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Limbic encephalitis: clinical and laboratory heterogeneity

***Abstract**: The limbic system is a complex set of brain structures that support a variety of functions, including sense of smell, instinctive behavior, emotions, memory, sleep, wakefulness and many others. It includes the olfactory bulb, olfactory tract, olfactory trigone, anterior perforated substance, cingulate gyrus, parahippocampal gyrus, dentate gyrus, hippocampus, amygdala, hypothalamus, mammillary body and midbrain reticular formation.*

The term "limbic encephalitis" means that the main area affected by inflammation or swelling appeared to be the part of limbic system. The core symptoms are subacute development of cognitive disorders, seizures, impairment of consciousness, sleep disturbances, some psychiatric symptoms (such as depression, irritability, hallucinations) and subacute development of short-term memory deficits. The main causes of limbic encephalitis are autoimmune process (paraneoplastic or non-paraneoplastic) and infections. The paper presents the full etiology-based classification of limbic encephalitis with the description of laboratory and radiologic findings specific for different forms of the disease.

***Key words:** limbic system, viral encephalitis, herpes simplex virus (HSV), epilepsy, diagnostics, medical case report.*

Definition

The limbic system is a complex set of brain structures that support a variety of functions, including sense of smell, instinctive behavior, emotion, memory, sleep, wakefulness and many others. The term was firstly introduced in 1952 by the American scientist Paul MacLean [1]. The structures that form limbic system are the following: the olfactory bulb, olfactory tract, olfactory triangle, anterior perforated substance, cingulate gyrus (responsible for the regulation of autonomic functions of heart rate and blood pressure), parahippocampal gyrus, dentate gyrus, hippocampus (long-term memory formation), amygdala (aggression and caution, fear), hypothalamus (regulation of the autonomic nervous system through hormones, regulation of blood pressure, heart rate, hunger, thirst, sex drive, sleep and wake cycle), mastoid body (memory formation) and midbrain reticular formation.

The term "limbic encephalitis" (LE) is used when the primary affected brain region (inflammation, swelling) includes the limbic complex (limbic system). Limbic encephalitis (LE) was described clinically for the first time in 1960 by Brierley and others [2], who have submitted observations of 3 cases of patients with subacute encephalitis, mainly affecting the limbic system.

In 1968 Corsellis et al. [3] suggested the term "limbic encephalitis" to describe patients with subacute short-term memory loss, dementia and involvement in the inflammatory process of the gray matter structures of the limbic system in combination with bronchial carcinoma. Thus they have established for the first time the link between LE and and systemic neoplasia.

Limbic encephalitis is characterized by subacute symptoms of cognitive disorders, seizures, lethargy, sleep disorders, certain psychiatric conditions (such as depression, irritability, hallucinations), and subacute short-term memory impairment. The most common causes of the LE are autoimmune process (paraneoplastic or nonparaneoplastic genesis) and infection.

Autoimmune limbic encephalitis

Autoimmune LE (like all autoimmune encephalitis) is a group of diseases caused by inflammation of the central nervous system (CNS) as the result of interaction of autoantibodies in cerebrospinal fluid and blood serum with specific neuronal antigens. In this case antineuronal antibodies directly affect two types of antigens: intracellular antigens or so-called "classic paraneoplastic antigens" and cell membrane's antigens.

The immune response against intracellular antigens is typically associated with cytotoxic T-lymphocytes, and responds poorly to therapies, while the immune attack against membrane antigens involves antibodies and due to that responds to medication better [4, 5, 6, 14].

Although it is usually described that the antigens in paraneoplastic LE are localized intracellularly and in non-paraneoplastic the localization takes place on the neural membrane, recent research data indicates that both types of antigens could be located both in the presence and absence of the tumor [4, 6, 7].

Paraneoplastic limbic encephalitis

Paraneoplastic neurological syndromes caused by antineuronal antibodies arise when the malignancy is localized outside the central nervous system expresses antigens identical to those

expressed by neurons (table). Thus, the immune response is manifested in the form of antibody synthesis, the aim of which is both tumor and specific areas of the brain. Most frequently the development of paraneoplastic LE is associated with tumors such as lung carcinoma (50%), predominantly small cells; testicular tumors (20%); breast carcinoma (8%); non-Hodgkin's lymphoma; teratoma and thymoma [8, 9, 15].

