Learning objectives

To illustrate the clinical-immunologic variants of limbic encephalitis (LE). To review the findings on conventional and advanced MRI techniques. To correlate the imaging findings with the clinical course, the evolution and outcome of the disease. To discuss the diagnostic considerations in patients with LE.
Background

LE is a neurological syndrome that has attracted increasing attention in the last few years and may present in association with cancer, infection, or as an isolate clinical condition. Patients usually present with rapidly progressive short-term memory deficits, psychiatric symptoms, and seizures. **Definite diagnosis requires either neuropathological or neuroradiological evidence of involvement of the limbic system besides the typical clinical syndrome.** Histopathology shows features of chronic encephalitis, that is infiltrating round cells (T lymphocytes) and activated microglial cells, which sometimes form nodules. Patients with LE (paraneoplastic or not) have CSF inflammatory findings, EEG or MRI abnormalities in the temporal lobes and antineuronal antibodies.

CT is usually not helpful, and positron emission tomography (PET) may illustrate the hypermetabolism of the limbic regions during the active phase of the disease, followed by hypometabolism in the chronic phase.

**Paraneoplastic Limbic Encephalitis** is an uncommon entity characterized by subacute onset, in days or up to 12 weeks, of seizures, short-term memory loss, confusion, and psychiatric symptoms, suggesting involvement of the limbic system. PLE is produced by an immunomediated response that can be caused by several types of tumor-induced autoimmunities against the nervous system. Serum antibodies against neural antigens expressed by the tumor (onconeural antibodies) have been demonstrated. Within the context of PLE, the following autoantibodies have been "well characterized", that is, they are sufficiently and dependably detectable and specifiable: anti-HU, Ma/Ta, CRMP5/CV2, and amphiphysin. What all of these onconeural antibodies have in common is that they are directed against antigens located intracellularly and disorders associated with intracellular autoantigens usually associate with cytotoxic T-cell mechanism and are less likely to improve than are disorders that associate with autoantigens in the cell membrane.

The tumors most commonly associated with PLE are the lungs (50%), testis (20%), and breast (8%); in patients younger than 40 years and without paraneoplastic antibodies, Hodgkin's lymphoma, immature teratoma, and thymoma are the most frequently associated tumors. Anti-Hu antibodies are specially frequent in patients with small cell lung cancer (SCLC) and anti-Ta (also called anti-Ma2) in patients with testicular germ-cell tumor.

Neurological symptoms can precede the cancer diagnosis in 60% of patients and so the detection of onconeural antibodies can be extremely useful in indicating the presence of a tumor and defining a given limbic encephalitis as paraneoplastic. However, although the specificity of these antibodies for a tumor is almost 100%, sensitivity is 60%; that is, 40% of the patients with PLE are negative for these antibodies. Treatment of the tumor appears to have more effect on neurological improvement than the use of immune
modulation and immunotherapy seems to be only insignificantly promising in relation to improve the patient's condition.

Rarely, we encounter a subgroup of patients with PLE, that harbor serum or CSF antibodies to antigens expressed in the cell membrane of neurons and dendritic processes of the neuropil of the hippocampus. These antibodies are named novel cell membrane antigens (nCMAgs) or neuropil antibodies. Their detection is more reliable in the CSF than serum and correlates with a favorable outcome and improvement with immunotherapy. Antibody titers have a tendency to disappear with neurologic improvement in a similar fashion as patients with non-paraneoplastic LE (NPLE) and positive voltage-gated potassium channels (VGKC) antibodies (whose antibodies are also directed against cell membrane antigens). The clinical picture is somehow different from the typical PLE and includes seizures and prominent behavioral and psychiatric symptoms, central hypoventilation and even hemiparesia, indicating involvement beyond the limbic area. Clinical improvement usually associates with improvement of MRI and FDG-PET abnormalities and a decrease of antibody titers.

**Non-Paraneoplastic Limbic Encephalitis (NPLE).** LE is not exclusively a paraneoplastic syndrome. There are patients with a clinical picture identical to PLE (seizures, memory loss, and confusion) but in whom an underling tumor cannot be found. The limbic encephalitis frequently associates with VGKC antibodies. It is well known that VGKC located on the cell membrane play an important role in the regulation of neuronal excitability by modulate resting membrane potential and control of the shape and frequency of action potentials. How these VGKC antibodies enter the central nervous system and whether VGKC antibodies alone can cause seizures and memory loss is not yet determined. Although recently described, emerging evidence suggests that NPLE can be more common than PLE.

