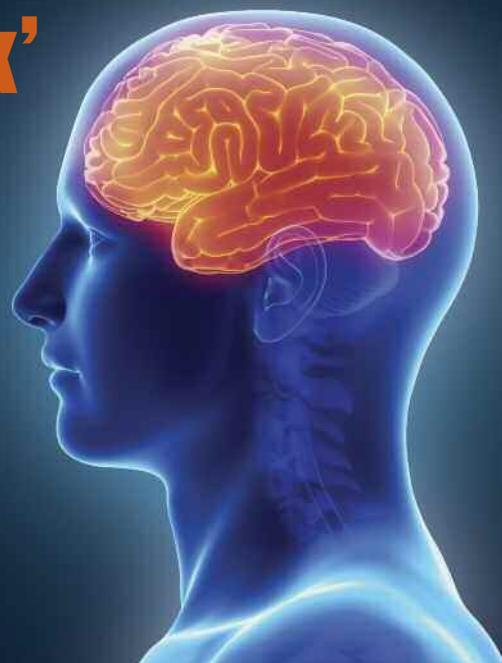


# Autoimmune Encephalitis: The ‘Brain Under Attack’

Individuals afflicted with this newly described group of disorders require swift and aggressive treatment, which often isn't possible due to misdiagnosis.

By Ronale Tucker Rhodes, MS



**IN 2017, DUKE** Health, a world-class academic and health-care system, posted an article titled “Brain Under Attack.” It chronicles the four-year journey to diagnosis of a 14-year-old boy, Lucas Quinones-Reed, who began developing baffling symptoms, including trouble speaking, walking and reading, a plummeting IQ, anxiety and violence. Lucas’ parents took him to numerous hospitals on the East Coast, but because of an inability to diagnose his symptoms, he was repeatedly admitted to psychiatric wards. Fortunately for Lucas, his father, who has an advanced degree in psychology, was convinced Lucas’ symptoms were neurological rather than psychological. So, when doctors at a hospital in Washington, D.C., recommended they “go to Duke,” it was the turning point in their nightmare. After meeting with Heather Van Mater, MD, a pediatric rheumatologist, and William Gallentine, DO, a pediatric neurologist, Lucas was diagnosed with Hashimoto encephalopathy, a rare and often misdiagnosed autoimmune disorder that causes brain inflammation.<sup>1</sup>

Lucas’ story isn’t unusual. It has been told before in a book released in 2013 about a 24-year-old reporter, Susannah Cahalan, who in 2009 was struck by autoimmune encephalitis (AE), a confounding illness that ravaged her mentally and physically. Her story became a *New York Times* best-selling book titled *Brain on Fire*,<sup>2</sup> which was made into a movie in 2016.

Yet, despite the attention these stories received, AE is still commonly misdiagnosed. The reason: It mimics so many other psychiatric disorders. And, because individuals afflicted initially present with psychiatric symptoms, an inflammatory

process is not suspected. What’s more, AE generally occurs sporadically in people with no family history of the condition.<sup>3</sup>

The term “autoimmune encephalitis” appears in the medical literature in the 1970s and 1980s. The first specific AE antibody was identified in 2005 when Joseph Dalmau, MD, described the anti-NMDA-receptor encephalitis type. Since then, the field of AE has expanded rapidly with more than 15 known types of AE today, including autoantibodies directed against NMDA, LGI1, CASPR2, VGKC-complex antibodies, AMPA and GABA.<sup>4</sup>

AE’s occurrence rate is about one in 200,000 per year. However, the true incidence of these syndromes is difficult to determine because the diagnosis may not be considered, many cases go unreported or a specific viral cause is never confirmed.<sup>5</sup> AE can affect patients of all ages, including infants and the elderly, with some types occurring more often in children and young adults. Like many autoimmune diseases, AE also occurs more frequently in women than in men, and it has been reported to be higher among African-Americans than Caucasians.<sup>6</sup>

## What Is AE?

Encephalitis is inflammation (swelling) of the brain. While there are different types of encephalitis, AE is a group of neurological diseases that occur when the immune system responds to a previous infection and inadvertently damages the brain through collateral damage or through direct effect by molecular mimicry (brain tissue similar to offending

micro-organism). Damage and inflammation can also occur when resident cells (microglia and dendritic cells are activated) (also known as the secondary or postinfectious type<sup>7</sup>) or when specific antibodies (immunoglobulins) present that cause the body to mistakenly attack healthy nerve cells in the brain, which disrupts synaptic processing and causes the nerve cells to no longer function properly.<sup>8,9</sup>

There are six main types of AE:<sup>9</sup>

- Acute disseminated encephalomyelitis (ADEM) accounts for approximately 10 percent of known cases. ADEM usually affects children and begins after a childhood exanthem (break out) or other viral infections and immunizations. Terminologies used to describe this include postviral, postinfectious or parainfectious. With ADEM, the white matter of the brain (that contains nerve fibers and myelin) is predominantly affected, and microscopically, there is invasion with immune cells egressing from the blood vessels that have destroyed the myelin.

