Review

Limbic encephalitis due to antineuronal antibodies

Neuropsychological Aspects

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Abstract: Limbic encephalitis (LE) is an encephalopathic syndrome caused by antineuronal antibodies against extracellular or intracellular neuronal structures. LE may present clinically with a variety of symptoms, including epileptic seizures, cognitive and memory deficits, and personality changes. Whereas LE mediated by antibodies against intracellular antigens is frequently of paraneoplastic origin and associated with a poorer prognosis, LE mediated by antibodies against extracellular or transmembrane antigens causes potentially reversible neuronal dysfunction and, given early diagnosis and treatment, is associated with a comparatively benign prognosis. We present and discuss four different cases of autoantibody-mediated LE, with different clinical outcomes and both with and without paraneoplastic origin. Red flags pointing to the diagnosis of antibody-mediated LE include rapidly progressing personality changes or memory deficits and disorientation, novel epileptic seizures, and a history of neoplasia.

Keywords: limbic encephalitis, autoimmune encephalitis, autoantibodies, LGI1, NMDA receptor, amphiphysin

Limbische Enzephalitis aufgrund von antineuronalen Antikörpern: neuropsychologische Aspekte

Zusammenfassung: Die limbische Enzephalitis (LE) ist eine Encephalopathie, die durch antineuronale Antikörper gegen extrazelluläre oder intrazelluläre neuronale Strukturen hervorgerufen wird. Die LE kann klinisch mit einer Vielzahl von Symptomen einhergehen, einschließlich (neu auftretender) epileptischer Anfälle, kognitivem Abbau und Gedächtnisdefiziten sowie Persönlichkeitsveränderungen. Während die LE, die durch Antikörper gegen intrazelluläre Antigene vermittelt wird, häufig paraneoplastischen Ursprungs ist und mit einer schlechteren Prognose einhergeht, verursacht die LE, die durch Antikörper gegen extrazelluläre oder transmembranöse Antigene vermittelt wird, eine potenziell reversible Hirnfunktionsstörung und ist bei frühzeitiger Diagnose und Behandlung mit einer vergleichsweise guten Prognose verbunden. Wir präsentieren und diskutieren vier verschiedene Fälle von autoantikörpervermittelter LE, mit unterschiedlichen klinischen Verläufen, sowohl mit als auch ohne paraneoplastischen Ursprung. „Red flags", die auf die Diagnose einer antikörpervermittelten LE hinweisen, sind rasch fortschreitende Persönlichkeitsveränderungen oder Gedächtnisdefizite und Desorientierung, neu auftretende epileptische Anfälle und (bösartige) Tumorerkrankungen in der Vorgeschichte.

Schlüsselwörter: Limbische Enzephalitis, Autoimmunenzephalitis, Autoantikörper, LGI1, NMDA-Rezeptor, Amphiphysin

Introduction

Limbic encephalitis (LE) is an encephalopathic syndrome caused by autoimmune-mediated interaction at the synaptic level, that may present clinically with a variety of symptoms including epileptic seizures, cognitive and memory deficits, personality changes, agitation, sleep disturbances, and other psychiatric symptoms such as depression and affective disturbances (Graus, 2010; Graus et al., 2016; Kelley et al., 2017).

LE can appear paraneoplastically, i.e., as a symptom of a malignant disease (eventually preceding the diagnosis of the neoplasia by years); but LE can also appear without any association to malignancy.

Among the antineuronal antibodies described as causing LE are both antibodies against intracellular structures (anti-Hu, Ri, Ma2, GAD, CV2, amphiphysin antibodies) and antibodies against extracellular structures (anti-GABAa/b-receptor, NMDA-receptor, AMPA-receptor, LGI1, CASPR2 antibodies). Whereas antibodies against intracellular antigens are very frequently associated with cancer, this does not hold for antibodies against extracellular (i.e., cell-surface or transmembrane) antigens (Graus et al., 2016). However, a finding of the latter should, too, prompt careful screening for potential malignancy.

Antineuronal antibodies known to be associated with paraneoplastic encephalopathies are anti-Hu, CV2, am-

phiphysin as well as Ma2- and GABAb-receptor antibodies, which are mostly described in association with small-cell lung cancer, though they have also been observed in malignomas of the breast, ovaries, and testes as well as in thymoma. Anti-NMDA-receptor antibodies are partly associated with ovarian teratomas (Armangue et al., 2014).

The present paper presents and discusses four different clinical cases of autoantibody-mediated LE, both with and without paraneoplastic origin. It also discusses the etiology and pathogenesis and addresses the neuropsychological aspects of LE relevant to clinical practice.

