Paraneoplastic syndromes and autoimmune encephalitis

Five new things

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Summary

We review novel findings in paraneoplastic syndromes including the Lambert-Eaton myasthenic syndrome, and then focus on the novel disorders associated with antibodies against cell surface antigens, discussing the importance and caveats of antibody testing, and providing an algorithm for interpretation of results. In anti-NMDAR encephalitis 2 novel findings include the recognition of a characteristic EEG pattern (“extreme delta brush”) in 30% of patients and the demonstration of a fronto-temporo-occipital gradient of glucose metabolism that correlates with disease activity. In limbic encephalitis, antibodies to GABA(B) receptor are the most frequently detected in patients with small-cell lung cancer who are anti-Hu negative, and antibodies to mGluR5 distinctively associate with Hodgkin lymphoma (Ophelia syndrome). We also address the syndromes associated with “VGKC-complex antibodies,” a problematic term that groups well-characterized immune-mediated disorders (LGI1, Caspr2) with others that lack syndrome specificity, are less responsive to treatment, and for which the target antigens are unknown.

During the last 40 years there have been 3 waves of interest in paraneoplastic neurologic disorders. The first occurred in the 1950s–1960s with the initial clinical and pathologic descriptions of some syndromes. Afterwards, interest in these syndromes waned until the 1980s–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. The identification of

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disorders that can occur as paraneoplastic or nonparaneoplastic syndromes and associate to antibodies against cell surface or synaptic proteins has resulted in a recent surge of interest. 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 review focuses on 5 new findings related to classical paraneoplastic syndromes and this novel group of disorders.

New findings in classical paraneoplastic syndromes

A clinically relevant finding on paraneoplastic syndromes relates to the Lambert-Eaton myasthenic syndrome (LEMS). A Dutch-English cooperative study examined 219 patients with LEMS with the goal of developing and validating a score that would identify those cases that were paraneoplastic.¹ The multivariate analysis identified age, smoking, weight loss, Karnofsky Performance Status, bulbar symptoms, and male sexual impotence as independent predictors for an associated small-cell lung cancer (SCLC). Based on these findings, a 0–6 scoring system was developed; the probability of having SCLC was over 90% in patients with a score of 3 or higher, 30% with a score of 2, and less than 2% with a score of 0 or 1.

Paraneoplastic myelopathy usually occurs in the context of widespread involvement of the CNS, named encephalomyelitis. A recent study described 31 patients who developed a rapidly progressive paraneoplastic myelopathy. The spine MRI demonstrated that 65% of the patients had T2 signal abnormalities that extended more than 3 segments and symmetrically involved the gray matter or spinal tracts, sometimes with contrast enhancement. SCLC and breast cancer were the most frequently associated tumors, and amphiphysin and CRMP5 the most common antibodies. The response to treatment was poor; only 3 of 26 treated patients had a good recovery.²

Paraneoplastic brainstem encephalitis occurs in three settings. Patients with Ma2 antibodies develop predominant upper brainstem involvement (hypokinesia, vertical gaze paresis) that may progress rostro-caudally. Patients with Hu antibodies present with involvement of the medulla that may progress rostrally, and can result in central hypoventilation. Patients with Ri antibodies develop opsoclonus, ataxia, and sometimes extrapyramidal rigidity. A new study indicated that patients with Ri antibodies may have jaw dystonia that interferes with mouth opening and nutrition, and episodic laryngospasm that may result in respiratory distress and death.³ Recognition of these complications is important because treatment with botulinum toxin may alleviate some symptoms.

Intracellular vs cell surface antigens: A paradigm change in CNS autoimmunity

The discovery of CNS disorders associated with antibodies against cell surface or synaptic proteins has radically changed concepts about CNS autoimmunity. 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. The contrast between these disorders is shown in the table, which also includes a third group with mixed clinical features where the antigens are intracellular synaptic proteins (reviewed in reference 4).

Table Intracellular vs cell surface antigens

	Intracellular, onconeural antigen	Intracellular, synaptic antigen	Cell surface or synaptic receptor
Antigens	Hu, CRMP5, Ri, Yo, Ma2	GAD, amphiphysin	NMDAR, AMPAR, GABA(B)R, LGI1, Caspr2, GlyR
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>Caspr2>NMDAR>LGI1>GlyR
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	Only ~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%)

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.

