Limbic encephalitis: A cause of temporal lobe epilepsy with onset in adult life

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Abstract

Limbic encephalitis (LE) was described in the 1960s as a clinical–pathological syndrome in adults. Initially, the paraneoplastic form was the center of interest. An increasing number of diagnostically valuable autoantibodies in patients’ sera (and cerebrospinal fluid) have been identified. Lately, the impact of non-paraneoplastic LE cases has been acknowledged. In the serum of some of these patients, antibodies against voltage-dependent potassium channels (VGKC antibodies) have been detected. The characteristic MRI course of LE patients has recently been described in detail: hippocampal swelling and T2/FLAIR signal increase are early findings. After a few months, the swelling regresses, followed by hippocampal atrophy with continuous signal increase. A general consensus on formal diagnostic criteria for all LE subsyndromes has not yet been reached. This article proposes such diagnostic criteria and formulates suggestions for treatment.

Keywords: Limbic encephalitis; Adult-onset epilepsy; Autoantibodies; Paraneoplastic neurological syndromes; Immunotherapy; Memory deficits; Mood disorders

1. Introduction

In recent years, the syndrome of noninfectious limbic encephalitis (LE) has received increasing attention by clinicians and neurological researchers alike. This is reflected by a marked increase in publications dealing with this issue (see Fig. 1). Temporal lobe seizures constitute a typical symptom of LE. Therefore, this syndrome is of interest to neurologists and epileptologists.

2. Historical and systematic overview of limbic encephalitis

2.1. First description of the syndrome

The term limbic encephalitis was first used by British neuropathologists and neurologists in the 1960s [1,2]. Brierley, Corsellis, and members of their team described six patients between the ages of 50 and 80. They died after a progressive neurological disease marked by a serious impairment of their episodic memory. Some also had epileptic seizures as well as affective disturbances. In addition to these limbic symptoms, disturbances in cerebellar or brainstem functions or symptoms of a polyneuropathy were observed to varying degrees in these patients. The autopsy examinations revealed signs of a chronic encephalitis with infiltration of round cells (lymphocytes) and microglial as well as astrocyte activation. Brierley notes that these changes proved to be “mainly affecting the limbic areas.” Nerve cell losses were also documented. According to the authors, the “limbic lobe” included the uncus, the amygdala, the hippocampus, the limen insulae, the hippocampal gyrus, and the cingulate gyrus. Other parts of the nervous system were also affected to varying degrees by the encephalitis, in particular, the brainstem, the cerebellum (in which a loss of nerve cells was also occasionally observed), and the spinal ganglia. In four of the six patients, Brierley and Corsellis found tumors (three of
these were lung tumors) on autopsy. The association of LE with cancer led to the concept of paraneoplastic limbic encephalitis (PLE).

2.2. Autoantibodies in patients with PLE

In the 1980s and 1990s, this concept was considerably strengthened when Jerome Posner’s laboratory at the New York Sloan–Kettering Center demonstrated that patients with a neurological syndrome combined with a (peripheral) tumor harbored serum autoantibodies (auto-abs) that reacted with the tumor tissue as well as with brain cells of test slices. The neurologists in New York named the auto-abs (apart from Hu abs) after the first letters of their index patients’ last names. The first ab they discovered (which was later also found in patients with PLE) was called Hu ab [3–6]. Later, additional “paraneoplastic” auto-abs were described. Within the context of PLE, the following auto-abs (apart from Hu abs) “well characterized”; that is, they are sufficiently and dependably detectable and specifiable [7]: Ma/Ta [8–10], CRMP5/CV2 [11–15], and amphiphysin [16,17] abs. What all of these abs have in common is that they are directed against antigens located intracellularly. A common method of searching for these auto-abs is as follows: first, diluted patient serum is incubated with an animal brain section (usually from rodents or primates after perfusion and fixation with paraformaldehyde [PFA]), in the sense of a screening procedure. Antibodies binding to brain cells are detected using immunohistochemical techniques, and their binding behavior is microscopically evaluated. In typical cases, the staining pattern indicates the specificity of the ab. A serum study using a Western blot against brain extract or recombinant antigen (Ag) is then used for confirmation. The specificity of these abs for a tumor is almost 100%. Sensitivity is 60%; that is, 40% of the patients with PLE are negative for these abs [18]. A tumor resection appears to be the best choice for improving the patient’s situation, or at least stabilizing the patient’s neurological deficits. Immunotherapy, on the other hand, seems to be only marginally promising in terms of improving the patient’s condition [19,20]. It should be noted that in long-surviving Hu ab-positive patients, there was no correspondence between the course of the ab titers and the clinical course [21].

