DIAGNOSIS AND MANAGEMENT OF PARANEOPLASTIC SYNDROMES

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During the last 40 years there have been 3 waves of interest for paraneoplastic neurological disorders.[1] The first occurred in the 1950-1960s with the initial clinical and pathological descriptions of some syndromes. Afterwards, interest for these syndromes waned until the 1980-1990s when specific neuronal antibodies and cytotoxic T-cell mechanisms against intracellular antigens were identified allowing for the development of diagnostic tests and suggesting pathogenic mechanisms. Recently, the identification of a group of disorders that can occur as paraneoplastic or non-paraneoplastic syndromes and associate to antibodies against cell surface or synaptic proteins has resulted in a new surge of interest.[2] The discovery of these disorders has expanded the field far beyond the concept of rare but intriguing syndromes. It has changed the clinical approach to patients of all ages affected by a wide variety of neuropsychiatric symptoms, and shifted paradigms in the understanding of how autoimmunity affects synaptic function, memory, and behavior. This presentation focuses in the change of concepts, contrasting the classical paraneoplastic syndromes with the recently described syndromes in which the autoantigens are on the cell surface.

1) Intracellular versus cell surface antigens: a paradigm change in paraneoplastic and CNS autoimmunity with important clinical implications

While classical paraneoplastic syndromes related to intracellular antigens tend to affect older individuals, almost always associate with cancer, and show limited response to treatment, some of the disorders related to cell surface antigens predominantly affect young individuals and children, may occur without cancer, and frequently respond to immunotherapy.[3] Moreover, classical paraneoplastic syndromes are usually monophasic while some of the new disorders show tendency to relapse with or without tumor recurrence. The contrast between these disorders is shown in Table 1 which also includes a third group with mixed clinical features where the antigens are intracellular synaptic proteins (reviewed in[4]).

Most of the novel cell surface antigens are well known proteins and receptors involved in synaptic transmission, plasticity, and neuronal excitability. Consequently, immune-mediated dysfunction of these proteins results in prominent neuropsychiatric symptoms, such as catatonia, psychosis, seizures, movement disorders, and rapidly progressive memory loss or dementia. Reports of patients who recovered after being comatose for several months has led to consider testing for these disorders and if positive, using immunotherapy and prolonged intensive care support in cases that otherwise would have been considered futile.[5, 6]

The clues that suggested that many of these syndromes were immune mediated came from establishing a link between a clinical phenotype, the presence of CSF or MRI abnormalities consistent with an inflammatory process, and the demonstration of serum or CSF antibodies that reacted with the neuropil of brain and cell surface of live neurons (indicating that the epitopes are extracellular). The identity of the antigens was subsequently established by direct precipitation of neuronal proteins using patient's serum or CSF,[2, 7 8] or a systematic screening of candidate antigens selected according to patient's symptoms.[9] Similar approaches have been recently used to identify the Delta/Notch-like epidermal growth factor-related receptor (DNER) as the target of Tr antibodies in patients with cerebellar degeneration and Hodgkin's lymphoma.[10]

2) Two examples of novel syndromes: Anti-NMDAR encephalitis and limbic encephalitis

Anti-NMDAR encephalitis

Since the description of anti-NMDAR encephalitis in 2007,[11] this disorder has become one of the most frequent and best characterized autoimmune encephalitis. The syndrome usually develops with a sequential presentation of symptoms, including prodromal symptoms (headache, fever) followed by behavioral changes, psychosis, sleep dysfunction (mainly insomnia), catatonia, decrease level of consciousness, dyskinesias, and autonomic instability which may require ventilatory support. Seizures can occur at any stage but most commonly occur early. A recent report of 577 patients showed that in most the spectrum of symptoms is similar to that previously reported (less than 4% had mono-symptomatic disease), although the first presenting symptom varies between children and adults.[5] While delusions, hallucinations, bizarre behavior and psychosis are frequent early symptoms in adults, abnormal movements, seizures, and focal or sensory deficits are the most common presenting symptoms in children. The clinical picture subsequently progresses as indicated above, but in children mechanical ventilation is less frequently required. The same study demonstrated that rituximab and cyclophosphamide were often effective when first line of therapies (corticosteroids, IVIg, or plasma exchange) had failed.

Limbic encephalitis

The term limbic encephalitis refers to an inflammatory or autoimmune process predominantly involving the limbic system. It may result from paraneoplastic immunological mechanisms in which the antigens are intracellular (Hu, Ma2, rarely amphiphysin) or from autoimmune disorders against cell surface antigens (LGI1, GABA(B) receptor, AMPAR, mGluR5, and rarely Caspr2). The novel aspect in the latter group, is the identification of GABA(B) receptor antibodies as the most common cause of paraneoplastic limbic encephalitis in patients with SCLC that are Hu antibody negative. This is important because GABA(B) receptor antibody-associated limbic encephalitis is more responsive to treatment than that associated to Hu antibodies (reviewed in[2]).