From a clinical point of view, the presence of temporal lobe seizures in 90% of the patients compared with 50% in patients with PLE is a hallmark of this type of NPLE and, when compared with any other type of LE, patients who have VGKC antibodies are less likely to develop CSF pleocytosis or intrathecal synthesis of IgG. Another remarkable characteristic of the "typical" patient with VGKC antibodies-associated NPLE is improvement under early-onset therapy with variable regimens of steroids, plasma exchange, and intravenous immunoglobulins in 70% of the patients. This improvement appears to be relatively consistent with the fall of serum VGKCs. Nevertheless, it cannot be assumed that patients with positive VGKC antibodies do not have a paraneoplastic disease, so the test should not be used to exclude a paraneoplastic origin.

Furthermore, there is another group of patients with acute noninfectious LE that, even after long follow-up, an underling neoplasia cannot be found and who do not harbor VGKC or nCMAg antibodies. Patients are usually young adults that experience an infective prodromal illness followed by an acute amnesic syndrome in association with temporal lobe seizures as a prominent symptom (symptoms evolved over less than 1 week). Even
though prolonged seizures have also been described as a cause of reversible signal change in the hippocampi, the striking similarity in the clinical features and imaging with cases with positive VGKC antibodies seems consistent with a common autoimmune basis. Treatment with immunotherapies including intravenous steroids, immunoglobulins, and plasma exchange should be considered in these cases. Patient recovery is variable and persistent cognitive impairment and seizures are a frequent result.

Differential diagnoses and clinical aspects - Based on recent studies, an approach to the investigation and acute management of patients with limbic encephalitis has been proposed. The first step is to obtain MRI of the brain and CSF examination. MRI abnormalities in the medial temporal lobes are helpful in confirming a diagnosis of limbic encephalitis, but normal imaging does not exclude the diagnosis. Medial temporal lobe abnormalities also occur with herpes simplex encephalitis and other disorders. Once an infectious cause has been excluded, the second step is to search for a tumour and an antineuronal antibody. There are no clinical, imaging or CSF abnormalities that are specific to any particular immune phenotype, but there may be clues to which tumour and antibody is present.

Symptoms resembling those of LE may result from several disorders, including steroid-responsive encephalopathy associated with autoimmune thyroiditis, systemic lupus erythematosus (SLE), Sjögren's syndrome, Wernicke-Korsakoff encephalopathy, primary psychiatric disorder, herpes simplex encephalitis, neurosyphilis, primary central nervous system (CNS) lymphoma, World Health Organization grade II or III glioma infiltrating the limbic system and others. Anterograde amnesia is the dominant early manifestation of Alzheimer's disease, but degenerative neurological disorders have a more insidious onset of symptoms than limbic encephalitis. Steroid-responsive encephalopathy associated with autoimmune thyroiditis is a diagnosis of exclusion, and may appear with or without MRI abnormalities. Neuropsychiatric disorders are common complications of SLE; however, they are usually associated with a variety of neurological syndromes (seizures, psychosis, dementia, chorea), and with a spectrum of pathological mechanisms such as ischemia, hemorrhage and vasculitis. Wernicke-Korsakoff encephalopathy is associated with typical FLAIR and DWI signal changes around the third ventricle and the periaqueductal gray matter. The mamillary bodies may be hyperintense on FLAIR images and show contrast enhancement on T1-Weighted images. Herpes simplex encephalitis is likely to present with a rapid deterioration over a few days with fever, headache, seizures and confusion. Medial temporal lobe lesions are usually seen on MRI, but more widespread abnormalities and haemorrhagic changes also may be present. The polymerase chain reaction (PCR) assay for HSV DNA in the CSF has a high specificity and sensitivity for herpes simplex encephalitis. Primary CNS lymphoma involving the limbic system may clinically resemble LE. However, on MRI, these cell-rich tumors are usually relatively hypointense on T2-weighted sequences and show (homogeneous) contrast enhancement. A glioma infiltrating the limbic system usually also grows into the thalami and the insular cortex. Acute limbic encephalitis
can develop in the first few weeks after allogeneic haemopoietic stem cell or solid organ transplantation. Most of these patients are afebrile, but they have a lymphocytic pleocytosis and bilateral MRI signal abnormalities in the uncus, amygdala, entorhinal cortex and anterior hippocampus with sparing of the parahippocampal gyrus. The PCR assay for human herpes virus type 6 (HHV6) in the CSF is positive in two-thirds of these patients, but an identical syndrome occurs in patients with a negative PCR assay. HHV6 has been identified in a few immunocompetent patients with focal encephalitis. Unilateral or bilateral hippocampal abnormalities are observed in one-fifth of patients with Japanese encephalitis, but most patients also have MR abnormalities in the thalami, substantia nigra and basal ganglia. Other flavivirus infections can present in a similar fashion.