Case reports

Case 1

A 35-year-old female patient presented with progressive memory and concentration impairment as well as complex partial seizures. Cerebral MRI showed increased T2 signaling in the hippocampus and amygdala (see Figure 1a). Diagnostic workup revealed highly positive anti-LGI1 antibodies in serum and CSF. In addition to antiepileptic treatment, extensive immunosuppressive therapy with methylprednisolone, followed by intravenous immunoglobulins, plasmapheresis, immunoadsorption, and finally administration of rituximab, was initiated.

Clinically, concentration and memory function improved after immunosuppressive therapy, though a slight mnestic impairment persisted. Cerebral MRI, conducted 6 years after the initial diagnosis of anti-LGI1 positive limbic encephalitis, showed constant atrophy of the hippocampus on both sides (right more than left) as residual after limbic encephalitis (see Figure 1b).

Anti-LGI1 positive limbic encephalitis can thus cause persistent damage to the CNS and has to be considered in the diagnostic workup of patients with cognitive deficits and epileptic seizures.

Case 2

A 20-year-old woman presented with changes in character and mild psychotic symptoms. Generalized epileptic seizures occurred in the course of the disease, and treatment of the patient was required in the intensive care unit. Similar symptoms (changes in character) had appeared at the age of 16 but had completely receded. Diagnostic workup revealed CSF pleocytosis (108/µl) and positive anti-NMDA receptor antibodies. cMRI revealed no structural abnormality.

The patient was treated with immunoadsorption, intravenous immunoglobulins, and finally administration of cyclophosphamide. This prompted an extensive search for teratoma or other neoplasia, but no evidence of neoplasia was revealed.

Clinically, the patient recovered completely, was able to complete her studies, and is now working as a fashion designer.

Thus, anti-NMDA-receptor-antibody-mediated limbic encephalitis may relapse, while a complete recovery from cognitive symptoms is possible.

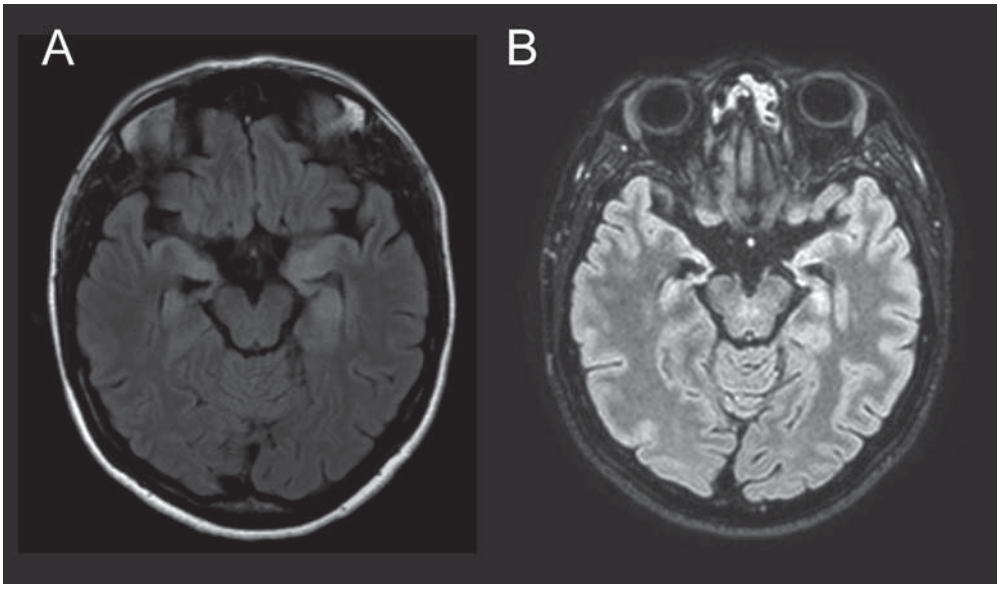

Figure 1a. Cerebral MRI imaging of a 35-year-old female patient with anti-LGI1 positive LE, showing increased signaling in the hippocampus and amygdala, indicative of autoimmune inflammation (fluid-attenuated inversion recovery [FLAIR], axial). **b.** Cerebral MRI imaging of the same patient as in Figure 1A, 6 years after diagnosis of anti-LGI1 positive LE, showing constant atrophy of the bilateral hippocampus (fluid-attenuated inversion recovery [FLAIR], axial).