Antibodies associated with paraneoplastic limbic encephalitis

[10, adapted by I.A. Kiselev]

Antibodies against membrane antigens	Antibodies against intracellular antigens
Anti-NMDA	Anti -Hu
Anti -AMPA	Anti -CV2/CRMP-5
Anti -GABAβR	Anti -Ma2

Radiological findings. Neuroimaging of the affected limbic area is identical regardless of the type of the detected antibodies. In some patients on magnetic resonance imaging (MRI) there are no lesions, especially in the presence of anti-NMDA antibodies (more than 50% of patients with paraneoplastic LE have a normal MRI result). Among patients with changes on the MRI, the most common findings are hyperintense signal on T2-weighted and FLAIR in mesial part of temporal lobe (hippocampus), and frontal-basal and insular areas. Other possible areas of lesions, especially in patients with anti-NMDA antibodies include cerebellum, basal ganglia and brain stem.

Antibodies against membrane antigens (anti-NMDA antibody). The aim of the impact of these antibodies are epitopes of heterometric NMDA receptors containing NR1 and NR2 domains localized predominantly in the hippocampus and anterior regions of the brain. Typically, their presence is associated with ovarian teratoma and occurs mainly in young women. The clinical picture of the disease usually resembles the flu, accompanied by psychiatric symptoms, seizures and impaired level of consciousness.

Antibodies against membrane antigens (antibodies anti-AMPA). AMPA-receptors are a subtype of glutamate receptors (GluR). Antibodies against GluR1 and GluR2 of AMPA-receptors or so called "new neuronal surface antigens" are concentrated mainly in the hippocampal nerve fiber interlacements. The GluR2 subunits are also expressed in the cerebral cortex, basal ganglia and cerebellum, causing the clinical picture to exceed the profile of the classic LE syndrome-complex. Mostly women are affected (90%), aged about 60 years, most cases are associated with small cell lung cancer, thymoma and breast carcinoma.

Antibodies against membrane antigens (anti-GABAβR antibodies). These antibodies react against GABAβ receptors (receptors for gamma-aminobutyric acid), in particular against the β1 subunit (GABAβ1). About half of the LE that are associated with the anti-GABAβR antibodies have been described in patients with small cell lung cancer. The predominant clinical manifestation is a subacute onset of focal or generalized seizures in frequent association with the classic symptoms of LE.

Antibodies against intracellular antigens (anti-Hu antibodies). In most cases LE that is associated with anti-Hu antibodies develops in patients with small cell lung cancer, although (in fewer cases) may be combined with thymoma or neuroblastoma. Clinically, symptoms may manifest a wide range of CNS disorders, including classic LE syndrome-complex. Brain MRI findings vary and may include hyperintensity in T2-regime in the mesial part of temporal lobe in case of isolated LE, failure or atrophy of the cerebellar cortex with the presence of cerebellar syndromes or hyperintense signal from the brain stem in case of its' affection.

Antibodies against intracellular antigens (anti-CV2 / CRMP-5 antibodies) – autoantibodies against cytosolic phosphoprotein response to kollapsin that is most highly expressed during development of the nervous system. The presence of anti-CV2 antibodies is associated with small cell lung cancer and (in fewer cases) with thymoma. The clinical picture of the disease is heterogeneous and may include LE syndrome-complex, cerebellar syndromes (paraneoplastic cerebellar degeneration), the involvement of the peripheral nerves (paraneoplastic polyneuropathy) and eyes (paraneoplastic optic neuropathy). Among the radiological findings, which vary, may be MR signs of LE, cerebellar degeneration, or, most commonly, striatal encephalitis.

Antibodies against intracellular antigens (anti-Ma2 antibodies). These antibodies are associated with predominant involvement of the limbic system, but can also indicate a failure of the hypothalamus and brain stem. They are detected in blood and / or cerebrospinal fluid, mainly in young men with testicular germinomas and, in fewer cases, in elderly patients with small cell lung cancer. Changes on MRI in 75% of all cases correspond to the LE picture or mixed picture of lesions of the limbic, diencephalic and stem areas of the brain.