In 2004, an international group of neurologists called PNSEURONET (http://www.pnseuronet.org) published diagnostic consensus criteria for paraneoplastic neurological syndromes. This publication determined the criteria for “definite” and “possible” paraneoplastic syndromes. On the one hand, this made it possible to compare published (or still to be published) patient groups; on the other hand, it set a minimum standard for the diagnostic evaluation of patients suspected of having a paraneoplastic syndrome. The demonstration of a “classic” clinical paraneoplastic syndrome (including the “limbic” one, on the basis of clinical signs and symptoms and morphological evidence of involvement of the limbic system) plus any of the above-mentioned “well-characterized” auto-abs, or a tumor within 5 years after onset of the neurological symptoms, permits the diagnosis of a definite paraneoplastic neurological syndrome. The most frequent sites of tumors in patients with PLE are the lung and testicles [18], but virtually any type of tumor is possible.

Lately, new types of onconeuronal antibodies directed against intracellular antigens have been detected in those with PLE: antineuronal nuclear abs type 3 (ANNA-3) [22], antiglial nuclear abs (AGNA) [23], and BR serine/threonine kinase 2 abs [24]. These findings have not yet been replicated by studies from other centers. Some of them may occur very rarely, and their specificity for a distinct clinical constellation has not been convincingly demonstrated yet. Therefore, their diagnostic relevance is uncertain. For details on these abs, see the original publications.

2.3. Non-paraneoplastic LE

Because of these landmark studies, LE was regarded exclusively as a paraneoplastic disease. There are, however, adult patients without a tumor whose clinical and neuroradiological presentation does not differ from that of PLE, and in whom (after epilepsy surgery or a diagnostic brain biopsy) a chronic lymphocytic–micronodular encephalitis was histologically verified [25]. Two groups of researchers—one in Oxford under Angela Vincent and one in the
Mayo Clinic under Vanda Lennon—published independently and almost simultaneously case studies on patients without a tumor manifesting “subacute” evolution of limbic syndromes. The patients harbored serum abs against voltage-gated potassium channels (VGKCs), and they did not have a neoplastic disease. They were therefore interpreted as having non-paraneoplastic LE (NPLE) [26,27]. VGKC abs had been known for their association with a disease of the peripheral nervous system, Isaac’s syndrome (acquired neuromyotonia) [28]. To confirm that the link between elevated VGKC ab titers and NPLE was genuine, the authors of the aforementioned series emphasized the unambiguous evolution of symptoms indicative of a disease of the limbic system. That VGKC abs are found in a disease of the peripheral nervous system, Isaac’s syndrome, as well as in a disorder of the central nervous system, NPLE, may seem confusing. This confusion is possibly even increased by the observation that VGKC abs are also detected in individuals with Morvan’s syndrome, a combination of neuromyotonia and a central nervous system disease with hypothalamic and limbic symptoms [29]. A plausible explanation of this phenotypic diversity is that VGKC abs specifically directed against VGKC subtypes (Shaker-type potassium channels Kv 1.1, 1.2, 1.6) are differentially associated with the above-named pathological conditions [30].

How dependably can it be assumed that VGKC ab-positive patients with LE do not have a paraneoplastic disease? A few patients with lung tumors and serum VGKC abs have been described in the literature [31,32]. Therefore, searching for possible tumors in patients with a VGKC ab-associated limbic disease continues to be indicated.