Case 3

A 30-year-old woman presented with vigilance reduction and delirium upon being admitted to the gynecological department for the surgical removal of an ovarian tumor. While cMRI showed no abnormality, lumbar puncture revealed CSF pleocytosis (56/µl); anti-NMDA receptor antibodies were positive in both serum and CSF. The gynecological resection of an ovarian tumor weighing approximately 5.7 kg was performed and was histopathologically confirmed as a teratoma. Because the patient showed complex focal seizures despite anticonvulsive medication and finally status epilepticus, analgosedation and intubation were performed. In addition to anticonvulsive medication, the patient was treated with intravenous immunoglobulins, methylprednisolone, rituximab, and finally cyclophosphamide.

Clinically, the patient recovered completely: One year after the diagnosis of anti-NMDA-receptor-positive limbic encephalitis, both clinical-neurological examination and neuropsychological testing revealed no abnormality.

Anti-NMDA-receptor-antibody-mediated limbic encephalitis thus need not but may occur related to neoplasia; the association of anti-NMDA-receptor-positive encephalitis with tumors, mostly ovarian teratomas, varies with age, sex, and ethnicity, and is reported in 9–55% of cases (Armangue et al., 2014).

Case 4

A 72-year-old male patient was admitted to the hospital because of confusion and cognitive decline within the last weeks. Neuropsychological testing revealed a severe dysexecutive syndrome, and CSF analysis resulted in a normal cell count, with ß-amyloid, tau protein, and phosphotau within normal ranges. Serological testing revealed highly positive anti-amphiphysin antibodies. PET-CT conducted to detect a tumor revealed hypermetabolic foci in the descending thoracic aorta, the left kidney, and the right iliac bone. Biopsy of the right iliac bone and the renal tumor revealed an undifferentiated sarcomatoid carcinoma as the primary tumor.

The patient was treated with high-dose glucocorticoids and immunoglobulins, which led to a temporal clinical improvement. A nephrectomy was performed to treat the tumor, and chemotherapy with docetaxel was established. However, reassessment 2 months later revealed massive progress of both lesions as well as new hepatic and muscular metastases. The clinical neurological symptoms had worsened as well; the patient was disoriented and nearly bedridden. Best supportive care therapy was initiated, and the patient finally died at home about 4 months later.

Thus, (paraneoplastic) LE can be associated with several different autoantibodies and different tumors including rare neoplasia such as angiosarcoma.

The etiology and pathogenesis of limbic encephalitis due to antineuronal antibodies

Anti-NMDA receptor encephalitis was originally described in 2007 (Dalmau et al., 2007). Since then, a rapidly growing literature characterizing autoimmune encephalitis due to antineuronal antibodies has emerged (Dalmau & Graus, 2018; Bien et al., 2020). Initially, anti-NMDA receptor encephalitis was thought to be exclusively a paraneoplastic disorder occurring in young females in association with an ovarian teratoma, but today it is appreciated as occurring with or without a tumor, in both male and female patients (Kayser & Dalmau, 2011). See Figure 2 for an example of the LE pathomechanism in a patient with an ovarian tumor.

Antibody-mediated LE can be due either to antibodies against intracellular neuronal antigens or to antibodies against extracellular (cell-surface or transmembrane) neuronal antigens. Whereas some of the triggers and clinical symptoms of both syndromes are similar, the pathogenic mechanisms and outcomes are different (Dalmau & Graus, 2018). Autoimmune encephalitis associated with antibodies against cell-surface structures, binding, for example, to the extracellular domain of receptors or ion channels, causes functional and potentially reversible neuronal dysfunction and is thus associated with a comparatively benign outcome (Dalmau et al., 2017). LE mediated by antibodies against intracellular antigens, in contrast, is assumed to cause structural and irreversible brain dysfunction. Neuronal loss is frequent and cytotoxic T-cell mechanisms predominate (Bien et al., 2012; Dalmau & Graus, 2018) and is thus associated with a poorer outcome.

Two potential triggers of autoimmune encephalitis are tumors and viral encephalitis, such as herpes simplex encephalitis (HSE; Dalmau & Graus, 2018). Some of the tumors implicated contain nerve tissue, or the tumor cells express the neuronal proteins targeted by the autoantibodies, so that it is assumed that this ectopic expression triggers the autoimmune response (Lancaster et al., 2010). Because HSE can trigger the production of antibodies against NMDA receptors, this might explain immune-mediated relapsing symptoms post-HSE (Armangue et al., 2015), which are reported to occur in 10–25% of cases (where HSV-1 is no longer detectable in the CSF in most cases; Joubert & Dalmau, 2019).

