What are the different types of Autoimmune Encephalitis?

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Receiving a diagnosis of autoimmune encephalitis can be a stressful and uncertain time for many patients and their families. And to make it even more confusing, doctors often don’t just give patients a diagnosis of autoimmune encephalitis, but rather anti-NMDAR or anti-Hu, or anti-GABA<sub>A</sub> encephalitis. There are many different types and subtypes of autoimmune encephalitis that can have distinct symptoms, underlying causes, and responses to treatment. However, the terminology that doctors use to refer to these different subtypes is complex and can sometimes feel like wading into a bowl of alphabet soup! Here, we will try to break down some of the ways that doctors distinguish types of autoimmune encephalitis to help patients and their families make sense of this complicated and rapidly evolving field.
What is autoimmune encephalitis?

Before we break down the different types of autoimmune encephalitis, it is important to understand what autoimmune encephalitis is. What do doctors mean when they use the term autoimmune encephalitis? The suffix -itis can be applied to any part of the body to describe an inflammatory state. So, when -itis is added to the end of the word encephalon (which is the ancient Greek word for inside the head), it means inflammation of the brain. Therefore, encephalitis is a word that describes any sort of inflammation in the brain.

But what exactly is inflammation? What does it mean when a part of the body is inflamed? Inflammation occurs when the body’s immune system is activated. Typically, the immune system is activated when there are invaders in the body, such as bacteria or viruses. Once the immune system is alerted to the presence of this invader, it tries to eliminate the invader using a variety of different weapons. Some of the weapons that the immune system uses are called antibodies. Antibodies act as signals for the immune system so that it knows where to direct its attack. One battalion of the immune system’s cell soldiers makes antibodies that specifically stick to the target. Then, the immune system sends another battalion of cell soldiers to eliminate the target that has been flagged by the antibody.

Even though the immune system’s main job is to mount attacks against invaders like bacteria and viruses, things can go wrong in the fog of biological warfare. Sometimes the immune system accidentally mounts an attack against healthy proteins in a person’s body. When the body’s immune system targets itself, it can result in what is called an autoimmune process (from combining auto-, meaning self, and -immune, as in the immune system).

Now we can put all of these terms together! When the body’s immune system accidentally targets healthy proteins in a person’s brain, resulting in inflammation in the brain, it is called autoimmune encephalitis. It is important to note that when the body mounts an autoimmune attack against the brain, it isn’t trying to target every healthy protein in the brain. Rather, it’s generally trying to target specific proteins that are found in the brain. When the immune system attacks these proteins, it can damage the proteins and the cells in which they are found. As a result, the type of autoimmune encephalitis and the symptoms associated with that autoimmune encephalitis are based on the type of protein that is targeted for attack by the immune system.

What part of the brain is affected by autoimmune encephalitis?

Though we are still relatively early in our understanding of how the brain works, we do know that different regions of the brain control different brain functions. For example, some areas of the brain are dedicated to controlling movement, whereas others are dedicated to processing sensory stimuli. One way in which these different regions of the brain are distinct is that their brain cells can contain different proteins. This means that when the immune system mounts an attack against a protein in the brain, this attack is targeted to the regions in the brain where that protein is found.
Therefore, the distinct types of autoimmune encephalitis target different regions in the brain and may affect different brain functions.¹

Doctors will sometimes describe a patient’s encephalitis based on which part of the brain they suspect is being attacked. Some common terms that you may hear a doctor use to describe autoimmune encephalitis include:

- **Limbic encephalitis**: inflammation of the limbic system. The limbic system includes brain regions such as the hippocampus, amygdala, and hypothalamus that are involved in emotional regulation. People with limbic encephalitis most commonly have changes in their mood and memory, along with seizures starting in the limbic system.⁶

- **Brainstem encephalitis**: inflammation of the brainstem which is the long stalk at the base of the brain that connects the brain to the spinal cord. The brainstem is the center of many important functions necessary for survival, so people with brainstem encephalitis can have problems ranging from abnormal eye movements to trouble swallowing or breathing.⁷

- **Encephalomyelitis**: inflammation of the brain plus inflammation of the spinal cord. Sometimes patients with autoimmune encephalitis can also mount an autoimmune attack on their spinal cord. Inflammation in the spinal cord interferes with the sensory and movement signals that are sent between the brain and the rest of the body, which can result in symptoms like weakness, paralysis, numbness, or tingling.⁸

**Is autoimmune encephalitis caused by a tumor?**

Another way that doctors distinguish between the types of autoimmune encephalitis is by using the terms paraneoplastic vs. non-paraneoplastic encephalitis. In paraneoplastic autoimmune encephalitides, the reason that the patient’s immune system is attacking their brain is that they have a tumor somewhere in their body.¹³ A tumor, which is a growth of abnormal cells, can be one of the most common causes of autoimmune encephalitis. This is because the abnormal cells in a tumor can sometimes do strange things to proteins normally found in the brain. For example, tumor cells can place a protein that is normally supposed to be inside of the cell on the outside of the cell, or they can begin to make a brain protein in a different part of the body where it is not normally supposed to be made. This can confuse the immune system, which causes it to attack a normal brain protein that it would otherwise leave alone.⁹

In contrast to these cases of paraneoplastic encephalitis, **non-paraneoplastic** autoimmune encephalitis occurs when there is an autoimmune encephalitis but doctors can’t find a tumor anywhere in the person’s body.¹ In these cases, what is causing the immune system to all of a sudden decide to attack a healthy protein in the brain is less clear. The cause of cases of non-paraneoplastic autoimmune encephalitis is the subject of ongoing and future research by many doctors and scientists.