A remarkable characteristic of the “typical” patient with VGKC ab-associated LE, from a clinical point of view, is improvement under early-onset immunotherapy (for details, see below). This improvement appears to be relatively consistent with the fall of an elevated serum ab titer [26,33]. From a technical point of view, it must be noted that these abs are detected by means of a radioimmunoprecipitation assay based on the use of the VGKC-binding snake poison dendrotoxin. Using the above-described immunohistochemical screening method on a PFA-perfusion-fixed rat brain succeeds more reliably in cerebrospinal fluid (CSF) than in serum.

The neurological phenotype of nCMAg ab-associated cases is different from the aforementioned subtypes: some of the affected patients have symptoms indicating central nervous system effects beyond merely the temporomedial areas, such as central hypoventilation, behavioral disturbance up to a psychosis, and mild hemiparesis. Not all patients manifest the typical temporomedial signal increase on FLAIR/T2-weighted brain MRI.

2.5. Acute nonherpetic LE

Another clinically distinct subsyndrome has been observed in Japan: an acute manifestation of LE with signs of an infectious central nervous system disease—fever, impaired consciousness, seizures, elevated C-reactive protein or erythrocyte sedimentation rate, mild CSF pleocytosis—but without evidence of infection with herpes simplex (or other) virus and without a peripheral neoplastic disease [39–41]. Epileptic seizures are almost always observed. MRI of the brain reveals, in virtually all patients, bilateral temporomedial signal increase and swelling during the acute stage. There is partial regression of the MRI abnormalities during the following months. There is little (reported) experience with immunomodulation or immunosuppression in these patients. Plasma exchange can be beneficial [42]. Untreated, patients recover, but do not reach their previous cognitive performance level.

2.6. Other non-paraneoplastic cases

Based on brain MRI findings (see next subsection) and extensive tumor searches with prolonged follow-up, other patients with NPLE have been diagnosed. They neither harbored VGKC or nCMAg abs nor did they suffer from
<table>
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<tr>
<th>LE subtype</th>
<th>Most informative patient series or review</th>
<th>Antibodies</th>
<th>Site of antigen(s) recognized by antibodies</th>
<th>Type of associated tumors</th>
<th>Frequency of temporal lobe seizures</th>
<th>Specific features, additional clinical signs</th>
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| “Classic” PLE with/without abs against intracellular ags | [18] | “Well characterized”: Hu abs, Ma abs, amphiphysin abs, CRMP5/ CV2 abs | Intracellular | Most frequent: lung, testis; any other possible | 50% | Involvement of additional CNS areas (cerebellum, brainstem, hypothalamus) | 34%/23%/7%/36%
[b] | Poor prognosis quoad vitam. In long-term survivors, progressive deterioration of neurological symptoms (Poepel et al., submitted for publication) |
| VGKC ab-associated LE | [26,27] | VGKC abs | Cell membrane | Usually non-paraneoplastic
Exceptionally: lung cancer, thymoma [31,32,54] | 90% | Hyponatremia in 80% of patients | 85%/15%/0%/0% [27] | Favorable on immunotx, sometimes even spontaneously |
| nCMAg ab-associated PLE | [34,35] | nCMAg abs (known antigens: EFA6A, NMDAR subunits) | Cell membrane | Ovary (teratoma), thymoma, rarely other | 90% | 88% of patients female (because of tight association with ovarian teratoma)
Frequent involvement of other CNS areas | 57%/43%/0%/0% [34] | Favorable on tumor-tx plus immuno-tx |
| Nonherpetic acute LE | [39,41] | ? | ? | Non-paraneoplastic | 90–100% | Infectious-like, acute onset | 95%/5%/0%/0% In 12%, cingulate gyrus lesions in addition to temporomedial lesions [41] | Mild to moderate deficits without immuno-tx |
| Other NPLE | [25] | ? | ? | Non-paraneoplastic | 100% | None | 50%/50%/0%/0% | Favorable on immuno-tx |

*a abs, antibodies; AGNA, antiglial nuclear antibodies [23]; BRSK2, BR serine/threonine kinase 2 [24]; CNS, central nervous system; CRMP, collapsin response mediator protein; LE, limbic encephalitis; nCMAg, novel cell membrane antigens; NMDAR, N-methyl-D-aspartate receptor; NPLE, non-paraneoplastic limbic encephalitis; PLE, paraneoplastic limbic encephalitis; tx, therapy; VGKC, voltage-gated potassium channel.