Antibodies against neuronal surface antigens can target ion channels (e. g., anti-GABAa/b-receptor, NMDA-receptor, and AMPA-receptor antibodies), but others have been found to be specific for receptor-associated or regulatory molecules (e. g., anti-LGI1, CASPR2, D2, and mGluR5-receptor antibodies). Because symptoms are responsive to immunosuppressive treatment, and because mutations in many of the antigens are reported to be linked to several neuropsychiatric disorders, the antineuronal antibodies are considered pathogenic (Irani et al., 2014; Pollak et al., 2016).

Importantly, the significance of antineuronal antibodies in patients with psychiatric disorders was addressed in several studies, investigating whether specific autoantibodies could be detected, resulting directly in psychosis or thought disorders, i. e., whether (some instances of) psychiatric conditions may be due wholly to brain-reactive antibodies. However, although a clear association between, say, schizophrenia and perturbations of autoimmunity has been described (Goldsmith & Rogers, 2008), evidence for specific antineuronal antibodies in psychosis has remained elusive. For example, anti-NMDA receptor encephalitis is considered a distinct entity from schizophrenia (Kayser & Dalmau, 2016).

Schou et al. (2016) report that anti-NMDA receptor IgG autoantibodies were rarely found in patients admitted to acute psychiatric care, while CASPR2 and GAD65 antibodies were more frequently encountered compared with healthy controls and psychiatric patients in earlier studies. Gaughran et al. (2018) report a matched case-control study of patients in first-episode psychosis, identifying a similar low prevalence (6 %) of anti-NMDA receptor and/or VGKC-complex antibodies in patients with first-episode psychosis as in controls (and thus do not recommend screening in isolation for these antibodies in the subset of patients with first-episode psychosis). Doss et al. (2014) report a high prevalence of NMDA receptor IgA/IgM antibodies in patients with different types of dementia but conclude that it remains unclear whether the presence of these antibodies in patients with neurodegenerative conditions simply reflects a biomarker for progressive brain disease or whether the antibodies directly contribute to the disease process. Still, autoimmune dementia might be an underrecognized diagnosis, and a subset of patients might benefit from early immunotherapy (Flanagan et al., 2010).

Neuropsychological aspects

The differential diagnosis of antibody-mediated LE should be considered especially in the presence of certain constellations of clinical neuropsychological symptoms ("red flags"). See figure 3 for a possible clinical course of LE.

In particular, the onset of amnesia, disorientation, and personality changes over a short time course (within days or a few weeks) should prompt a search for VGKC-complex and other antineuronal antibodies (Irani et al., 2014). Novel epileptic seizures, too, should prompt cMRI and CSF diagnostics to reveal evidence of autoimmune encephalitis due, for example, to LGI1 or CASPR2 antibodies.

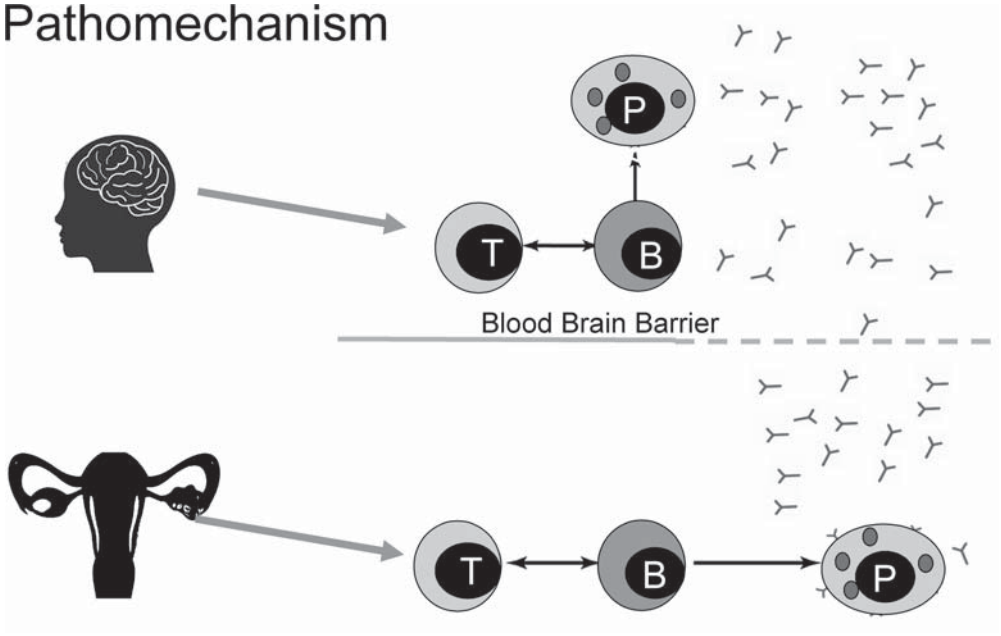

Figure 2. Possible pathomechanism of paraneoplastic LE in a patient with ovarian tumor: T and B lymphocytes are activated by the tumor, so that the latter produce autoantibodies that pass the blood-brain barrier and are directed, for example, against cerebral NMDA receptors.