**Which protein in the brain is the immune system trying to attack?**

Perhaps the most specific way in which doctors can distinguish between different types of autoimmune encephalitis is by determining exactly which protein in the brain is being targeted. As discussed above, when the immune system mounts an attack
against its target, it makes antibodies to specifically flag this target. These antibodies circulate in the blood and/or the fluid that bathes the brain. Therefore, if doctors can collect these antibodies, they can provide a clue about which protein the immune system is targeting.

As doctors and scientists have identified more antibodies involved in autoimmune encephalitis, they have started to name these types of autoimmune encephalitis after the antibody that is present. For example, one of the most common forms of autoimmune encephalitis is caused by the body mounting an attack against the NMDA receptor, which is a protein found on the surface of many cells in the brain.\(^\text{10}\) These antibodies against the NMDA receptor are called “anti-NMDA receptor antibodies” so these patients are said to have “anti-NMDA receptor autoimmune encephalitis.” Some of the most common types of autoimmune encephalitis that are named based on the antibody found against their protein target are listed in the table below.

<table>
<thead>
<tr>
<th>Antibody</th>
<th>% of Cases with Presence of Tumor</th>
<th>Common symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-NMDAR</td>
<td>40% (varies)</td>
<td>Limbic encephalitis, psychosis, repetitive movements, unstable blood pressure and heart rate, decreased breathing, seizures</td>
</tr>
<tr>
<td>Anti-AMPAR</td>
<td>70%</td>
<td>Limbic encephalitis</td>
</tr>
<tr>
<td>Anti-GABA(_A)</td>
<td></td>
<td>Severe, prolonged seizures</td>
</tr>
<tr>
<td>Anti-GABA(_B)</td>
<td>70%</td>
<td>Limbic encephalitis, frequent seizures</td>
</tr>
<tr>
<td>Anti-Caspr2</td>
<td>40%</td>
<td>Limbic encephalitis, confusion, abnormal muscle tone</td>
</tr>
<tr>
<td>Anti-LGI1</td>
<td>&lt;10%</td>
<td>Limbic encephalitis, seizures</td>
</tr>
<tr>
<td>Anti-Hu</td>
<td>&gt;90%</td>
<td>Limbic encephalitis, problems with cognition</td>
</tr>
<tr>
<td>Anti-Ma2</td>
<td>&gt;90%</td>
<td>Limbic encephalitis, brainstem encephalitis</td>
</tr>
<tr>
<td>Anti-CV2/CRMP5</td>
<td>&gt;90%</td>
<td>Limbic encephalitis</td>
</tr>
<tr>
<td>Anti-Amphiphysin</td>
<td>&gt;90%</td>
<td>Limbic encephalitis, widespread paralysis</td>
</tr>
</tbody>
</table>

Table Caption: Different antibodies that are found in patients with autoimmune encephalitis are associated with distinct symptoms and the likelihood that the disease is a result of having a tumor somewhere in the body. Adapted from Davis & Dalmau – *Autoimmunity, seizures & status epilepticus* (2013).\(^\text{11}\)

In some patients, doctors are unable to find an antibody that is known to be associated with autoimmune encephalitis, even if the doctor is pretty sure that the patient’s symptoms are caused by an autoimmune encephalitis. This might be because either the patient’s immune system is not making an antibody, or doctors don’t yet have a laboratory test that is capable of identifying an antibody associated with that patient’s disease. These cases of autoimmune encephalitis are said to be seronegative.\(^\text{12}\) Doctors and scientists are still looking to identify new proteins and antibodies that are associated with autoimmune encephalitis in hopes of providing a more specific
diagnosis for patients who would have previously been thought to have seronegative autoimmune encephalitis.

It is important to remember that autoimmune encephalitis can look different in every patient. For example, one patient may be diagnosed with anti-NMDA encephalitis after she has multiple seizures and is found to have an ovarian tumor. Whereas another patient may be diagnosed with anti-NMDA encephalitis after he has dramatic changes in his personality and memory, but doctors are not able to find a tumor. Nevertheless, breaking down a disease into distinct boxes can help guide doctors in their diagnostic and treatment decisions for an individual patient. And a greater understanding of the subtypes and causes of autoimmune encephalitis may be crucial for developing more targeted and effective treatments for this uniquely challenging disease.

References:

1. Dalmau, J. & Rosenfeld, M. R. *Paraneoplastic and autoimmune encephalitis*.