[b] Note that the study [18] included patients investigated prior to 2000, suggesting that MRI studies were not as sensitive as today’s.
[c] Possibly biased because study comes from an epileptology department.
an acute febrile disease before onset. These patients seem to have a relatively favorable prognosis if consequent immuno-therapy is done. Temporal lobe seizures seem to be a prominent symptom in these patients [25]. It can be expected that additional diagnostic procedures will lead to an improved diagnostic classification of such patients in the future.

For a summary of the characteristics of these LE sub-syndromes, see Table 1.

3. Brain MRI findings in LE

In serial MRI scans of the brain of patients with “classic” PLE and NPLE, temporomedial swelling and T2/FLAIR signal increase can be observed during the first weeks or months of the disease. These changes are most clearly observed if the medial temporal lobe is scanned in coronal T2 or FLAIR images with thin slices (2–3 mm) in an orientation perpendicular to the hippocampal axis. This imaging technique represents a considerable gain in diagnostic sensitivity. It is established in the imaging workup of patients with epilepsy suspected of having temporal lobe seizures [43,44]. Only rarely is gadolinium enhancement observed in patients with LE. Over the course of several months the swelling recedes, while there is constant signal increase. Finally, hippocampal atrophy with persistently increased signaling emerges. This represents the residual (final) stage. It cannot be distinguished from the MRI tomographic correlate of hippocampal sclerosis. This evolution of MRI findings is observed for all LE subtypes known so far [38,41,45,46]. An example is illustrated in Fig. 2. Long-term persistence of hippocampal signal increase without clear-cut atrophy may occasionally be observed in “classic” PLE [46,47].

The most relevant MRI differential diagnosis is a temporomedial glioma. As a general rule, this transgresses the anatomical borders of hippocampus and amygdala and then infiltrates the insular cortex and thalamus [46]. Another differential diagnosis is hippocampal swelling caused by status epilepticus or a series of seizures [48–53], which can also evolve into hippocampal sclerosis. Viral encephalitis, in particular herpes simplex virus (HSV) encephalitis, must be excluded through CSF examination including HSV polymerase chain reaction and HSV ab testing. Presently, it cannot be determined how relevant CSF examination is as an independent positive criterion for the diagnosis of LE. Clearly identified LE cases show, at most, a slight increase in cells, protein, and, at times, oligoclonal banding in CSF. Due to the absence of appropriate control groups, the sensitivity and specificity of such findings remain uncertain. For now, the diagnostic role of a CSF examination remains, aside from the emerging testing for neuropil abs, the means for excluding or proving infectious encephalitis.

4. Formal diagnostic criteria

Diagnostic criteria have so far been established in the above-described stringent form only for the so-called “definite” PLE cases [7]. Because these criteria are highly specific, their sensitivity is low. In particular, patients with newly described ab reactivities (e.g., nCMAg abs) or those with NPLE subsyndromes are not included here. It should be noted that these patient groups may strongly profit from...
early therapy. Diagnostic procedures justifying therapeutic interventions with an improved balance between sensitivity and specificity are, therefore, highly desirable. In the following, we suggest more universal diagnostic criteria for LE (paraneoplastic and autoimmune non-paraneoplastic forms):

Clinical “limbic” signs that manifested in adulthood no longer than five years previously\(^1\) must be regarded as an indispensable diagnostic prerequisite. The patient concerned must have at least one of the following symptoms: disturbance of episodic memory, epileptic seizures of temporal semiology, or affective disturbances with a prominent lability of mood and lack of inhibition. Additional parts of the central or peripheral nervous system may be involved. In addition to the clinical characteristics, one of the following additional features must be observed and verified: neoplasm, LE-associated auto-ab, temporomedial FLAIR/T2 signal increase on an MRI scan that is not otherwise explainable,\(^2\) or a chronic lymphocytic–microglial LE demonstrated on histopathological examination of a brain specimen. These criteria are summarized in Table 2. The postulation for at least one of these additional criteria is based on the experience that although none of these criteria are obligatory, each one by itself seems to have a high diagnostic specificity within the context of the corresponding clinical signs.