If, besides neuropsychiatric symptoms, the patient's case history includes neoplasia – or if the patient shows indirect evidence pointing to a malignant disease, such as fever, night sweats, or weight loss of unknown cause – a search for antineuronal antibodies, in particular against intracellular neuronal antigens, should be prompted. Besides initiating an immunosuppressive therapy, if possible, resection of the tumor should be performed as causal therapy.

Dementia with subacute onset (1–6 weeks) and/or rapid progression, especially in patients with coexisting organ-specific autoimmunity (e.g., thyroid autoimmunity), may be due to autoimmune encephalitis and not neurodegeneration, so that an immunotherapy trial should be considered (Flanagan et al., 2010; Rössling & Prüss, 2020).

The benefit of screening for antineuronal antibodies is to date unclear for patients with first-episode psychosis (Gaughran et al., 2018). However, the presence of additional symptoms, such as epileptic seizures, focal neurological, and/or motor symptoms (tremor, myoclonus) and especially infectious prodrome with fever, should prompt consideration of an organic origin of the psychosis.

Outlook

Within the last 10–15 years, a rapidly increasing amount of literature has emerged characterizing LE due to antineuronal antibodies, both as a paraneoplastic condition and in patients with no association to malignancy. Accordingly, substantial progress in developing specific therapeutic strategies has been made.

However, the clinical significance of antineuronal antibodies in several psychiatric and neurological conditions, such as psychosis and dementia, is to date unclear. Further work is needed to elucidate a potentially autoimmune pathophysiology in a subset of patients with these conditions.

In conclusion, red flags pointing to the diagnosis of antibody-mediated LE include personality changes and disorientation over a short-term course, novel epileptic seizures or focal neurological symptoms, and a history of neoplasia. Identifying patients with possible LE is crucial, as causal therapies for autoimmune-mediated encephalitides are available, and, especially for non-paraneoplastic LE with antineuronal antibodies against extracellular structures, early diagnosis and treatment are associated with a comparatively good prognosis.

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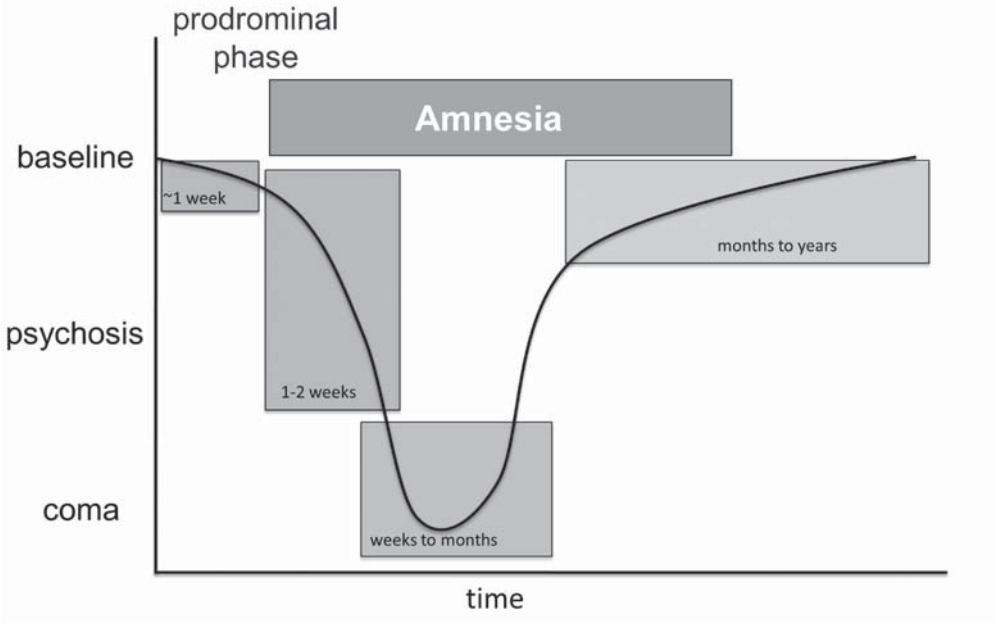

Figure 3. Typical clinical course of LE: Psychosis, personality change, and amnesia occur after a prodromal phase of 1–2 weeks, eventually followed by vigilance mitigation up to coma. After recovery, deficits need not, but may, persist for years after initial diagnosis.

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