Nonparaneoplastic limbic encephalitis

Antibodies against the antigens of the voltage-gated sodium channels. Nonparaneoplastic LE is classically described as a secondary one in proportion to the presence of antibodies to the voltage-gated sodium channels, especially in their Kv1.1 subunit. However, these antibodies may

be directed to other proteins of the same channels: LGI1 (leucine-rich glioma inactivated protein 1), CASPR2 (contactin-associated protein-2) and contactin-2. Clinically, patients with LE that is associated with antibodies to voltage-gated sodium channel show the classic triad of memory impairment, confusion and seizures. Another very revealing diagnostic criterion is the presence of hyponatremia. The presence of anti-CASPR2 antibodies is not exclusive to nonparaneoplastic LE, because it correlates significantly with the presence of tumors, in particular thymoma. MR pattern in 50% of patients presents an increased T2 signal from mediobasal parts of temporal lobe of the brain, some of the findings may be unilateral.

Anti-GAD antibodies. Glutamic acid decarboxylase (GAD) is an intracellular enzyme needed to convert the exciting neurotransmitter glutamate into inhibitory neurotransmitter GABA (gamma-aminobutyric acid), and its deficiency is manifested in the form of motor hyperexcitability and mental hyperexcitability of the CNS. Anti-GAD antibodies are markers for many autoimmune diseases, such as avoidant syndrome, cerebellar ataxia and temporal lobe epilepsy. In most cases, the presence of anti-GAD antibodies is accompanied by autoimmune processes and is associated with the pathogenesis of type 1 diabetes, although some patients have connection with the presence of a tumor.

Parainfectious limbic encephalitis

Despite the broad spectrum of description of viral, bacterial and fungal pathogens associated with LE, the most frequent etiologic factors include viruses, particularly herpes simplex virus type 1 (HSV-1), which is responsible for not only the development of viral encephalitis in general, but for LE in particular. It was shown that among immunocompetent patients in more than 70% of all cases LE development was due to the persistence of HSV-1 in neurons in the limbic system of the brain. The most common cause among immunocompromised patients, particularly those infected with HIV, as well as in patients with a history of bone marrow or stem cells transplantation is considered to be other types of herpes simplex virus, such as herpes simplex virus type 2 (HSV-2) and human herpes virus types 6 and 7 (HHV-6 and HHV-7).

Typically, the clinical manifestations of parainfectious LE associated with viruses of the family Herpes viridae include subacute epileptic seizures, persistent fever, disorders of short-term and operative memory and lethargy (sleepiness), which usually progress more rapidly than in other forms of LE and lead to a rapid decrease of the level of consciousness [4, 11]. The diagnostic method of choice in this case is the technique of polymerase chain reaction (PCR) to

identify the genome of deoxyribonucleic acid (DNA) of herpes viruses in the liquor (sensitivity and specificity of methods are close to 94% and 98% respectively) [4, 5, 11]. Although there is a risk of a false-negative result in the first 48-72 hours from the onset of symptoms, and after 10 days of the acute period [5]. CSF analysis may also reveal pleocytosis and increase of protein, but these findings are nonspecific for parainfectious LE.

Radiological findings. MRI is the "gold standard" for detection of brain lesions in 90% of patients with LE associated with HSV-1. Examination usually reveals bilateral symmetrical changes on T2 and FLAIR images, including: hyperintense foci of edema, hemorrhage or necrosis and affection of basal parts of temporal lobes and the orbital regions of the frontal lobes with the spread to the insular region. Basal ganglia are usually not affected. Diffusion-weighted imaging (DWI) enable to visualize the cytotoxic edema. Pathological uptake of contrast agent (gadolinium) is not detected in the initial stages of the disease, but can be observed in the hippocampal region of the cortex as the disease progresses, usually 1 week after the onset of symptoms. Microhemorrhages at mediobasal parts of the cerebral hemispheres in the early stages of development of this type of LE are a particular finding and most characteristic of the subacute phase of the disease. Using the method of proton magnetic resonance spectroscopy (MR spectroscopy) in the parainfectious LE it is possible to identify a decrease of N-acetylaspartate (NAA) and elevation of damaging neurotransmitters of glutamate- glutamine complex (Glx) at various sections of the limbic system, more often in the hippocampus [12, 13, 16, 17].

