Limbic Encephalitis

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This factsheet aims to provide people affected by Encephalitis, their families, friends and carers with a better understanding of limbic Encephalitis.

The limbic area of the brain controls many types of activities including memory, learning, and emotions such as sexual desire, love, anger, sadness and jealousy. The main regions of the limbic area include the hippocampus, thalamus, hypothalamus and amygdala.

The term “Limbic Encephalitis” (LE) is used when the doctors think that the main area of the brain that is inflamed (swollen) or not functioning properly is the limbic system. The symptoms of limbic encephalitis include memory loss, seizures, confusion, disturbances of sleep and psychological disturbances such as altered personality or behaviour.

There are several causes of Limbic Encephalitis, and often the underlying cause is not found.
Causes of Limbic Encephalitis

Most forms of encephalitis fall into 2 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 a component of the limbic area.

1. Infectious causes

Any infection of the brain can potentially cause an inflammation of the limbic area of the brain. But a number of viruses seem to target this area particularly, such as the herpes simplex virus (HSV). Some people may therefore be given the diagnosis of “Limbic Encephalitis” 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 area of the brain”, but this is rather a long term.

2. Autoimmune causes

The major role of our immune system is to recognize and get rid of 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 area 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)

Often it is not known why the immune system starts to react with the limbic area in the brain. But occasionally this happens because the person has a growth, such as a cancer. In this case the antibodies
are made by the patient in their attempt to attack the growth. Doctors call this “Paraneoplastic” Limbic Encephalitis. Most individuals with PLE will turn out to have a cancer of the lung, thymus gland, the breast or the testis.

In many cases, PLE can be diagnosed by testing for one of a group of paraneoplastic autoantibodies in the patient’s blood. The condition may improve or at least stabilise if the cancer is detected and treated effectively, but unfortunately in many cases treatment does not cure the patient’s neurological symptoms, probably because the immune system has damaged the brain cells.

b) Non-paraneoplastic Limbic Encephalitis (NPLE) has only been clearly recognised in the last few years. Doctors began to identify patients who had the symptoms of paraneoplastic limbic encephalitis but who did not have any of the marker paraneoplastic antibodies in their blood and never developed a tumour. Most importantly, many of these patients improve if they are treated with drugs that suppress the immune system. These drugs include steroids, intravenous immunoglobulins and plasma exchange. 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 tissue, particularly the hippocampus and other limbic areas.

A number of specific brain protein targets for these antibodies have been discovered over the last 3 years. The specific antibody targets may be why people have different symptoms.

- **Voltage-gated potassium channel complex antibody**

  This antibody targets proteins that are tightly linked in with the potassium channels in brain. The majority of these antibodies target Lgi1 (leucine-rich glioma inactivated 1). Lgi1 is a protein
that appears to be important in controlling electrical activity within the brain.

It is thought that this type of Autoimmune Encephalitis is currently not tested for enough and therefore may be missed. The main reason for this is the current lack of awareness of the condition. Another reason might be because the symptoms and the brain scans can look very similar to people with infectious Encephalitis. Two helpful tests that can assist doctors to try to tell the difference between these conditions include

- the lumbar puncture results are often abnormal in infection
- a low blood salt (sodium) level is often seen in potassium channel complex / Lgi1-antibody associated encephalitis.

Potassium channel complex/ Lgi1 antibodies have recently been found in people with a particular type of seizure problem, which may start before the onset of full-blown limbic encephalitis. So this might mean that doctors could start treatment sooner and try to improve the outcomes for patients, such as trying to reduce amnesia and confusion.

Antibodies against other protein in the voltage-gated potassium channel/LGI1 complex, such as Caspr2 (contactin-associated protein 2) and contactin-2, have been shown to also cause autoimmune limbic encephalitis; but this is less common.

- **AMPAR and GABABR antibodies**
  Antibodies against two other receptors in the brain, AMPA and GABAB, are now known to be less common causes Autoimmune Limbic Encephalitis. The majority of these patients have an underlying tumour. However, this is a form of Paraneoplastic Limbic Encephalitis that can often respond to treatment relatively well (see above).

- **NMDAR-antibodies**
Another antibody that can cause encephalitis is the NMDAR antibody. This disease may be associated with a growth such as a cancer. This antibody usually causes Encephalitis involving several brain regions, but it can rarely cause a Limbic Encephalitis. (Please see the NMDAR-antibody factsheet for further details)

Treatments of autoimmune encephalitis
The diagnosis of Autoimmune Encephalitis is particularly important because the disease is potentially treatable with medicines that dampen down the immune system called immunosuppressive. These include steroids, immunoglobulin (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, washed and then put back into the vein in a drip). All these drugs have known side-effects but their benefits are generally felt to outweigh possible side-effects.

Future Challenges
As this disease was only 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.
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