Some antibodies against intracellular neuronal antigens do not necessarily associate with cancer. In a study of 121 patients with GAD65-antibody associated syndromes, 15 (12%) fulfilled criteria of paraneoplastic syndromes (including among other limbic encephalitis). The risk for cancer increased with age, male sex, and the presence of coexisting neuronal cell-surface antibodies.[12] Another neuronal-specific antibody that associates with non-paraneoplastic limbic encephalitis is directed against adenylate kinase 5 (AK5). This disorder is clinically similar to the paraneoplastic form of limbic encephalitis (although the patients do not have cancer) and is refractory to treatment.[13, 14]

Table 1: Intracellular versus cell surface antigens

	Intracellular, onconeuronal antigen	**Intracellular, synaptic antigen**	**Cell surface or synaptic receptor**
Antigens	Hu, CRMP5, Ri, Yo, Ma2	GAD, amphiphysin	NMDAR, AMPAR, GABA(B)R, GABA(A)R, LGI1, Caspr2, GlyR, DPPX, IgLON5
Age	Predominantly older individuals	Usually adults	All ages, some syndromes predominate in children
Tumor association	Yes	Varies with antigen	Varies with antigen, and age. GABA(B)R>AMPAR>NMDAR> Caspr2. Infrequent tumor: LGI1, GlyR, GABA(A)R.
Function of the antigen	Unclear for many antigens	Known	Known
Relation syndrome-antigen function	No	Yes	Yes
Main pathogenic mechanism	Cytotoxic T-cells, antibodies (?)	Cytotoxic T-cells and antibodies	Antibodies
Response to treatment	Only 10-30% had mild response	~60% have partial improvement	Substantial or full recoveries in ~75-80%
Relapses	Infrequent (usually monophasic and irreversible)	Infrequent (symptoms may fluctuate)	Varies with antigen (10-25%)

3) Antibody tests, interpretation, and caveats

The epitopes of classical intracellular or onconeuronal antigens (Hu, Yo, Ri, CRMP5, Ma2, amphiphysin) are linear, resistant to protein denaturation, and therefore the antibodies can be detected by immunoblot or ELISA, as well as immunohistochemistry using mammalian brain, most commonly rat or mouse. These antibodies are almost always detectable in both serum and CSF.

In contrast, most antibodies to cell surface or synaptic proteins are directed against conformational epitopes, and the reactivity is usually lost when the antigen is denatured so that these antibodies cannot be detected by standard immunoblot. Rather, detection of these antibodies requires either an immunohistochemistry protocol adapted to cell surface antigens, the use of cultures of live neurons, or cell-based assays in which recombinant antigens are expressed in mammalian cells (reviewed in[15]).

In many patients with encephalitis related to antibodies against cell surface or synaptic proteins the antibodies are not only synthesized systemically but also within the CNS, as demonstrated by the frequent detection of intrathecal synthesis of antibodies and the presence of plasma cells in brain or meninges.[16] Therefore, there are several caveats regarding the interpretation of antibody titers in these disorders. First, serum titers may fluctuate without accurately reflecting the activity of the disease in the CNS. These fluctuations are often caused by plasma exchange or IVIg that efficiently reduce antibody levels in serum but not CSF. Second, in patients with chronic active disease, serum antibodies can be negative while CSF antibodies remain elevated.[17] Third, patients who have recovered from the encephalitis may have detectable antibodies in serum, and even CSF, during months or years although the titers are usually lower than those identified during the active phase of the disease. Therefore, for initial and follow-up measurement of titers, the best approach for all antibodies to cell surface or synaptic proteins is to examine both, serum and CSF.

Analysis of antibody titers can be useful in several clinical settings, such as determining the effects of treatment, if the reappearance of symptoms represents a relapse, or if chronic symptoms are due to active disease (persistently elevated titers) or a burned out process (low or absent antibody titers). Decisions about treatment should be based on clinical assessment, not only the antibody titers.[15]

Implications and the value of the clinical examination

An overall implication of the recent advances discussed here is that antibody testing does not replace clinical evaluation. The new scoring system to predict paraneoplastic LEMS is an example of the importance of the clinical examination.[18] Moreover, most paraneoplastic neuropathies do not associate with antibodies and therefore, the diagnosis depends on clinical suspicion and exclusion of other etiologies.

The clinical evaluation and diagnostic tests for classical paraneoplastic syndromes of the CNS have not changed substantially in the last 10 years. The approach to treatment is also similar; that is, the major concern should be in identifying the tumor and treating it promptly; in general, immunotherapy has a limited effect, although if patients are diagnosed early and immunotherapy is directed against T-cell mechanisms some patients do significantly improve.

As far as the novel disorders associated to antibodies against cell surface antigens is concerned, one needs to appropriately integrate the immunologic findings with the clinical assessment.[15] If a well-known antibody is identified in a patient whose clinical picture that does not match the expected syndrome, particularly if the antibody is only detected in serum, re-evaluation of serum and CSF is strongly recommended. Recognition of these disorders is very important because 1) some are frequent, 2) the phenotypes can be identical to those of classical paraneoplastic syndromes, but in contrast they are treatment responsive. For example, if a patient with SCLC develops limbic encephalitis, the etiology could be related to Hu-immune mechanisms, which means cytotoxic T cell mechanisms and with limited response to treatment, or GABA(B) receptor antibodies, which means, antibody-mediated and highly responsive to treatment.[19]

The focus of the treatment should be the clinical picture and not the antibody titers.[15] The paradigm is similar to other antibody-mediated disorders, such as myasthenia gravis or LEMS, where patients may fully recover but still have detectable antibodies in serum. However, in paraneoplastic or autoimmune encephalitis the target organ is behind the blood-brain-barrier, and in many of these disorders the antibodies are synthesized in the CNS by long lived plasma cells.[20] The understanding of these concepts is critical, otherwise treatment approaches to down regulate the immune response in the CNS are not considered, resulting in delayed recoveries and suboptimal outcomes.

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