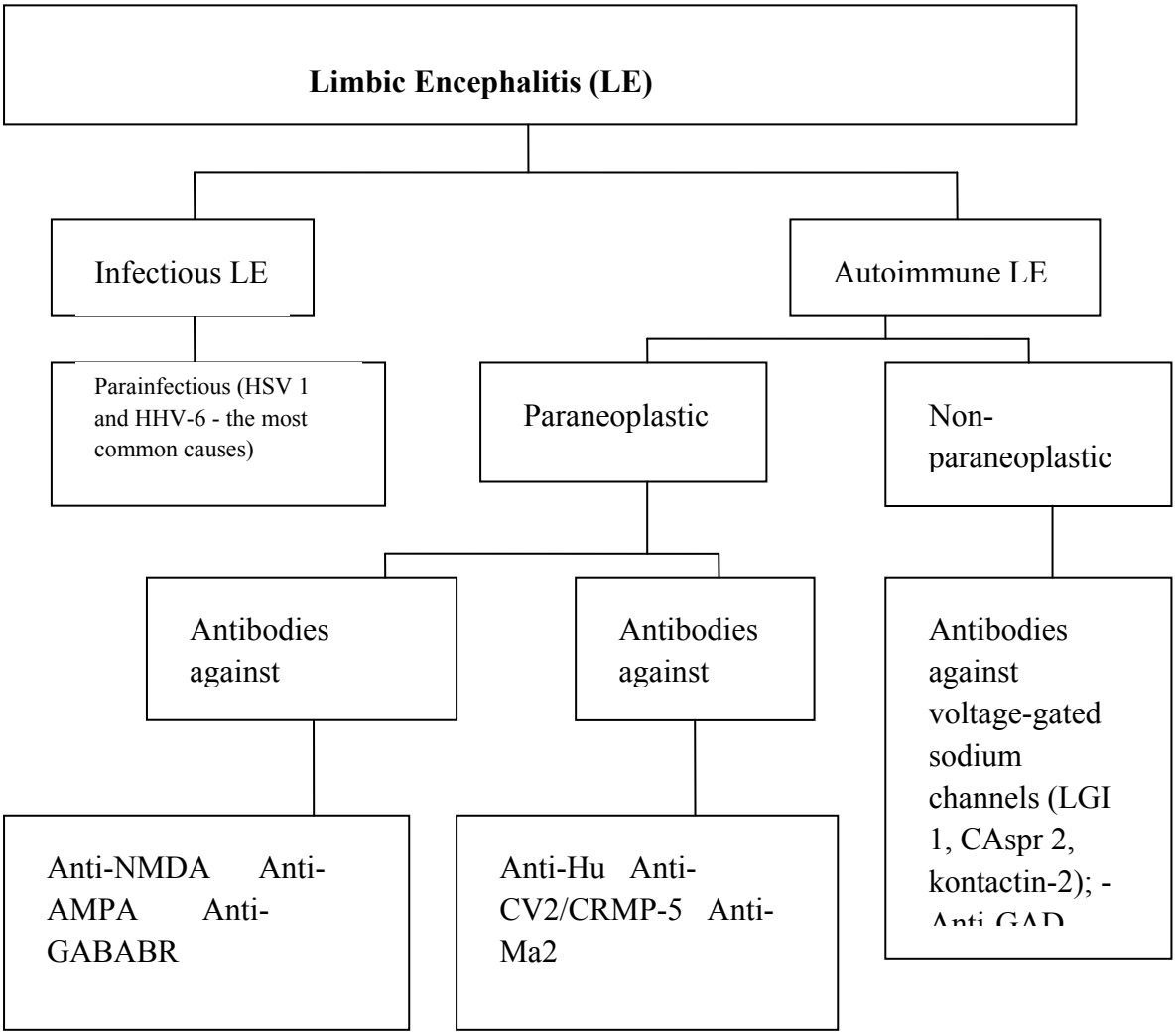

Figure 1. Aggregate classification scheme of limbic encephalitis according to the etiological principle [10, adapted by I.A. Kiselev]

