes of some antibodies are able to fix complement, this mechanism does not appear to play a relevant role in these diseases.

New treatment strategies and response to treatment

Approximately 70-80% of patients with encephalitis associated to antibodies against cell surface or synaptic proteins respond to treatment; in the other 20-30% (depending on the disease) the responses to treatment are limited or absent. Disorders associated with amphiphysin or DNER (Tr) antibodies are less responsive to treatment.

An important concept is that the immune targets of these disorders are located behind the blood-brain-barrier and that many patients have intrathecal synthesis of antibodies by plasma cells within the brain and meninges. Therefore, a treatment approach recently proposed is the use of two levels of immunotherapy, including steroids, IVlg, and/or plasma exchange (first line), and rituximab and/or cyclophosphamide (second line). IVlg and plasma exchange would eliminate circulating blood antibodies, while rituximab would eliminate B cells reducing their role as antigen presenting cells and preventing the subsequent development of plasma cells (see Figure 3 in )

Steroids and cyclophosphamide would decrease the inflammatory infiltrates and production of pro-inflammatory cytokines. In a cohort of 577 patients with anti-NMDAR encephalitis, about 50% responded to first line immunotherapies (and tumor removal when appropriate). Among the 50% of patients who did not respond to first line therapy, those who received second line immunotherapy had better outcomes than those who did not.

Prognostic factors of good outcome included, prompt immunotherapy and no need of admission to ICU. The number of relapses was decreased by prompt use of immunotherapy, and second line immunotherapy.

A novel concept that emerges from the study of these forms of autoimmune encephalitis is that patients who are comatose for weeks or months can still fully recover. The duration of symptoms (speed of improvement) and degree of recovery are different among disorders and among patients with a specific syndrome. For example, although patients with limbic encephalitis and LGI1 antibodies usually improve faster than patients with anti-NMDAR encephalitis, their outcome at 2 years does not appear to be better. In a recent study on anti-LGI1 encephalitis, only 35% had fully recovered 2 years after disease onset. In contrast, patients with anti-NMDAR encephalitis often develop more severe symptoms, requiring longer hospitalizations, but eventually 80% have full or substantial recoveries and return to their activities. On the other hand, young adult patients with anti-NMDAR encephalitis recover better than older patients (81% versus 64% had good outcome after 2 years follow-up in the study noted above).

Remaining questions and new problems

The 4 most frequent questions raised by clinicians are, 1) when to suspect these disorders, 2) how to diagnose them, 3) how to treat them, and 4) when to stop treatment. Current experience suggests that any rapidly progressive encephalopathy of unclear etiology, particularly if accompanied by inflammatory CSF findings (although these could be absent), and multifocal symptoms with or without MRI changes should raise suspicion of an immune mediated process. FLAIR-T2 MRI abnormalities (without substantial enhancement) involving medial temporal lobes occur frequently in patients with typical limbic encephalitis, and should increase the suspicion of an immune mediated process, keeping in mind that the MRI findings could be the result of seizures. A comprehensive clinical approach to the diagnosis of autoimmune encephalitis has recently been published.

The diagnosis of autoimmune encephalitis is confirmed by demonstration of antibodies in serum and CSF. Antibodies may be detectable only in CSF depending on the stage of the disease and treatments. Analysis of CSF is particularly important if results of serum testing do not fit with the syndrome; in some of these patients re-testing for antibodies in CSF and serum shows that the initial serum test was misinterpreted.

The treatment should be based on the type of syndrome and immune response. All encephalitis with antibodies against cell surface or synaptic proteins should be treated with immunotherapy and removal of the associate

tumor, if appropriate. Current experience suggests starting with first line immunotherapies (e.g., steroids and IVlg or plasma exchange) and proceeding to second line immunotherapy if there is no response in 2-3 weeks. The efficacy of rituximab in anti-NMDAR encephalitis (reducing also the number of relapses) has led to increasingly use this treatment as part of the first line immunotherapies. One should keep in mind that except for anti-NMDAR encephalitis, the efficacy of second line immunotherapy has not yet been demonstrated in other autoimmune encephalitis (only anecdotal cases reported). The type of tumor screening, extent of tumor search, and frequency of screening varies with the disorder (Table 1) and with patient’s age. An outstanding question is when to stop the treatment. This is particularly pertinent to patients with very slow improvement. Current experience suggests giving preference to the clinical assessment rather than antibody titers. Follow-up of titers may help in cases of suspected clinical relapses; to ascertain if patients with a prolonged clinical course and limited improvement have active disease or a burned out process, and to monitor whether a specific treatment results in a progressive decrease of antibody titers. However, we have found that frequent monitoring of titers has limited utility. Given that antibodies may remain detectable in serum and CSF long after patient’s recovery, continuation or discontinuation of immunotherapy should rely on clinical judgment. Finally, two problems have recently emerged; First, the simplification of diagnostic tests leading to false positive or negative results. These false results can be avoided or substantially reduced by testing CSF (or serum and CSF), instead of serum alone. As recently shown, any test result that does not fit with the described syndrome should be confirmed using CSF or by a research laboratory.

The second problem relates to the appearance of many different disorders reported with antibodies against “VGKC-complex proteins”. There are 3 concepts that should be kept in mind when a patient is diagnosed with “VGKC-complex antibodies”, 1) the target antigens are not the VGKC, 2) the two known targets are LGI1 and Caspr2, and each associates with well-characterized syndromes, and 3) when the antibodies do not react with LGI1 or Caspr2, the clinical significance is unclear given that the syndromes many not even be immune mediated, and such VGKC-complex antibodies can be found in normal subjects. A recent study suggests that VGKC-complex antibodies (negative for LGI1 and Caspr2 antibodies) have no clinical value.

Reference List