### 5. The question of the appropriate extent of tumor search

If a patient is suspected of having LE, a tumor search is mandatory. There is, however, no consensus on the extent and degree of sophistication of the diagnostic procedure to be followed. The most sensitive procedure for finding even small tumors is \(^{18}F\)fluorodeoxyglucose positron emission tomography (FDG-PET) of the whole body, ideally in conjunction with CT co-registration. In patients with LE who

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\(1\) This suggestion is based on the assumption that the active inflammatory disease period in LE usually does not exceed this period. VGKC ab recede markedly within 2 years, even without therapy [54], and in an ab-negative PLE, no histopathological signs of inflammation may be detected after a disease course of 2 years [55]. On the other hand, there are (very rare) patients with paraneoplastic syndromes—if a patient survives over a longer period—that relentlessly progress for several years [56] and exhibit persistent high levels of Hu ab, thereby suggesting an ongoing immune process [21]. The LE subsyndromes probably differ in their tendency to become chronic. At this time, therefore, it is not possible to postulate a general limitation of time as a diagnostic criterion. Nevertheless, it is certainly very rare to observe a patient with an active inflammatory process due to LE after a disease period longer than 5 years. The use of this 5-year criterion has an additional advantage: It integrates the consensus rule [7] that a neoplasm needs to be detected within 5 years of onset of neurological symptoms to be regarded as the underlying cause of a “PLE.”

\(2\) Any patient with TLE with disease onset in adulthood and MRI evidence of hippocampal sclerosis may thus also potentially fall into this diagnostic category. Previous experience, however, postulated the existence of “secondary hippocampal sclerosis,” that is, related to a remote brain insult (“initial precipitating injury”) [57,58] or extrahippocampal brain lesions (“dual pathology” [59,60]). Therefore, should cases with a history of a previous febrile seizure, encephalitis, head trauma, or other concomitant brain lesion be exempted from the tentative diagnosis of LE? It may be suggested that in those cases, tumor and antibody searches are done, as proposed here. If these are negative, the hippocampal sclerosis should be regarded as “secondary,” that is, linked to the previous brain injury or lesion rather than a feature of NPLE. In “idiopathic” cases of hippocampal sclerosis with TLE manifestation in adult life, however, the aforementioned diagnostic guidelines should be applied without reservation.
test positive for a paraneoplastic well-characterized ab, whole-body FDG-PET has proven to be very effective. In several series it was possible to visualize malignant tumors in such patients by this technique even when conventional tumor searches had been negative [61–63]. If the application of this procedure is not limited to cases of well-characterized paraneoplastic auto-ads then, not unexpectedly, false-positive findings are possible; that is, hypermetabolic areas are discovered that, when histologically examined, do not contain any tumor cells (e.g., nonspecific inflammation is observed instead) [64]. With this in mind, it appears appropriate to recommend a diagnostic procedure adapted to the individual’s risk profile. The procedures practiced in our department are summarized in Table 3.

### 6. Differential diagnoses

The following alternative diagnoses need to be considered: viral encephalitis caused by HSV and other herpesviruses like human herpesvirus 6 (usually in immunocompromised patients [65]), WHO grade II or III glioma or primary central nervous system lymphoma infiltrating the limbic system, Wernicke–Korsakoff encephalopathy, steroid-responsive encephalopathy associated with autoimmune thyroiditis (SREAT, former term: Hashimoto’s encephalopathy) [66,67], systemic lupus erythematosus [68], and neurosyphilis [69].

### 7. Treatment

Data on LE therapy are limited to a few case studies and case series. The following statements must therefore be viewed with considerable reservation.