Although autoimmune limbic encephalitis is rare, it probably is under-recognised. MRI abnormalities in the medial temporal lobes after prolonged or multiple seizures often have been attributed to seizure-induced cytotoxic oedema and gliosis, but some of these patients may have had limbic encephalitis. It may be difficult to differentiate limbic encephalitis from an acute confusional state or a psychiatric disorder. MRI and CSF examination are often, but not always, helpful indicators of an inflammatory process. Identification of an anti-neuronal antibody helps in the diagnosis of limbic encephalitis. Rapid diagnosis of limbic encephalitis is important, because the neurological disorder associated with antibodies to antigens in neuronal cell membranes or the anti-Ma2 antibody often responds dramatically to immunotherapy and treatment of the underlying tumour.

Five patients ( 2 female, 3 male, ranging from 46-70y ), were diagnosed and treated for LE in our hospital, one paraneoplastic and four non-paraneoplastic cases. Diagnosis was made according to the following criteria:

1. compatible clinical presentation (short-term memory impairment, seizures, confusion, hallucinations)
2. bilateral signal abnormalities in the mesiotemporal lobes
3. electroencephalographic demonstration of temporal lobe epileptic activity
4. increased protein content or elevated IgG synthesis in the CSF and
5. negative CSF PCR and negative serum/CSF IgM antibody testing for HSV and related herpesviruses.

We retrospectively reviewed the initial and follow up ( from one month to three years ) MRI studies of all patients.

All patients underwent an extensive screening for underlying neoplasia, during admission and follow-up, and also were tested against antineuronal antibodies.
Patient 1 presented with acute onset of symptoms and anti-Hu positivity. Screening revealed lung oat cell carcinoma. The patient was put on steroids and chemotherapy. Six months later, he had a marked neurological improvement. He died 18 months later due to widespread metastatic disease.

Patients 2, 3, 4 presented with subacute onset of symptoms. Screening for underlying neoplasia and testing for anti-onconeural antibodies gave negative results. They were all put under combined treatment with steroids +/- plasma exchange. All patient's condition started to improve, 1 to 3 months following their admission.

The 5th patient had a 2-year history of symptoms. At previous hospitalizations, she was misdiagnosed as having diffuse low-grade astrocytoma and thus was put on a combined regimen with temozolamide, dexamethasone and valproic acid with no alteration of her neurological condition. The wrong diagnosis was based on the stereotactic brain biopsy report (revealing moderate astrocyticis) and misinterpreted MR Spectroscopy scans. Following her admission to our department the patient underwent investigation for latent neoplasia and serum anti-onconeural antibodies that was negative. However testing for antibodies against glutamic acid decarboxylase gave very high titers (>10,000). She was put on immunosuppressive treatment with oral prednizolone and plasma exchange. During a 10-month follow up she had a moderate improvement, consisting in better control of seizures and a limited ability to retain recent information.

All patients underwent brain imaging evaluation shortly after admission as well as 1, 3 and 6 months afterwards. One of them was followed up for 2.5 years. In all patients MRI abnormalities were apparent on the initial examination.

Conventional sequences (plain and contrast enhanced T1W, T2W and FLAIR images) revealed swelling and T2 prolongation affecting the hippocampi and medial temporal lobes (cortical and subcortical) in a symmetric or asymmetric pattern. Extratemporal involvement was additionally noticed in patient 5 in insular cortex and supracallosal gyri. According to the literature, it is not uncommon to find anomalies outside these areas, especially in the brainstem, thalamus, basal ganglia, and cerebellum. The distribution of lesions is not dissimilar to herpetic encephalitis. None of them showed contrast enhancement although it has been described in 10-30% of patients with LE.

