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 and amygdala. The limbic areas of the brain control many functions including memory, learning, and emotions such as aggression. In addition, some of these limbic areas are susceptible to seizures, which 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. Infectious encephalitis – caused by direct invasion of the limbic area of the brain by a bug, usually a virus.
2. Autoimmune encephalitis – caused by the person’s own immune system reacting against parts of the limbic system.

1. 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.

2. Autoimmune causes

A major role of our immune system is to recognize and eliminate infection. But sometimes parts of the immune system called ‘antibodies’ 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 (neoplasm) 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 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. 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 of these 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.

Types of antibodies

A number of specific brain protein targets for these antibodies have been discovered over the last years and this variety may explain why people have different symptoms. 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.**

- **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).

- **NMDAR-antibodies**

Another antibody that can cause NPLE or PLE is the NMDAR antibody. This disease may be associated with a growth such as a cancer, particularly 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).

It should be noted that the brain imaging and the routine lumbar puncture results may be normal in autoimmune limbic encephalitis.

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 immunosuppressive 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, particularly in autoimmune encephalitis associated with antibodies to NMDAR, LGI1 and CASPR2. All these drugs have known side-effects but their benefits are generally felt to outweigh possible side-effects in these conditions.

Future challenges in autoimmune encephalitis

As these autoimmune diseases have only been recently described, there is still much to be done to raise awareness amongst clinicians. Future research aims to understand the biological mechanisms by which this antibody affects the excitability of the brain, and hence causes disease. Researchers also hope to discover further antibodies which may allow other autoimmune encephalitis forms to be diagnosed. 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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