10.4414/sanp.2023.03274 | 2023;174(2):40–43 | Swiss Arch Neurol Psychiatr Psychother

Review article | Peer reviewed article

A narrative review

Neuropsychiatric symptoms of autoimmune limbic encephalitis between neurology and psychiatry

Sirine Dehmani[a], Joelle N. Chabwine[a,b]

[a] Neurorehabilitation Division, Fribourg Hospital, Meyriez-Murten, Switzerland; [b] Laboratory for Neurorehabilitation Science, Department of Neuroscience and Movement Science, Medicine Section, Faculty of Science and Medicine, University of Fribourg, Switzerland

Summary

Historically, several brain structures implicated in emotional regulation were commonly grouped under the umbrella of the "limbic system". However, the conceptual definition, as well as the constitutive anatomy and the function of the limbic system changed several times, as the knowledge of the brain evolved. The limbic system, initially defined as a "border" zone located at the edge of the encephalon, functionally lays at a "clinical" border between psychiatry and neurology. Limbic encephalitis (LE) illustrates this concept well. Indeed, although being an authentic neurological disease, its (early) psychiatric symptoms are increasingly being recognised and paid attention to. However, the heterogeneity of these symptoms (often falsely related to a purely psychiatric disease at initial stages) adds to the diagnosis difficulty, which often delays the right therapy and worsens the disease outcome.

While LE can be infectious (mainly herpetic) or autoimmune, through this narrative review, we aim to provide a conceptual overview of the limbic system anatomy and function, to summarise the current understanding and management of the autoimmune LE and to describe and analyse neuropsychiatric manifestations of autoimmune LE, as well as their treatment. We hope to help clinicians to identify and diagnose (autoimmune) LE (especially early neuropsychiatric symptoms) with the shortest delay, in order to initiate appropriate treatment on time.

Introduction

The limbic system

Historically, the term 'limbic' was first introduced by Thomas Willis (1664) to name a cortical region surrounding the brainstem (limbus is the Latin word for 'border') [1]. Later, Paul Broca (1878) described the existence of a wide brain area that he called 'le grand lobe limbique' because, more than just being a simple functional area, it encompassed several lobes [2]. Located at the "limbus" (edge) of the brain hemispheres [3], the limbic system was mainly understood as an olfactory structure common to all mammalian brains, although Broca already argued that limbic functions were not limited to olfaction [4]. In 1937, James Papez described a circuit of cerebral connections (the Papez circuit) linking action and perception to emotion [5], which mainly included the cingulate cortex, the anterior thalamic nucleus, the hypothalamic mammillary bodies and the hippocampus [6]. According to Papez, emotion arises either from cognitive activity through the hippocampus or from visceral and somatic perceptions via the hypothalamus [4]. Later, MacLean (1949, 1952) observed autonomic reactions (e.g., changes in the respiratory pattern, blood pressure and heart rate) generated by the stimulation of the rhinencephalon, being the reason why he referred to the rhinencephalon as the "visceral brain" [3] and coined the term "limbic system" after the later, focusing on the functional instead of an anatomic system. In this perspective, the amygdala, the septum lucidum and the prefrontal cortex were adjoined to the previously described structures of the Papez circuit [7].

As neuroscience progressed, the limbic system underwent multiple redefinitions over time, alongside a greater knowledge and understanding of brain structures and functions. However, constitutive structures (all supratentorial) remained roughly similar to those defined by Broca, Papez and the others (see above) [8]. Recently, Heimer and Van Hoesen [9] highlighted the importance of the basal forebrain regions (including the striatum, globus pallidus, hippocampus, septal nuclei, hypothalamus, nucleus basalis of Meynert and the central and medial amygdaloid nuclei), owing to their functional and anatomical connections with the limbic region [6].

Brain regions constituting the limbic system participate in diverse neural pathways integrating emotion with sensory-motor and cognitive functions [6]. While the limbic system was initially suggested as the only structure involved, more or less exclusively, in the emotional regulation, it is now considered to be part of the brain system, controlling visceral

and autonomic processes [1], while also participating in various cognitive functions (e.g. spatial memory, learning, motivation, emotional and social processing) [8]. Alternative functional models are currently proposed, including distinct networks related to different functions instead [4].

