Teaching Course 12

Current Treatments in Neurology - Level 1

Paraneoplastic and autoimmune encephalitis

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Introduction

Paraneoplastic syndromes are combinations of symptoms and signs resulting from damage to organs or tissues that are remote from the site of a (malignant) neoplasm or its metastases.(1) In the fifties and sixties of the 20th century, cases and small series were published, linking encephalitis and lung cancer and myasthenia with lung cancer (the Lambert-Eaton myasthenic syndrome, LEMS). Paraneoplastic neurological syndromes (PNS) are quite rare as probably less than 1% of all cancer patients have them. However, some tumors are more prone to develop PNS like small cell lung cancer or thymoma. It took twenty more years to identify the first antibodies, Hu and voltage-gated calcium channel (VGCC) antibodies, and some others have been detected since. Despite initial optimism about a possible anti-tumor response by the body itself, soon the interest in these syndromes faded somewhat as most patients had no or poor response to
therapy, especially those with central nervous system diseases, like paraneoplastic cerebellar degeneration or paraneoplastic limbic encephalitis.

The identification of antibodies against membrane-bound extracellular antigens, and especially the discovery of anti-N-methyl-D-aspartate receptor (NMDAR) antibodies, has ignited new enthusiasm all over the world. These antibodies are found in patients previously not identified as suffering from an autoimmune disease, tumors are less frequent and response to therapy is good in most patients.

This teaching course aims to discuss both the classical and the novel antibody-associated disorders.

**Intracellular versus extracellular antibodies**

We can discriminate antibodies against at least two different types of antigens: 1) the nuclear and cytoplasmatic antigens, and 2) the cell surface and synaptic (extracellular) antigens. This characterization has direct implications for diagnostic workup, treatment and outcome.

**Nuclear and cytoplasmatic antigens**

The proteins these antibodies target are located intracellularly, mainly in the nuclei of the neurons. As most of these antibodies are associated strongly with cancer, and as the target antigens are expressed by both neurons, and cancer cells, these are collectively called paraneoplastic of onconeural antibodies. The antigens are not readily accessible by the antibodies, and the antibodies are unlikely to be pathogenic. Active and passive transfer of antibodies into mice have failed to induce a neurological disease. In addition, up to 20% of SCLC patients might harbor HuD antibodies, while less than 1% of SCLC will develop an Hu neurological...
syndrome. The antibodies are therefore considered epiphenomena, and a cytotoxic T-cell mediated immune response against neurons is more likely. Response to immunotherapy is poor, perhaps due to irreversible neuronal damage. Antibodies belonging to this group are among others Hu, Yo, CV2, Ma, and Ri.

Cell surface and synaptic (extracellular) antigens

Antigens of this second category are located at the outside of the cell, on the membrane or in the synapse. The antibodies can therefore directly target the antigens. Best-known are anti-NMDAR antibodies, but over the last 9 years over 10 novel antibodies have been discovered, a.o. antibodies against the leucine-rich glioma-inactivated protein 1 (LGI1), contactin-associated protein-like 2 (Caspr2), α-amino-3-hydroxy-5methyl-4-isoxazolepropionic acid receptor (AMPAR), the γ-aminobutyric acid receptor-A and B (GABA_{A}R and GABA_{B}R), dipeptidyl-peptidase-like protein-6 (DPPX), and the glycine receptor (GlyR). All of them are associated with encephalitis.

The disease pathways associated with these antibodies against cell-surface antigens differ from those related to the previous two groups of intracellular antigens in several important aspects. First, the cell-surface target antigens are disrupted by the antibodies. This has been studied most extensively in anti-NMDAR encephalitis: antibodies bind directly to the NMDAR and cause the receptor to move away from the synapse and to get internalized, disrupting inhibitory neurotransmission. Passive transfer of NMDAR antibodies to mice causes an encephalopathy, reversible upon cessation of antibody infusion.(5) Second, there is much less consistent association with malignancy. Third, symptoms can be reversed with treatment, although not always to a full extent. Last, the symptoms relate to
the disruption of the target antigen, as mimicked by pharmacological disruption or genetic mutation.

**Clinical phenotypes and epidemiology**

Almost all phenotypes have been described with different types of antibodies, and vice versa. However, some phenotypes are more likely to be related to PNS or antibody-mediated diseases, or to specific antibodies. I will try to provide some rules of thumb. In the central nervous system the parts most likely to be affected are the limbic system and the cerebellum, although the brain stem can be affected as well. In most patients the onset will be subacute (within 6 or at least 12 weeks). MRI might be abnormal in most patients with a limbic encephalitis, as well as the CSF will show pleocytosis in many. Unfortunately MRI might show no abnormalities in cerebellar degeneration (until later in disease) or in the majority of patients with anti-NMDAR encephalitis. As most phenotypes can fit into more than one antibody-associated disease, testing of panels is recommended. Still, a thorough history and examination might help to identify the correct antibody: predominant seizures might point towards NMDAR, GAD65, LGI1, GABA$_6$R or GABA$_4$R, while faciobrachial dystonic seizures are probably pathognomonic for LGI1.(6) Prominent psychosis will point towards NMDAR or AMPAR, while cerebellar degeneration fits with Yo, Hu, VGCC, GABA$_6$R, Caspr2 or GAD65. Less commonly asked items like diarrhea and weight loss should raise suspicion for DPPX, while rigidity, myoclonus and startle should alert you to look for GlyR, GAD or DPPX. Recently a proposition paper was published to guide the physician with a patient with possible autoimmune encephalitis to optimize recognition and diagnosis and offer early treatment.(7)
Although initially described in patients between 50 and 70 years of age, as PNS mainly occur at this age, the new antibodies are also found in younger patients, and even in children. The best example is anti-NMDAR encephalitis as the median age is 21 years.\(^8\), but also GABA_\text{A}R encephalitis can occur in children. As disorders as anti-NMDAR or AMPAR encephalitis share neurological and psychiatric features, we should be vigilant to diagnose these patients at the psychiatry ward. Therefore the field of autoimmune neurology has broadened beyond the clinical neurology and psychiatrists, intensive care physicians and pediatricians should be alert to these diseases.