Diffusion-weighted imaging (DWI) showed normal diffusivity in all patients. The observed hyperintensity represents T2 shine-through effect as confirmed on apparent diffusion coefficient (ADC) mapping. DWI could be a valuable tool to differentiate LE from herpetic encephalitis since the later, usually, shows restricted pattern. However, swelling and restricted diffusion in the hippocampus has been described in patients within 48 hours
of acute symptomatic seizures or status epilepticus. Therefore, restricted pattern can be found in patients with LE as a result of frequent (subclinical) temporal lobe seizures.

Chemical Shift Imaging (CSI) was performed in patient 5. Short TE spectra showed increased myoinositol (ml) and choline (Cho) and decreased N-acetylaspartate (NAA) levels, slightly different to the unique report from the literature on MR Spectroscopy, both having in common elevated ml levels. The observed pattern of marked increase in ml/Cr, moderate increase in Cho/Cr ratio and marked decrease in NAA/Cr ratio has been described in infiltrative low grade glioma and diffuse gliomatosis. In patients with LE, where pathological examination has been performed, inflammatory infiltrates, microglial proliferation, gliosis, and neuronal loss are found in the brain regions affected on neuroradiological studies. Increased ml levels reflect the gliosis and NAA is a marker of neuroaxonal integration.

Repeat MR imaging usually shows complete regression of mesial temporal lesions. If swelling persists or is present for longer than around 6 months, it is usually associated with a lack of clinical improvement, despite anti-inflammatory or immunomodulatory therapy.

In all our patients resolution of the mass effect of the lesions occurred one to three months after start of the treatment but abnormal signal resolved 3 to 6 months later on. We noticed some degree of temporomesial atrophy in patient 2 and marked degree in patient 5, on six months and 3 years MR follow up. In most patients, progressive temporomesial atrophy develops, which is clearly visible around 1 year after disease onset. Taking this temporal evolution into consideration, one should be aware that hippocampal sclerosis may have developed out of LE.
Images for this section:

**Fig. 0:** FIG.1 Patient 1, initial evaluation. Coronal FLAIR, axial DWI images and corresponding ADC map show swelling and T2 prolongation in the medial temporal lobes.

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**Fig. 0:** Fig.2 Patient 1, MR study one month later. Coronal FLAIR Image, axial DW Image and corresponding ADC map. Significant resolution of the abnormalities one month after the onset of symptoms.

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**Fig. 0:** Fig 3. Patient 2, initial and six months later coronal FLAIR images. Initial swelling and T2 prolongation of hippocampal structures bilaterally, end up in atrophy.

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**Fig. 0:** Fig 4. Patient 5, MR study six months after the onset of symptoms without treatment, unchanged from initial evaluation. Axial FLAIR, DWI images and corresponding ADC map. Swelling and striking hyperintensity (T2 prolongation) of cortical and subcortical mesial temporal lobes and limbic structures.

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Fig. 0: Fig.5. Patient 5, MR study 1 1/2 -year after the onset of symptoms without treatment. Both abnormal signal and swelling persist but appear quite reduced.

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**Fig. 0:** Fig. 6. Patient 5, 3D CSI (TR/TE = 1500/35) 1 1/2 year after the onset of symptoms without treatment. Single-voxel spectra A. of the normal brain and B. of the abnormal regions. The affected brain displays increased mI/Cr and Cho/Cr and decreased NAA/Cr ratio. Compared to study performed one year before, current study shows more prominent increase in mI/Cr and slight increase in NAA/Cr ratio.

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**Fig. 0:** Fig. 7. Patient 5, MR study almost 3 years after onset of symptoms, revision of the diagnosis, being under appropriate treatment. Axial FLAIR image demonstrates significant atrophy of the medial temporal lobes.

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Conclusion

MRI reveals the involvement of the affected structures, suggests the diagnosis of LE and monitors the response to therapy. Nevertheless, MR imaging findings should be interpreted cautiously, mainly those arising from the new techniques because of the overlap with other entities.
References