The limbic system remains a constantly evolving anatomical and physiological concept encompassing several brain areas and functions, considered either as a whole made of connected structures or as a set of disparate regions with questionable functional relationships.

Table 1: Autoimmune LE antibodies according to antigen localisation* [12, 24]

Antibodies against surface antigens (neurons and synapses)	Antibodies against intracellular antigens (neurons)
Glutamatergic receptors: NMDA, AMPA, mGluR1, mGluR5	
Voltage-gated channels: VGKC (LGI1, CASPR2), VGCC	Anti-Hu, Anti-Ri, Anti-CV2/CRMP5, Amphiphysin, Anti-Yo, Anti-Ma2 (Ta), GAD, CRMP5
GABA receptors: $GABA_BR$	
Glycine receptors: GlyR	

* For the abbreviations, refer to the abbreviation list.

Limbic encephalitis

Limbic encephalitis (LE) is an acute or subacute inflammatory process involving limbic structures. The inflammation can be infectious (mainly herpetic) or purely autoimmune, hence the classical distinction between herpetic and non-herpetic origin in the characterisation of LE [10]. Among herpetic LE (HLE), the herpes simplex virus 1 (HSV1) is the most frequent cause, even if the human herpes virus 6 (HHV6) may be suspected in immunodeficient patients [11]. Other infectious aetiologies (neurosyphilis, Whipple's disease and primary human immunodeficiency virus infection) are rare. Autoimmune LE can be paraneoplastic or non-paraneoplastic, depending on suspected/demonstrated association with a cancer or not [12].

List of abbreviations

AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionacid
CASPR2: Contactin-associated protein 2
CV2/CRMP5: Collapsin response mediator protein 5
CSF: Cerebrospinal fluid
EEG: Electroencephalography
GABA: Gamma-amino-butyric acid
GAD: Glutamic acid decarboxylase
Gly: Glycine
LE: Limbic encephalitis
HHV6: Human Herpes Virus 6
HLE: Herpetic limbic Encephalitis
HSV1: Herpes simplex virus 1
IVIg: Intravenous immunoglobulins
LGI1: Leucin-rich glioma-inactivated 1
mGluR1: Metabotropic glutamate receptor 1
mGluR5: Metabotropic glutamate receptor 5
MRI: Magnetic resonance imaging
NMDA: N-methyl-D-aspartate
VGCC: Voltage-gated calcium channel complex
VGKC: Voltage-gated potassium channel

Aim of the study

In this review, we will focus on autoimmune LE, which in the recent era has often raised, the discussion about the difficulty of so-called "neuropsychiatric" symptoms and the sometimes confusedly approach between neurology and psychiatry, delaying the right diagnosis and appropriate management of patients [13].

Methods

For this short narrative review, we mainly searched within the PubMed and the Google scholar databases without time limitation (main search in 2020, complementary search ending in 2021) for the following terms: "limbic system", "limbic encephalitis", "neuropsychiatric symptoms", "psychiatric symptoms", "autoimmune", and "autoantibodies". We pragmatically selected, first from the abstracts and secondarily through the full texts, the articles that contained meaningful and informative data.

Autoimmune limbic encephalitis

Autoimmune LE supposedly underlies mechanisms related to IgG autoantibodies targeting either neuronal surface proteins or intracellular antigens. A number of antibodies have been identified (a detailed list showing their target and location is found in the table 1) [14], among which, cell surface antibodies are associated with lower risk of malignancy and antibodies targeting intracellular species tend to be more related to cancers, hence their characterisation as "onconeural antibodies" [14, 15]. However, there is no way to clinically distinguish paraneoplastic from non-paraneoplastic autoimmune LE solely based on the antibody species due to several overlaps [16].

