EPILEPSY AND AUTOIMMUNE ENCEPHALITIS

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Introduction

The first reports of associations between limbic encephalitis and tumors date back to the 1960s. In these patients, most patients had both cognitive disturbances and seizures. The first antigens for paraneoplastic syndromes were detected in the 1980-1990s. In these classical paraneoplastic syndromes the antibodies are directed to intracellular antigens, like Hu and Yo. In the year 2007, the discovery of N-methyl-d-aspartate receptor (NMDAR) antibodies was a major breakthrough recognizing cell surface proteins as antigens in encephalitis.[1] Over ten other cell surface antigens and their respective clinical syndromes have been reported since. In contrast to the classical syndromes, disease occurs in younger patients as well, patients are also seen by non-neurologists like psychiatrists and pediatricians, and patients tend to have a more favorable response to immunotherapy.[2] Only a minority of these patients have an associated tumor, although the incidence of cancer differs per antigen.[3;4] Several of these novel antibodies cause seizures or status epilepticus, mostly (but not always) with other neuropsychiatric symptoms. Recognition of specific seizure types might point towards certain antibodies, thereby enhancing early diagnosis. This is very important as most encephalitides do not respond well to anti-epileptic drugs, but improve on immunotherapy.

This part of the teaching course will provide an overview of the syndromes associated with antibodies directed to membrane bound or synaptic proteins, focusing on those with frequent or prominent epilepsy. This will encompass encephalitis with leucin-rich glioma inactivated protein 1 (LGI1) or contactin-associated protein-2 (Caspr2) antibodies, formerly known as voltage-gated potassium channel (VGKC) complex antibodies, also discussing the "double negatives"; in addition we will discuss γ-aminobutyric acid receptor type B and type A encephalitis (GABAbR and GABAaR, respectively). Finally we will cover the frequency of autoimmune encephalitis in the group of patients with chronic epilepsy or status epilepticus. N-methyl-d-aspartate receptor (NMDAR) encephalitis and Alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) encephalitis are discussed separately in this teaching course.

VGKC-complex antibodies

Antibodies to the voltage-gated potassium channel (VGKC) were initially detected in patients with acquired neuromyotonia, a peripheral nerve disorder characterized by muscle cramps, impaired relaxation and stiffness.[5] A pathogenic role of anti-VGKC antibodies was subsequently suspected in Morvan syndrome, showing neuromyotonia accompanied by autonomic and cognitive symptoms and insomnia. The similarity of the central nervous system symptoms of Morvan syndrome with symptoms seen in limbic encephalitis has led to the analysis and identification of anti-VGKC antibodies in two patients with limbic encephalitis in 2001.[6] Antibodies were eventually thought to be directed to the Kv1.1, 1.2 and 1.6 subunits of the VGKC receptor.[7] However, the exact role of VGKC-antibodies remained controversial as no laboratory succeeded in showing staining with serum in VGKC-transfected cells. In the year 2010, this reconsideration led two laboratories to identify simultaneously that these antibodies are not directed to the subunits of the VGKC itself, but to the VGKC-associated proteins leucine-rich glioma-inactivated protein 1 (LGI1) and contactin-associated protein 2 (Caspr2).[8;9] These two antibodies and the respective clinical phenotypes are discussed below.

anti-LGI1 encephalitis

Patients with anti-LGI1 encephalitis show the typical features of limbic encephalitis such as seizures, memory deficit, confusion and behavioral problems. A minority of the patients show autonomic dysfunction. Hyponatriemia is common (~60%).[8;9] Typical for anti-LGI1 encephalitis is the occurrence of faciobrachial dystonic seizures (FBDS) or tonic seizures. These brief involuntary abnormal movements are unilateral, involving the arm, usually ipsilateral face and less commonly the trunk or a leg. FBDS occur very frequent, up to 100 times per day.[10] Subtle focal seizures (~65%) and FBDS (~45%) mostly occur before onset of memory disturbance. Later in disease course, patients will have one or several tonic-clonic seizures. MRI will frequently show hippocampal T2 hyperintensity, while a lumbar puncture most frequently will be completely normal.[11] In 2015, specific T2/T1 hyperintensities of the basal ganglia have been described in a considerable part of FBDS patients, early in disease course,[12] although more recent studies show relatively low frequencies of these specific abnormalities.[11;13] EEG will be abnormal, when the disease is pronounced, but FBDS are not caught on EEG.

