INTRODUCTION – OVERVIEW OF AUTOIMMUNE NEUROLOGY

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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 late forties of the 20th century, the idea of paraneoplastic neurological syndromes was suggested by Denny-Brown in two patients with rapidly progressive sensory neuropathy and a lung cancer at autopsy, without evidence of metastases. In the two next decades other 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.

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.[2] 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 In this short overview I will touch many topics shortly and try to provide some basic fundament. The other presentations will cover each topic more thoroughly.

Intracellular versus extracellular antibodies

We can discriminate antibodies against three different types of antigens: 1) the nuclear and cytoplasmatic antigens, 2) intracellular synaptic antigens, and 3) the cell surface and synaptic (extracellular) antigens.[3] This characterization has direct implications for diagnostic workup, treatment and outcome.

<u>Nuclear and cytoplasmatic antigens</u>

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.[4] 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 Hu, Yo, CV2, Ma, Ri, and Tr/DNER.

Intracellular synaptic antigens

Amphiphysin and glutamic acid decarboxylase-65 (GAD65) are both intracellular proteins, but unlike the antigens discussed previously, the epitopes can be exposed to antibodies during fusion of synaptic vesicles and reuptake. GAD65 is related to stiff person syndrome (SPS) and cerebellar ataxia, but has also been associated with limbic encephalitis and epilepsy. Amphiphysin antibodies are linked to SPS as well, but also encephalomyelitis, and breast cancer. There is some experimental evidence for both antibody-mediated effects, and T-cell mediated effects. Also clinically some patients respond well to immunotherapy, while other patients do not respond at all. Which effect is more important for the clinical syndrome is unknown, and remains controversial.

Cell surface and synaptic (extracellular) antigens

Antigens of this third 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 ($GABA_AR$ and $GABA_BR$), , 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 a 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, $GABA_BR$ or $GABA_AR$, 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, $GABA_BR$, 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]

In the peripheral nervous system, neuromuscular junction disorders and to a lesser extent neuropathies are linked to antibodies: myasthenia gravis caused by acetylcholine receptor antibodies or LEMS caused by VGCC show distinct clinical phenotypes and can be confirmed by antibody testing and by repetitive nerve stimulation. Subacute sensory neuronopathy can associated with Hu or CV2 antibodies, while chronic idiopathic demyelinating neuropathy has recently been linked to Contactin-1 antibodies.[8]

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.[9], but also $GABA_AR$ 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).[9] 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 $GABA_BR$, while many autoimmune diseases in the patient or same family might hint towards a more autoimmune prone disease. Guidelines for tumor screening are available.[10]

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