Paraneoplastic LE have been associated with nearly all types of cancer. Despite the absence of absolute specificity, there is a trend for some malignancies to be associated to particular antibodies [14]. In addition, it should be noted that the absence of cancer does not imply non-paraneoplastic, as paraneoplastic LE can occur long before (tumour undiagnosed in 50-80% of patients at the time neurological symptoms manifest) [17], concomitantly or after the diagnosis of cancer [14]. Thus, investigations in search of cancer should be systematically warranted in presence of autoimmune LE. European guidelines recommend such screening for five years following the occurrence of LE [10, 14]. Thereafter, the probability for autoimmune LE to be paraneoplastic becomes low [10].

On a clinical ground, LE share several typical patterns, namely the so-called triad made of anterograde amnesia, seizures and psychiatric symptoms [13], while the disease course begins with flu-like symptoms. Atypical manifestations such as chronic pain and other sensory symptoms, nystagmus, cerebellar ataxia or visual loss, are not rare (~80% of patients with LE) [18]. The basic LE workup includes lumbar puncture and brain magnetic resonance imaging (MRI) [11]. Recently, Graus et al. defined four criteria for the diagnosis of autoimmune LE [10] (table 2), consisting of subacute symptoms (<3 months) suggesting the limbic system involvement, bilateral imaging of abnormalities in the medial temporal lobes, either abnormal cerebrospinal fluid (CSF) or electroencephalogram (EEG) and reasonable exclusion of other possible causes.

A differential diagnosis between HLE and autoimmune LE has to be made primarily, given the dramatic consequences on therapeutic orientation and the need to rapidly initiate the most appropriate treatment. Table 3 shows subtle differences that can give orientation to clinicians [11], even if such an early differentiation remains challenging [12]. The highest differentiating criteria appear to be the acute symptoms onset and fever (sensitivity 0.92, specificity 1) and the absence of basal ganglia involvement (sensitivity 0.82, specificity 1),

Table 2: Diagnostic criteria of autoimmune LE according to Graus et al.* [10]

N°	Criteria
1	Subacute onset (rapid progression of less than three months) of working memory deficits, seizures or psychiatric symptoms suggesting involvement of the limbic system. At least one of the following: • CSF pleocytosis (white blood cell count of >5 cells per mm^3) • EEG with epileptic or slow-wave activity involving the temporal lobes
2	Bilateral brain abnormalities on T2-weighted fluid-attenuated inversion recovery MRI highly restricted to the medial temporal lobes
3	Bilateral brain abnormalities on T2-weighted fluid-attenuated inversion recovery MRI highly restricted to the medial temporal lobes
4	Reasonable exclusion of alternative causes

* For the abbreviations, refer to the abbreviation list.

whereas paraclinical investigations have poor sensitivity [19] and specificity (except in autoimmune LE the presence of autoantibodies in the serum and/or the CSF [19, 20] and in HLE the identification of the causing infectious agent).

In practice, above-mentioned complementary tests are not useful as single diagnostic tools. Clinicians should therefore base their autoimmune LE diagnosis on clinical criteria (indication of limbic system involvement, acute or subacute course) and indications from paraclinical results, even when specific autoantibodies are missing (e.g., absence of evidence for infectious aetiologies) [10]. Finally, other possible causes of the rapidly evolving dementia [21] have to be ruled out, such as systemic inflammations, toxic-metabolic conditions and rare infectious conditions including the Creutzfeldt-Jakob disease [14].

In general, autoimmune LE responds well to comprehensive immunotherapy. First-line immunotherapy, consisting of steroids, intravenous immunoglobulins (IVIg) and plasmapheresis is effective in the great majority of patients with autoimmune LE. The second-line immunotherapy, including rituximab and cyclophosphamide [22, 23], can be used for the minority of non-responders [24], sometimes in association with first-line treatments [12, 24]. Paraneoplastic LE appears to have a worse prognosis than non-paraneoplastic LE [12], even if treating the associated cancer significantly improves the outcome [12, 24].