As already indicated, therapy for patients with PLE with abs against intracellular antigens tends to be frustrating. The best result is achieved by (successful) tumor therapy. This can lead to improvement or, at least, cessation of the progression of the neurological deficits [19]. Immunosuppressive or modulating therapy (e.g., corticosteroids or intravenous immunoglobulins [IVIG]) does not appear to have negative effects on the prognosis of the tumor and, so, can be an add-on therapy, possibly leading to an improved outcome in some cases [18–20]. There are no reports that indicate which kind of immunotherapy should be used [70]. Patients are usually treated with one or more of the following: IVIG, plasma exchange, or steroids. PLE without onconeuronal antibodies and that with Ma2 antibodies (with or without anti-Ma1) [10] seem to respond better to immunotherapy. For practical purposes, it has been recommended that 500 mg intravenous methylprednisolone be administered for 5 days. Should this stabilize or improve the situation, then this treatment can be repeated every 6–8 weeks. If the disease is progressive, 0.4 g/kg body wt IVIG should be administered on 5 consecutive days (i.e., a total dose of 2 g/kg body wt). If there is still no response, plasma exchange of cyclophosphamide (e.g., 750 mg/m² body surface intravenously every 4 weeks) can be considered. It is emphasized that even restraining disease progression should be considered a success. If after two or more therapeutical interventions there is still no stabilization or improvement, long-term therapy or additional immunotherapeutic attempts should not be considered [71].

For patients with PLE with neuropil abs, a combination of tumor therapy (as a rule tumor resection plus possibly radiation or chemotherapy) and steroid treatment, which is sometimes complemented by IVIG, plasma exchange, or other immunosuppressants, seems so far to offer the best chance of at least partial reestablishment of neurological and cognitive performance [35].

In VGKC ab-associated cases, IVIG, plasma exchange, or corticosteroids seems to lead to improvement of neurological and cognitive performance in many patients [26,27].

For ab-negative LE cases, even less is known. Antibody-negative individuals with PLE appear to have a rather negative prognosis even under therapy [18]. At least some ab-negative patients with NPLE respond to high doses of steroids [25].

For initial management of patients suspected of having LE, these ab-based differentiations are irrelevant, because the results of the ab tests are available only after several
weeks. It is therefore recommended that immunotherapy be initiated immediately after the tentative diagnosis of “LE” (which comprises exclusion of the most relevant differential diagnosis, in particular, HSV encephalitis) [72].

8. Open questions

Many questions remain unanswered. In particular, the question of the etiopathogenesis of LE with characterization of the immunodominant antigen or antigens and of the effector cells or substances responsible for brain damage is of high interest. Today it is generally assumed that the onconeural auto-ants directed against intracellular antigens are highly relevant for diagnostic purposes, but do not play a pathogenic role. Instead, T lymphocytes probably have a decisive role in damaging the central nervous system (for a review of these aspects, see [73]). Conceivably, VGKC abs and the recently discovered NMDAR abs play a pathogenic role. The formal proof (in particular, passive disease transfer to laboratory animals) of this attractive hypothesis has not yet been rendered. A modern, detailed histopathological study of the encephalitic changes in LE brain specimens (obtained in diagnostic brain biopsies or in postmortem studies) could help determine which pathological effector mechanisms are involved. In this context, it would be of interest to examine why the frequency of LE, particularly of novel subtypes, seems to be increasing in recent years. In Japan, an Urgent Conference on Limbic Encephalitis was held at Ichikawa in November 2002 because of growing concern over the increasing numbers of identified cases [39]. (It could, however, be that the growing use and the increasing sensitivity of MRI account for this apparent increase in cases.) Finally, it would be desirable to reach an international consensus on the diagnostic criteria for LE and treatment recommendations.

9. Summary and recommendation

LE should be considered a differential diagnosis in any adult patient with newly developed temporal lobe epilepsy (which is a rare event in adults) [74,75] and/or rather quickly (over days to weeks) a mnestic disturbance. Affective disturbances, particularly loss of inhibition and lability of mood, are typical psychopathological symptoms. None of the symptoms described are necessarily observed in LE. Thus, the disease can be observed in any neurological center as well as in inpatient and outpatient departments specializing in epilepsy, memory disturbances, and mood disorders. Patients with LE developing in childhood or adolescence have not been described so far. However, it cannot be excluded that such a constellation can also occur. If LE is suspected, MRI of the brain, acquiring thin T2/FLAIR slices perpendicular to the hippocampal axis, should be performed; tumor and auto-ab searches should also be done. Once the diagnostic criteria for LE have been fulfilled, long-term immunotherapy is recommended; in paraneoplastic cases, tumor treatment has priority.

References

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