Anti-LGI1 encephalitis is infrequently paraneoplastic(~10%). Recently, HLA-DR7 and HLA-DRB4 were specifically linked to non-paraneoplastic anti-LGI1 ecenphalitis, suggesting that a paraneoplastic origin was more likely if another HLA-type was found.[14;15]

Immunotherapy is effective, with early response of seizures and slow recovery of cognition. At long-term follow up, most patients have mild to moderate residual cognitive deficits with spatial disorientation and persistent amnesia for the disease period.[11] If treated with immunotherapy, most patients will no longer suffer from epilepsy. However, cognitive dysfunction might remain an issue and recent studies have published less favorable overall outcome and cerebral atrophy.[13;16]

anti-Caspr2 encephalitis

Caspr2-antibodies associate with a treatable disorder that predominantly affects elderly men.[17] Although onset can be subacute, part of the patients will develop the disease more slowly (over a year). Most patients will have limbic encephalitis, Morvan syndrome or a clinical phenotype in between. The resulting syndrome may vary among patients but it usually includes a set of well-established symptoms: encephalopathy, cerebellar symptoms, peripheral nervous system hyperexcitability, dysautonomia, insomnia, neuropathic pain or weight loss.[18] Seizures will be present in just over half of the patients, but are generally not the most prominent symptom in this disease. CSF is unremarkable in ~65% of patients, while MRI is only abnormal in ~30% of cases. Needle EMG will usually show fasciculations or hyperexcitability when patients have peripheral nervous system complaints. Overall, high clinical suspicion is necessary to consider this diagnosis and underdiagnosis is likely. Tumors, usually thymoma, are found in ~20% of patients. Patients almost invariably profit from prompt immunotherapy or tumor treatment, favoring a low threshold for requesting Caspr2 antibody testing..

“double negative” patients

Around half the patients testing positive in the VGKC-radioimmunoassay (VGKC-RIA) do not have anti-LGI1 or anti-Caspr2 antibodies. This is an emerging heterogeneous group of patients. The clinical significance of a positive VGKC-RIA in these patients is controversial, which poses a threat for both under- and over diagnosis as well as under- and over treatment. Initially, high VGKC titers were considered relevant, while low positive titers could be relevant or not. Later, positive VGKC results were associated with inflammation, without specification what type of inflammation. The use of several cut off values for positive VGKC-RIA titers and the tendency to perform grouped analysis of all VGKC-RIA positive patients (including LGI1 and Caspr2), even after the discovery of the LGI1 and Caspr2 subtypes, is a significant limitation in reviewing clinical symptoms and response to treatment.[19] Until recently, no study included matched controls to assess the real additional value of positive VGKC-results. In our recent assessment of VGKC-positive patients (LGI1 and Caspr2 negative), we matched every patient to two VGKC negative patients, and results were considered blindly without knowledge of VGKC result or treatment response. Evidence for autoimmune inflammation was ~20% in all patients, not different between patients with or without positive VGKC results. Evidence for autoimmune inflammation was mainly found in patients with limbic encephalitis/encephalomyelitis, but not in other clinical phenotypes, like isolated epilepsy or psychosis. VGKC-positivity in the absence of antibodies to LGI1 and Caspr2 therefore is not a clear marker for autoimmune inflammation and seems not to contribute in clinical practice. No cut-off value for the VGKC-titer is appropriate to discriminate between patients with and without autoimmune inflammation.[20]