Neuropsychiatric symptoms in autoimmune limbic encephalitis

Neuropsychiatric syndromes constitute by a set of neurological, psychiatric or a mixture of both category symptoms, recalling neurological or psychiatric diseases or indistinctly both. The limbic system is among the brain areas most likely to display such symptoms [8, 25]. Neuropsychiatric symptoms are present in 20% of autoimmune LE. Furthermore, one third of these patients are inadequately admitted in psychiatric divisions at first evaluation [18] and about 80% of those with anti-N-methyl-D-aspartate (NMDA) receptor (NMDAR) antibody encephalitis present to psychiatric providers first [13, 26–28]. These observations, in addition to the high burden of long-lasting complications when the LE treatment is delayed, point out the importance of early recognition or suspicion of an underlying somatic disease in presence of psychiatric symptoms. The typical triad mentioned earlier (anterograde amnesia, seizures and psychiatric symptoms ranging from personality change to delirium [13]) should be highly evocative.

Unusual psychiatric symptoms (listed in table 4) should cue suspicion of an underlying organic process (in this case, autoimmune LE), especially if the first-line psychiatric workup is unrevealing [13, 18]. On the other hand, the following features should trigger cautiousness and attention regarding autoimmune LE as possible aetiology and warrant appropriate patient orientation and workup: abnormal age of symptom onset such as late-onset mania [29], associations between catatonic features or multiple other symptom presentations with delirium, subacute anterograde amnesia [10], personality change [10], early neurocognitive decline and non-auditory hallucinations [30], abrupt or florid symptom onset [31], rapid [32] or fluctuating progression of symptoms [33] and resistance to conventional psychiatric interventions [23].

Although there is no specificity for LE neuropsychiatric symptoms regarding antibody species, some interesting epidemiological observations can be made. Anti-NMDAR antibody LE includes psychosis, mania, depression or catatonia [13], often progressing to seizures, dysautonomia and hypoventilation [34]. Three out of eleven patients with anti-metabotropic glutamate receptor 1 autoantibody LE exhibit cognitive impairment, describe paranoia and auditory hallucinations [35], while anti-leucin-rich glioma inactivated 1 antibodies are closely associated with seizures (among which, faciobrachial dystonic seizures appear to be pathognomonic [36]), as well as anti-gamma-aminobutyric acid B antibodies [37]. LE is less commonly associated

Table 3: Indicative frequency of symptoms and investigation results in HLE versus autoimmune LE* [11, 12, 24, 37, 40]

	HLE	Autoimmune HLE
Acute onset**	+++	+
Fever**	+++	+
Psychiatric symptoms***	+	+++
Cancer	–	++
Normal neuroimaging (brain MRI)	+	++
Normal brain MRI or CSF	–	++

* For the abbreviations, refer to the abbreviation list. ** Symptoms observed <7 days before consultation. *** Behavioural disorder, depression and psychosis. – In general, absent, + Low frequency, ++ Medium frequency, +++ High frequency.

Table 4: Psychiatric and neuropsychiatric symptoms raising suspicion for autoimmune LE adapted from [13]*

Psychiatric symptoms	Personality change
	Multiple symptom presentations
	Non-auditory hallucinations
	Catatonic features not attributable to a primary psychiatric disorder (especially when comorbid with delirium)
Neuropsychiatric symptoms	Unexplained delirium
	Early neurocognitive decline
	Subacute anterograde amnesia
Symptom history	Abnormal age of symptom onset, such as late-onset mania
	Rapid progression of symptoms
	Fluctuating symptoms, changing over days to weeks
	Symptoms resistant to conventional psychiatric therapies

* For the abbreviations, refer to the abbreviation list.

with anti-contactin-associated protein 2 antibodies [13].

Management of neuropsychiatric symptoms in autoimmune LE is primarily based on aetiological treatment. However, one should be cautious as some immune therapies are susceptible of exacerbating psychiatric symptoms directly (e.g., steroids) [38] or indirectly (e.g., rituximab, through progressive multifocal leukoencephalopathy [39]). Symptomatic treatment should be appropriately conducted as needed (e.g., benzodiazepines, mood stabilisers, neuroleptics, etc.), although LE patients seem to poorly respond to classical psychiatric medication [13].