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, or a systematic screening of candidate antigens selected according to patient's symptoms. 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 lymphoma,⁵ and the dopamine receptor (D1, D2) as autoantigen of nonparaneoplastic chorea and other neuropsychiatric disorders.⁶

Antibody tests and titers

The epitopes of classical intracellular or onconeural 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 or ELISA. 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

Figure 1 Algorithm for interpretation of antibody tests

Most patients with disorders associated with antibodies to cell surface antigens have high titers of antibodies in serum and CSF (not included in this figure). However, rare instances of patients whose serum is reported with low titer of antibodies (without CSF antibodies) should be carefully re-evaluated to confirm the antibody findings. Immunohistochemistry using rodent brain and cultures of neurons (examples shown in pictures) are always positive if the serum has antibodies to the following antigens: NMDAR, AMPAR, LGI1, Caspr2, GABA(B) receptor, mGluR5 and mGluR1 receptors. The pattern of reactivity with brain varies depending on the antigen.

antigens are expressed in mammalian cells. Commercial and clinical laboratories use cell-based assays for determination of this type of antibodies and while these assays are highly specific they are not without problems. Indeed, the specificity and sensitivity of these assays vary among laboratories even when the same techniques are used. Because the reading of the tests is done by visual assessment, the interpretation of low serum titers can be misleading and some sera produce nonspecific background reactivity that may be interpreted as a positive result, although this rarely occurs when CSF is used. An algorithm for antibody interpretation is shown in figure 1.

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 (figure 2). 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. Third, patients who have recovered from the encephalitis may have detectable antibodies in serum, and even CSF,

Figure 2 Infiltrate of plasma cells in the brain of a patient with anti-NMDA receptor encephalitis

Plasma cells are shown labeled with CD138, a marker highly specific for plasma cells and plasmablasts.

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). However, decisions about treatment should be based on a comprehensive clinical assessment, not only the antibody titers.

New findings in anti-NMDAR encephalitis and limbic encephalitis

Anti-NMDAR encephalitis Since the description of anti-NMDAR encephalitis in 2007, 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, catatonia, decreased level of consciousness, dyskinesias, and autonomic instability which may require ventilatory support. Seizures can occur at any stage but most commonly occur early. Analysis of 565 patients recently presented at the annual meeting of the American Academy of Neurology showed that in most the spectrum of symptoms is similar to that previously reported (less than 4% had monosymptomatic disease), although the first presenting symptom varies between children and adults.⁷ 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.

The diagnosis of this disorder is based on the demonstration of NR1 IgG antibodies in serum or CSF. No other specific tests have been identified but two recent studies indicate that some EEG and brain FDG-PET abnormalities may potentially be useful. One study showed that 7 of 23 (30%) adult patients had a unique electrographic pattern that the authors

The discovery of CNS disorders associated with antibodies against cell surface or synaptic proteins has radically changed concepts about CNS autoimmunity.

named “extreme delta brush” (EDB) due to its resemblance to the delta brush EEG pattern seen in premature infants.⁸ Typical neonatal delta brushes are a combination of delta activity with superimposed 8–20 Hz fast activity; they are frequently symmetric but are not typically synchronous, can be seen in any head region, but are less common in frontal regions, and typically disappear by 1 month post-term. In contrast, the EDB pattern of patients with anti-NMDAR encephalitis consists of a nearly continuous combination of delta activity (1–3 Hz) with superimposed fast activity (20–30 Hz) usually in the [beta] range; it is most often symmetric and synchronous, and is detected broadly across all head regions with predominance in frontal regions. In all patients studied, this pattern was present continuously from the earliest available EEG, did not vary with sleep-wake cycles, and did not change significantly with stimulation or level of arousal. Detection of the EDB pattern significantly associated with prolonged hospitalization; the pattern resolved when the patients improved. Prospective studies will determine the true frequency of this pattern.

Another study showed that patients with anti-NMDAR encephalitis had relative frontal and temporal glucose hypermetabolism associated with occipital hypometabolism.⁹ This gradient of brain glucose metabolism correlated with clinical disease severity, and normalized when the patients recovered. Given that similar changes have been observed in psychosis induced by NMDAR antagonists, the FDG-PET pattern is likely a consequence of impaired NMDAR function.

Limbic encephalitis The term limbic encephalitis refers to an inflammatory or autoimmune process predominantly involving the limbic system. It may result from paraneoplastic immunologic 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 reference 4).

A recently identified autoantigen of encephalitis in patients with Hodgkin lymphoma (Ophelia syndrome) is mGluR5. The syndrome is highly similar to limbic encephalitis, but the MRI may show involvement beyond the limbic system. Treatment of the tumor and immunotherapy resulted in clinical recovery (reviewed in reference 4).

