Limbic encephalitis

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The term ‘limbic encephalitis’ (LE) describes the condition when limbic areas of the brain are inflamed (swollen) and consequently not functioning properly. The main regions of the limbic system include the hippocampus, amygdala and cingulate cortex. These limbic areas control many functions including memory, learning, and emotions such as aggression. In addition, some of these limbic areas are susceptible to seizures, explaining why these are a common feature of limbic encephalitis.

Symptoms

The symptoms of LE include memory loss, seizures, confusion, disturbances of sleep and psychological problems such as altered personality or behaviour.

Causes

Most forms of LE fall into two main categories:

1. Autoimmune encephalitis – caused by the person’s own immune system reacting against parts of the limbic system.
2. Infectious encephalitis – caused by direct invasion of the limbic area of the brain by a bug, usually a virus.

1. Autoimmune causes

A major role of our immune system is to recognize and eliminate infections. But sometimes parts of the immune system may instead react with proteins of our own body to cause autoimmune diseases. When this reaction is against proteins of the limbic areas of the brain, this is called ‘autoimmune limbic encephalitis’.

There are broadly two forms of autoimmune limbic encephalitis: paraneoplastic limbic encephalitis (PLE) and non-paraneoplastic limbic encephalitis (NPLE).

a) Paraneoplastic limbic encephalitis (PLE)

Sometimes when the immune system starts to react with the limbic areas, this happens because the person has a tumour in their body which activates the immune system. This activated immune system can,

in turn, attack the brain. Doctors call this 'paraneoplastic' limbic encephalitis as the tumour (a neoplastic lesion) affects the brain from a distance, via the immune system.

In many cases, PLE can be diagnosed by testing for one of **paraneoplastic autoantibodies** in the patient's blood and spinal fluid. Most individuals with PLE have a cancer of the lung, thymus gland, ovary, breast or testes. More rarely, other cancers can initiate the condition. The outcome is very dependent on the underlying tumour and the precise condition, often classified by the antibody. In some cases, the condition may improve or at least stabilise if the cancer is detected and treated effectively. However, unfortunately, in many cases treatment does not significantly improve the patient's neurological symptoms, probably because the immune system has irreversibly damaged the brain cells and the tumour cannot be controlled successfully.

b) Non-paraneoplastic limbic encephalitis (NPLE)

NPLE has only been clearly recognised in the last few years when doctors began to identify patients with symptoms similar to those with PLE but who did not have any of the marker paraneoplastic antibodies in their blood and never developed a tumour. However, research in the last decade ha shown that NPLE is far more common than PLE.

It is becoming increasingly clear that NPLE is caused, at least in part, by specific antibodies in the patient's blood that target the patient's brain, particularly the hippocampus and other limbic areas. Many patients improve if they are treated with drugs that suppress the immune system and reduce the levels of the antibodies. These drugs include steroids, intravenous immunoglobulins and plasma exchange and Rituximab. Each comes with its own potential benefits and set of side effects.

Types of antibodies

A number of specific brain proteins are targeted by these antibodies. These have been discovered by researchers over the last years. Each condition is now named after the antibody target, and this variety largely explains the different symptoms experienced in different forms of NPLE. The main established antibodies and their associated features are described below:

- **LGI1/CASPR2 (previously termed voltage-gated potassium channel complex antibodies)**

Encephalitis associated with LGI1 (leucine-rich-glioma inactivated 1) and CASPR2 (contactin-associated protein 2) antibodies are in a different factsheet called **LGI1/CASPR2 antibody encephalitis.** These often affect males in later life and most patients benefit from immune therapies. In these forms of LE, around 50% of patients will have normal routine CSF and MRI examination findings.

- **GAD65-antibodies**

GAD65 antibodies are likely not directly causative. They often occur in young females, whose symptoms typically manifest over several months, with focal (small) seizures and memory loss, plus mood changes (both anxiety and depression are common). Patients with this condition often show a limited response to current immunotherapies and to anti-seizure medications. Tumours are rare in this illness.

- **NMDAR-antibodies**

Another antibody that can cause NPLE or PLE is the NMDAR antibody. This disease may be associated with a tumour, particularly an ovarian teratoma, in around 30% of cases. This antibody usually causes encephalitis involving several brain regions, but it can sometimes cause a pure LE (Please see the anti-NMDAR encephalitis factsheet for further details).

- **AMPAR and $GABA_{B/A}R$ antibodies**

Antibodies against two other receptors in the brain, AMPA and $GABA_{A/B}$, are less common causes of autoimmune limbic encephalitis. Although the majority of these patients have an underlying tumour, this is a form of Paraneoplastic Limbic Encephalitis that can often respond to treatment relatively well (see above PLE).

Patients often ask about following antibody levels in these conditions. However, this is not of proven value. For example, many patients can have persistent antibodies after successful immunotherapies. More importantly, it is valuable to follow the patient's clinical status and consider adjusting medications accordingly.

Diagnosis and Treatment

Diagnosing limbic encephalitis can be challenging, especially in cases where routine tests like MRI scans or lumbar punctures do not reveal clear abnormalities. Often, the diagnosis is confirmed through blood or spinal fluid tests that detect specific antibodies.

Treatments of autoimmune limbic encephalitis

The diagnosis of autoimmune encephalitis is particularly important because the disease is potentially treatable with medicines that dampen down the immune system. These medications are called "immunotherapies" and include steroids, immunoglobulins (a blood product given into the vein in a drip) and plasma exchange (when some of a person's blood is taken out from a vein, and the plasma part of the blood which contains antibodies is separated and replaced with new plasma and then put back into the vein in a drip). More recently Rituximab, a form of immune medication which targets cells in the body which produce antibodies (termed B cells), has come into use, and some patients may receive a chemotherapy called cyclophosphamide. All these drugs aim to dampen the immune system and each has a profile of known side-effects.

2. Infectious causes

Many infections of the brain can potentially cause inflammation of the limbic areas. A number of viruses, such as the herpes simplex virus (HSV) seem to preferentially target this area. Some people may therefore be given the diagnosis of LE whilst others are given the diagnosis herpes simplex encephalitis for the same condition. A clearer way for people would be to say that the person has 'herpes simplex virus encephalitis affecting mainly the limbic areas of the brain', but this is rather long-winded. There are also groups of

patients who can have LE caused by other herpes viruses including HHV6 – typically in the setting of a stem cell transplant, or other significant immmunosuppression.

Also, a few cases may have previously undetectable viruses or microbes which are found by modern techniques of 'metagenomics', developed by researchers over the last few years.

Future challenges in limbic encephalitis

As many of these diseases have only been recently described, there is still much to be done to raise awareness amongst clinicians. Future research aims to defein emore of these by identifying more targets of patient antibodies, and to understand the biological mechanisms by which these antibodies affect the excitability of the brain, and hence cause disease. Knowing this would allow us to offer patients more targeted therapies which may have equivalent benefits, but fewer side effects, by comparison to current immunotherapies. In addition, ongoing research is trying to understand how to best target the cells which produce antibodies and hence tailor therapies in patients with autoimmune encephalitis.

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