Limbic Encephalitis

What is limbic encephalitis?

Limbic encephalitis is a type of autoimmune encephalitis (AE) that targets the brain's *limbic system*. The limbic system is a group of brain structures that underlie memory and emotion (Fig. 1). The term limbic encephalitis is slightly misleading, however. The disease does not affect all areas of the limbic system and frequently involves non-limbic regions as well[1]. The classification, however, can be useful to categorize several specific types of encephalitides that target similar regions of the brain and thus result in common symptoms, even though they may arise from different antibodies and underlying causes. Some of the more common types of AE that fall into this category are caused by antibodies against LGI1, the $GABA_B$ receptor, and the AMPA receptor.

The major brain structures of the limbic system include the *amygdala* and the *hippocampus* (Fig. 1). The amygdala is critical in regulating emotion while the hippocampus is primarily responsible for creating new memories. Regardless of the root cause, the different types of limbic encephalitides disproportionally affect these regions[1]. This is likely because these regions contain higher levels of the proteins that the antibodies target. Even when doctors cannot identify the antibody that is causing encephalitis, scientists can determine which areas of the brain have high levels of antibody activity. By exposing rodent brains to the cerebrospinal fluid (CSF) from patients containing the antibody, the scientists see that binding of the antibody to neurons is much higher in the hippocampus, for example, than other areas[1].

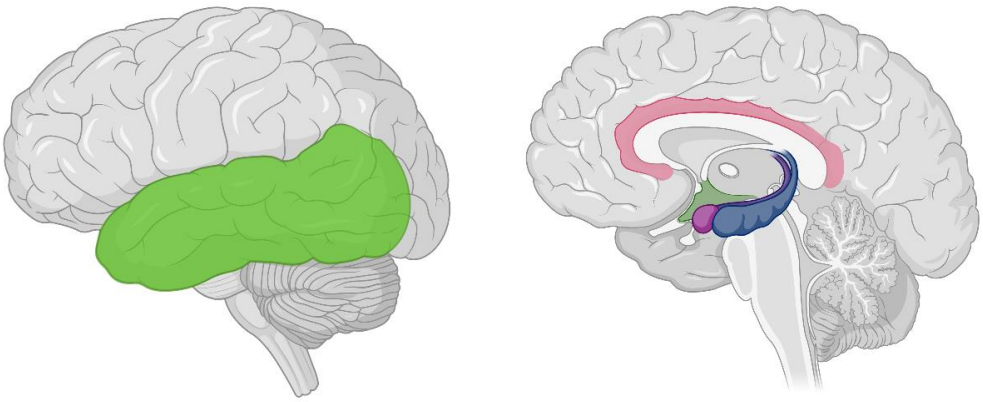

Figure 1. The Limbic System. The temporal lobes (green, left) are located on the sides of the head, behind the ears. The image to the right shows the inside of the brain. The temporal lobe houses the hippocampus (blue, right), and the amygdala (purple, right) which are two of the major brain structures that make up the limbic system.

While the symptoms and progression of limbic encephalitis vary widely, there are several commonly experienced symptoms due to the similarities in affected brain regions. Patients typically become irritable, depressed, and have trouble sleeping. These signs may rapidly give way to seizures, hallucination, and severe short-term memory loss[1]. As the disease progresses and begins to involve other parts of the nervous system, symptoms vary even more widely based on which antibody is present. For example, patients with antibodies against an

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intracellular protein called Hu experience loss of sensation and even loss of reflexes due to spinal cord neuron damage[2].

What causes limbic encephalitis?

There are two main causes of limbic encephalitis: viruses and an autoimmune response. An infection with a virus such as the herpes-simplex virus (HSV) can cause a disease called viral encephalitis[1,3]. In this case, it is the virus itself that attacks the cells in the limbic system. Thus, while it is a type of limbic encephalitis, it is not an autoimmune disease since it is a foreign agent that is attacking the brain rather than the body's own antibodies. Viral infections can, however, trigger a patient's own immune system to attack the brain, resulting in autoimmune encephalitis[3].

Non-viral causes result from an autoimmune response involving either cytotoxic T-cells or antibodies. Cytotoxic T-cells arise as a result of a cancerous tumor. In limbic encephalitis, these T-cells target proteins inside neurons (common proteins targeted are Hu and Ma2)[2,4]. In contrast, limbic encephalitis caused by antibodies rather than cytotoxic T-cells may develop in response to cancerous tumors or benign tumors. In fact, many cases of limbic encephalitis are not associated with tumors at all[5]. These antibodies target proteins on the surface of neurons like the $GABA_B$ receptor, the AMPA receptor or, in the case of LGI1 limbic encephalitis, the voltage gated potassium channel complex[5]. In either case, neuronal damage is found in limbic regions, explaining why similar symptoms may be observed with these seemingly distinct diseases[1,5].

Diagnosis and treatment

When patients present with symptoms indicating a possible diagnosis of limbic encephalitis, there are several diagnostic tests that are typically performed to confirm the diagnosis. An electroencephalogram (EEG) is administered to measure electrical brain activity. EEG electrodes are placed throughout the scalp, allowing doctors to pick up seizure-like activity in the brain and often isolate where in the brain the seizures originate. EEGs from patients with limbic encephalitis frequently suggest involvement of the *temporal lobe*[1]. The temporal lobe houses the amygdala and hippocampus and is therefore often the source of seizures in limbic encephalitis. A magnetic resonance imaging (MRI) scan is also performed which gives doctors an image of the brain. Differences in contrast can indicate that the blood brain barrier is compromised in the temporal lobe, giving the antibodies access to neural tissue[1]. Finally, doctors can take samples of patients' CSF, which may have increased immune cells and other markers of inflammation[1]. However, the findings of any one of these diagnostic tests can be normal which can make diagnosis challenging. Therefore, the results from all tests are considered when making a diagnosis.

Despite the devastating effects autoimmune limbic encephalitis may have on patients, many people are able to fully recover following treatment, though long-term recovery depends on the specific type of encephalitis[1,5]. The treatment involves removal of the tumor or other growths that initiated the antibody or T-cell production. In cases where antibodies against cell-surface proteins were present, removing the root cause along with a course of steroids and immunotherapy to restore the immune system can be an extremely successful treatment. In cases where cytotoxic T-cells attack intracellular proteins, patients often continue to experience symptoms even after removal of the tumor[2]. A variety of T-cell therapies can be tested to see if any lead to improvement in individual patients[1]. The hope is that future and ongoing research on

treatment-resistant types of limbic encephalitis will guide individualized care and improve patient outcomes.

References:

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