Conclusion and limitations

The limbic system, initially defined at the "edge" of the brain hemispheres, currently encompasses various structures involved in several functions of the emotional regulation and its cognitive, autonomous or somatic (sensory) counterparts, concordant with the increasing knowledge of the brain's structural and functional organisation. Limbic dysfunction, as illustrated by autoimmune LE symptoms, involves both neurological and psychiatric symptoms, thereby defining a clinical "border" between neurology and psychiatry.

Neuropsychiatric manifestations are frequent in autoimmune LE and deserve clinicians' attention. Furthermore, the difficulty to disentangle their primary psychiatric versus somatic origin, which often delays the initiation of the appropriate treatment, remains one of the challenging issues in managing autoimmune LE. In this review, we circumscribed clinical boundaries of LE with a special focus on neuropsychiatric symptoms of autoimmune LE, towards which we wished to raise clinicians 'awareness. In addition, we attempted to give some key messages regarding clinical diagnosis and workup, with the aim to reduce a delay of diagnosis and treatment.

This narrative review was not exhaustive and a more systematic review would have covered the topic more completely. Nevertheless, we made the effort of focusing on the most important and helpful messages for clinicians in their practice. Neuropsychiatric symptoms are poorly documented in autoimmune LE (and other neurological diseases), hence the lack of studies comprehensively characterising them. We therefore hope this review will contribute to increase the awareness of practitioners and prompt them to seek and report such symptoms more frequently, especially in neurological diseases such as autoimmune LE.

Take-home message

From a somatic point of view, psychiatric symptoms of acute/subacute evolution should warrant a minimal workup including brain imaging, CSF analysis and EEG in search of LE stigmata. After excluding infectious aetiologies (mainly HSV1 and in some specific cases HHV6), any LE should be considered to be autoimmune. From a psychiatrist perspective, any syndrome presenting with atypical patterns, especially when associated with neurological symptoms, should be rapidly referred to a neurologists for appropriate investigation and treatment targeting. Due to poor sensitivity of complementary investigations for autoimmune LE, appropriate immune therapy should be initiated as soon as possible (after ruling out infectious aetiologies), based on clinical arguments, even if paraclinical evidence (e.g., presence of MRI lesions, identification of specific autoimmune antibodies) is missing. In addition to this first-line aetiological treatment, management of neuropsychiatric symptoms in autoimmune LE remains symptomatic.

Correspondence
Dr Joelle N. Chabwine
Neurology Division
Internal Medicine Department
Fribourg Hospital
P.O. Box
CH-1708 Fribourg
Joelle.chabwine[at]unifr.ch

Disclosure statement
No financial support and no other potential conflict of interest relevant to this article was reported.

Recommended references

2 Pessoa L. Hof P.R. From Paul Broca's great limbic lobe to the limbic system. J Comp Neurol 2015, 523, 2495-2500, doi:10.1002/cne.23840.
10 Graus F, Titulaer MJ, Balu R, Benseler S, Bien CG, Cellucci T, et al. A clinical approach to diagnosis of autoimmune encephalitis. Lancet Neurol 2016, 15, 391-404, doi:10.1016/S1474-4422(15)00401-9.
21 Rosenbloom MH, Atri A. The evaluation of rapidly progressive dementia. Neurologist 2011, 17, 67-74, doi:10.1097/NRL.0b013e31820ba5e3.
24 Shojima, Y, Nishioka, K, Watanabe, M, Jo, T, Tanaka, K, Takashima, H, et al. Clinical Characterization of Definite Autoimmune Limbic Encephalitis: A 30-case Series. Intern Med 2019, 58, 3369-3378, doi:10.2169/internalmedicine.3029-19.
25 Mega, MS, Cummings, JL, Salloway, S, Malloy, P. The limbic system: an anatomic, phylogenetic, and clinical perspective. J Neuropsychiatry Clin Neurosci 1997, 9, 315-330, doi:10.1176/jnp.9.3.315.

References
You will find the full list of references online at http://doi.org/10.4414/sanp.2023.03274.

Sirine Dehmani
Neurorehabilitation Division, Fribourg Hospital, Meyriez-Murten, Switzerland