Clinical significance of “VGKC-complex antibodies”

The term “VGKC antibody” has been used to define antibodies demonstrated with a radioimmunoassay (RIA) in which a complex of brain proteins that includes the Kv1.1 and K1.2 subunits of the Shaker family of VGKCs are labeled with radioactive dendrotoxin. Serum with antibodies against any protein of this complex and not necessarily the VGKC will precipitate the radioactive-labeled complex and results in a positive test. For many years, “antibodies to VGKC” were considered characteristic of nonparaneoplastic limbic encephalitis, neuromyotonia, and Morvan syndrome. However, recent studies demonstrated that the two main targets of these antibodies are leucine-rich glioma inactivated 1 (LGI1) and contactin-associated protein related 2 (Caspr2).¹⁰ Identification of these antigens has clarified, in part, the diversity of symptoms previously attributed to

Figure 3 VGKC-complex antibodies

The term "VGKC-complex antibodies" refers to antibodies that are not directed against VGKC but to other proteins (LGI1, Caspr2); detection of these antibodies associates with well-defined syndromes. However, the same term also refers to antibodies against unknown antigens that associate with a large variety of symptoms; the clinical significance of these antibodies is unclear and the location of the antigens (cell surface or intracellular) is unknown.

"VGKC antibodies." Antibodies to LGI1 associate with limbic encephalitis, hyponatremia, and in some patients, brief myoclonic-like movements, characterized as tonic seizures that precede or associate with the encephalitis. In contrast, antibodies to Caspr2 associate with a broader spectrum of symptoms including encephalitis, Morvan syndrome, and sometimes neuromyotonia or painful neuropathy.

Antibodies LGI1 and Caspr2 are specifically identified with cell-based assays, but the RIA dendrotoxin assay cannot discriminate between the two. To adapt the new findings to the continuing use of the RIA dendrotoxin assay, investigators and clinical laboratories coined the term "VGKC-complex antibodies."¹¹ Consequently, there is now an emerging heterogeneous group of patients who are positive for VGKC-complex antibodies but are negative when tested specifically for LGI1 and Caspr2 antibodies (figure 3). Symptoms associated to these antibodies include peripheral neuropathy identified in swine abattoirs, encephalitis in children, FIRES (fever-induced refractory epileptic encephalopathy in school age children), epilepsy, and Creutzfeldt-Jakob disease, among others. However, the specific target antigens or even the location of the epitopes (cell surface vs intracellular) are unknown. Some of these disorders such as the neuropathy in swine abattoirs respond to immunotherapy, while others (FIRES, encephalitis in children) are less responsive, suggesting different pathogenic mechanisms. Therefore, if a test is reported positive for "VGKC-complex antibodies," two questions to ask are 1) What is the identity of the target antigen, LGI1, Caspr2, or is it unknown? and 2) If unknown, is the antigen expressed on the cell surface or intracellular? Expression on the cell surface would predict an increased likelihood of response to immunotherapy.

Main implications of the 5 new advances discussed here

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. As far as the novel antibodies to cell surface antigens are concerned, there are caveats to keep in mind, and one needs to appropriately integrate serologic findings with the clinical assessment. If a well-known antibody is identified in a patient whose clinical picture does not match the expected syndrome, particularly if the antibody is only detected in serum, re-evaluation of serum and CSF is strongly recommended.

Physicians should focus on treating the patient and not the antibody titers. 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.

The understanding of these concepts is critical; otherwise treatment approaches to downregulate the immune response in the CNS are not considered, resulting in delayed recoveries and suboptimal outcomes.

Paraneoplastic syndromes and autoimmune encephalitis: Five new things

- *In patients with the Lambert-Eaton myasthenic syndrome, a novel scale based on clinical features predicts which patients have an underlying small-cell lung cancer.*
- *The autoimmune encephalitis associated with antibodies to cell surface and synaptic proteins can occur with or without cancer, affect children and young adults, and respond to treatment.*
- *Antibodies to cell-surface antigens are determined with highly specific cell-based assays. The sensitivity and specificity of the results increase when both serum and CSF are tested. Treatment of patients with these disorders should be based on a comprehensive clinical assessment, not only on antibody titers.*
- *In anti-NMDA receptor encephalitis the identification of a characteristic EEG pattern, “extreme delta brush,” and a fronto-temporo-occipital gradient of glucose metabolism may help in the diagnosis and follow-up of this disorder.*
- *Determination of “VGKC-complex antibodies” should be complemented with molecular characterization of the antigens (LGI1, Caspr2, unknown). While antibodies to LGI1 or Caspr2 have syndrome specificity and the associated symptoms often respond to immunotherapy, antibodies to unknown antigens lack syndrome specificity and the response to immunotherapy is less predictable.*

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