**Tumors and epidemiology**

Some antibodies are almost invariably related to tumors, like Yo antibodies and ovarian cancer or breast cancer. This is true for most classical paraneoplastic antibodies. Others are less likely to be paraneoplastic or the association depends on age and gender: anti-NMDAR encephalitis is linked to ovarian teratoma in 50% of fertile women (12-45 years of age), hardly associated with cancers in young children, and linked to somatic cancers in ~25% of elder patients (male or female).\(^8\) Similarly, age and gender might be used to shorten the differential diagnosis, and decide tumor chance: in very young children with opsoclonus myoclonus syndrome (OMS), one should think of Hu antibodies and neuroblastoma, in young adults of ovarian teratoma in the absence of antibodies and in elder individuals it could be related to Ri-antibodies and breast cancer. In general tumor frequency depends largely by antibody type, but can be slightly different based on clinical phenotype. Patients with more than one antibody have an increased risk of tumors, like Hu and GABA_\text{A}R, while many autoimmune diseases in the patient or same family might hint
towards a more autoimmune prone disease. In over 90% of paraneoplastic disorders, the patient and physicians are not yet aware of the tumor. Guidelines for tumor screening are available.(9)

**Treatment**

Treatment is aimed at both the removal of antibodies and symptomatic treatment. Removal of antibodies should be achieved by: 1) halting the trigger of the immune response, the tumor, if present, and 2) inhibiting the overactive immune system. Symptomatic treatment can consist of seizure control, psychiatric medication, and critical care management. It is obvious that these patients should be treated by a multidisciplinary team.

**Cancer treatment**

Early detection and treatment of the underlying tumor is of highest importance, both increasing the chance of curing the cancer, and offering the patient a better chance to respond to immunotherapy. Low(er) Karnofsky score due to neurologic deficits caused by encephalitis should not lead to refraining from cancer therapy. Especially in the newly described AIE, with antibodies against extracellular antigens, most neurologic deficits can be reversible once the antibody load diminishes.

**Immunotherapy**

The extent and effect of immunotherapy highly depends on the type of antibody. In general, patients with onconeuronal antibodies, like Hu and Yo, respond poorly to immunotherapy and often stabilization is the best achievable. Nevertheless, most patients will receive some form of immunotherapy, most often steroids and immunoglobulins. Some patients might
respond better, like those with opsoclonus myoclonus in anti-Ri syndrome and younger patients with limbic encephalitis associated to anti-Ma2 antibodies.

In the second category, the circulating autoantibodies are aimed at extracellular proteins, like the NMDA receptor, and proven pathogenic. Immunotherapy is targeted at antibody removal. Most treatments are derived from other autoimmune neurological diseases, like Guillain-Barre syndrome and myasthenia gravis, or from other specialisms like rheumatology and hematology. Most evidence in AIE has been gathered with anti-NMDAR encephalitis, including one large, partially prospective cohort study.(8) For the other encephalitis types, mainly smaller cohorts or cases series have been published, and treatment options are similar to anti-NMDAR encephalitis. There is no doubt about the effect of immunotherapy, but the types and regimens are all expert opinion only. Generally, we can discriminate first-line immunotherapy, second-line immunotherapy and less used or chronic immunotherapy.

Effect of treatment in anti-NMDA encephalitis is relatively extensively examined. In a large cohort study, 96% of patients were treated with first-line immunotherapy and 27% of patients with second-line therapy. Early treatment leads to better outcome and treated patients are at lower risk for a relapse. Of all patients treated with first-line therapy, 50% showed improvement in 4 weeks. In those showing no improvement after first-line therapy, second-line immunotherapy was an independent factor for favorable outcome.(8)

First-line immunotherapy consists of high dose corticosteroids (intravenous or oral), intravenous immunoglobulins (IVIg).and/or intravenous plasmapheresis (PLEX). Second-line therapy consists of rituximab, cyclophosphamide, or both combined. Azathioprine, tacrolimus and/or mycophenolate mofetil can be used as chronic immunotherapy, but due to
slow effect they are often less useful in acute phases. The choice of drug is dependent on patient specific features and experience of the treating physician. PLEX can be difficult to use in children, psychiatric patients and during severe autonomic storms at ICU.\(^{10}\) Treatment in children is comparable to adults, but there is preference for rituximab over cyclophosphamide initially as second-line immunotherapy. No difference in efficacy has been shown, but there is more expertise with rituximab. In addition, there is a fear of potential adverse effects, including premature gonadal failure, infertility and long-term malignancies. Although physicians should be very careful about long-term risks, most studies about the risks of cyclophosphamide originate from the 50s and 60s, using oral medication in far higher cumulative doses. Results of therapy in children are slightly better than in adults, probably due to earlier and more aggressive treatment.\(^{8}\)

When there is high suspicion of AIE, with fitting clinical picture and progressive course of disease, first-line therapy can be started despite of definitive diagnosis, once diagnostic samples have been obtained.\(^{7}\)

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Reference List