Anti-GABAb-receptor encephalitis
Encephalitis with GABAbR antibodies was discovered in 2010.[21] Almost invariably the limbic system is targeted and patients suffer from severe, refractory epilepsy or status epilepticus, despite aggressive anti-epileptic treatment. Incidentally, patients also harbor symptoms of opsoclonus myoclonus or ataxia. MRI shows temporal T2 hyperintensities in ~65% of the patients. CSF is more sensitive than serum to detect GABAbR antibodies. Over half of the patients have a small-cell lung cancer (SCLC). In 90% the SCLC has not been discovered before the encephalitis. Contrary to other paraneoplastic syndromes associated to SCLC, like the anti-Hu-syndrome, anti-GABAbR encephalitis responds very well to immunotherapy and chemotherapy. Unfortunately, the long-term prognosis is still dictated by the tumor, when present.[22]

Anti-GABAa-receptor encephalitis
Anti-GABAaR encephalitis has only been described very recently, and occurs in patients at all ages (median 25 years, range 3-65).[23] Patients with high antibody titers in both serum and CSF have a highly stereotypical clinical phenotype with refractory seizures, cognitive deficits and memory issues. The MRI will typically show non-specific T2 hyperintense lesions. The disease develops into refractory status epilepticus, leading to pharmacological coma. Patients tend to improve on immunotherapy, although some died at the intensive care unit due to complications. The role of GABAaR antibodies in serum only is somewhat controversial. Some patients have a similar clinical phenotype, although somewhat milder, suggesting the same pathogenic mechanism. However in some patients additional antibodies (like NMDAR and GAD65) are found with alternative clinical phenotypes, casting doubt on the specificity of these GABAaR antibodies in serum only.[24]

Autoimmune encephalitis as cause for status epilepticus or chronic epilepsy
It is also important to consider how frequently antibodies are found in patients with epilepsy, and whether these antibodies always are relevant. Due to the short history of these novel antibodies, little is known. The only cohort study found antibodies in 11% of patients with chronic epilepsy.[25] Of these 416 patients, 176 were considered cryptogenic at inclusion. The antibodies identified were VGKC in 20 patients (1 LGI1, 19 “double negative”), anti-glycine receptor (GlyR) in 11, while NMDAR and GAD65 were present both in 7 patients. As discussed before, the value of VGKC-test positivity (LGI1/Caspr2 negative) might not be clinically irrelevant. The specificity of GlyR in serum is ~95%, so it is difficult to assess the real value of this association. The retrospective nature of the study and the lack of some patient-specific information (a.o. CSF) complicate further assessment. LGI1, NMDAR and GAD65 are more consistently linked to epilepsy. As GAD65 is an intracellular antigenic target, it is controversial whether these antibodies are actually pathogenic or a biomarker.[3] Low titer GAD65 antibodies can occur in healthy subjects as well, especially in those with type 1 diabetes. However, neurological complaints are associated only with high titers (RIA >1:1,000; ELISA ~>1:10,000; cell-based assay +; immunohistochemistry +).[26;27] Most patients with GAD65 antibodies have some neuropsychiatric symptoms as well (behavior, walking difficulties, stiffness). As these are often considered “functional complaints” by many physicians, these can create difficulties with recognition (even if treated by neurologists for their epilepsy). However, in a substantial part of the patients with high titer GAD65 antibodies immunotherapy will improve the symptoms and induce seizure reduction. It is currently impossible to predict in which patient immunotherapy will be effective, so every patient with high titer GAD65 antibodies deserves a trial with immunotherapy. Summarizing, antibodies can be found in patients with chronic (focal) epilepsy, but prospective studies investigating antibodies in epilepsy cohorts are urgently needed.

Status epilepticus is a life-threatening condition, and regularly no clear causal trigger is found. A recent retrospective study in patients with status epilepticus, with a negative initial diagnostic screening to identify the cause, identified a probable autoimmune cause in 37% of those (25% with known antibodies, the most prevalent anti-NMDAR, but also anti-LGI1, anti-Caspr2, anti-GAD65, anti-Hu, and anti-CV2).[28] Antibody analysis and treatments used were too fragmented to warrant firm conclusions. However, antibody-mediated encephalitis should be considered in every status epilepticus without known cause, especially when refractory.

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