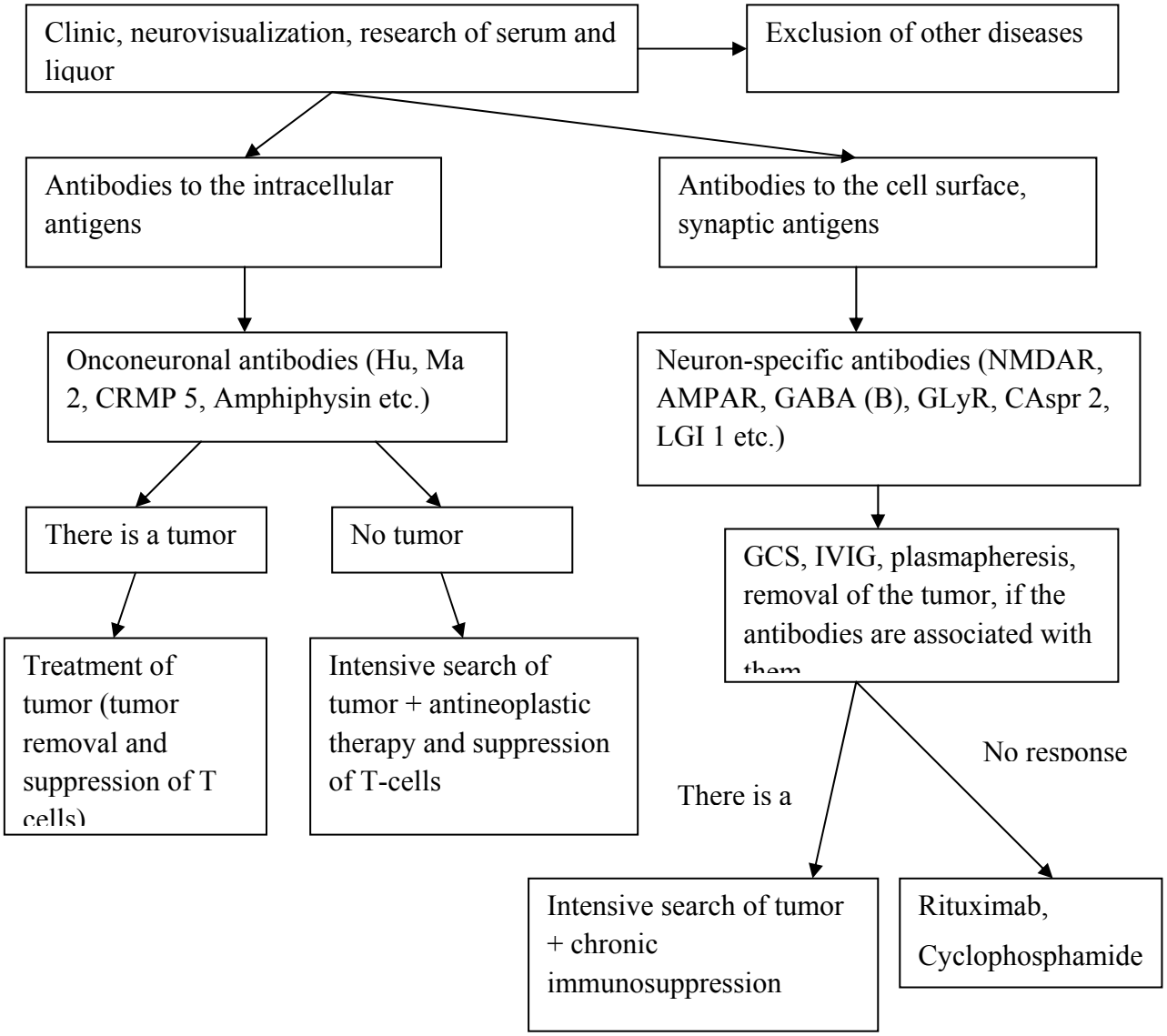

Figure 2. Algorithm for the diagnosis and treatment of autoimmune limbic encephalitis [21, adapted by N.A. Shnayder]

Conclusion

Thus, the limbic encephalitis is an actual problem of modern health care. Its incidence (in particular, parainfectious LE) is high, as well as the frequency of undiagnosed cases with the latent course. Late diagnosis of LE entails great economic and social losses for society due to the high risk of forming hard- to- treat symptomatic focal epilepsy, disability of working-age patients, chronic course (more often remittent) of the disease, with underlying chronic replicative relapse of herpes virus infection [18, 19], which require a comprehensive approach to diagnosis and treatment of the disease from the neurologist-epileptologist (Fig. 1, 2). Collaboration of the neurologist- epileptologist with a radiologist, a clinical neurophysiologist and immunologist allows reducing considerably the incidence and severity of LE complications, improving life

quality of the patients [20] and prognosis due to stabilization of pathological process in the presence of adequate pathogenetic therapy of symptomatic epilepsy even in the conditions of primary chronic course of LE [12].

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