When ADEM occurs in children, they may have a history of infection such as a cold, sore throat or tummy upset two weeks to four weeks before they become ill, which inappropriately activates the immune system causing inflammation of the nerve coverings, disrupting function.

- Anti-NMDAR encephalitis occurs when antibodies react with the N-methyl-D-aspartate (NMDAR) protein receptor, which may result in disruptive mood and movements.

- Hashimoto's encephalopathy is a rare condition that can affect all age groups but typically affects females around 50 years old. Recent insight about this disorder shows it may not represent a single diagnosis, but rather a syndrome that includes a number of specific conditions. In Hashimoto's encephalopathy, the antithyroid antibodies are thought to be the likely biomarker.

- Rasmussen encephalitis, also called Rasmussen's syndrome, is a rare, progressive, chronic encephalitis that occurs mainly in children (mostly in 6- to 7-year-olds) but 10 percent of cases can occur in adolescents and adults. It typically strikes healthy individuals, and no more than an estimated two new cases per year are identified in large epilepsy centers.

- Limbic encephalitis is a condition in which limbic areas of the brain are inflamed, resulting in improper function. The limbic system includes the hippocampus and amygdala, which is responsible for memory, learning and emotions such as aggression. Most forms of limbic encephalitis fall into two main categories: 1) infectious encephalitis caused by

direct invasion by a virus and 2) autoimmune encephalitis caused by the person's own immune system reacting against part of the limbic system.

- LGI1/CASPR2-antibody encephalitis occurs when the immune system produces antibodies that target leucine-rich glioma inactivated 1 (LGI1) or contactin-associated protein 2 (CASPR2) in the brain. Unlike most autoimmune diseases, men are affected twice as often as women.

## AE'S OCCURRENCE RATE IS ABOUT ONE IN 200,000 PER YEAR.

### Symptoms of AE

With AE, a wide range of neuropsychiatric symptoms can be exhibited depending on the intensity of the inflammation and the areas targeted. And, these symptoms may appear at different times and different levels of intensity. Commonly associated symptoms include:<sup>4,10</sup>

- Cognitive impairment
- Memory difficulties
- Seizures
- Ataxia
- Involuntary movements
- Slowed or loss of ability to speak
- Rapid, pressured or involuntary speech
- Behavioral changes such as agitation
- Loss of inhibition
- Hallucinations (visual or auditory)
- Paranoid thoughts
- Severe anxiety
- Sleep disruption, including severe insomnia
- Partial or complete loss of appetite for extended periods
- Food and drink tasting inedible or triggering nausea
- Excessive eating without feeling sated
- Decreased level of consciousness (to the point of unresponsiveness, catatonia or coma)
- Weakness or numbness of part of the body
- Loss of balance
- Vision changes

Signs and symptoms of AE often occur two to three weeks after the initial infection and progress rapidly over several weeks or months. In the classic presentation, there is often a distinct phase known as the prodromal stage in which the illness is developing. In AE, prodromal symptoms, if they occur, are flu-like symptoms that include headache, fever, nausea, vomiting, diarrhea or upper-respiratory tract symptoms.

Following the prodromal phase, seizures are the dominant feature seen in children, whereas in adults, psychiatric symptoms are the dominant feature. In addition, common behavioral and personality changes early on include psychosis, aggression, inappropriate sexual behaviors, panic attacks, compulsive behaviors, euphoria or fear.

Psychiatric symptoms may fluctuate in severity and duration. Cognitive impairments or abnormalities such as thinking, memory loss and, especially, the ability to retain new information may be impaired, and seizures, problems

with concentration and reasoning are severe enough that they interfere with daily functioning.

Eventually, AE leads to a progressive decrease of level of consciousness that can progress to coma. All these signs and symptoms are often occurring within the first few days to several weeks of the disease appearing.<sup>11</sup>

## Causes of AE

Encephalitis is usually caused by a virus (i.e., measles and rubella), but other infectious agents (including bacteria) can also be the cause. In fact, infection with many different viruses can lead to encephalitis,<sup>4</sup> and AE can be caused by complications resulting from viral infection. However, in more than 50 percent of encephalitis cases, the exact cause of the illness is not tracked down.<sup>7</sup>

Some types of AE “termed postinfectious encephalitis” such as ADEM are caused by infection. Other forms of AE are associated with detecting specific antibodies (that help remove foreign antigens such as viruses and bacteria) in blood such as voltage-gated potassium channels (VGKC) complex (anti-LGI1 and Caspr2), NMDA receptor, GAD, AMPAR and GABA antibodies. The reason these antibodies are produced by the immune system in people with AE is not known in most cases, but sometimes a tumor (benign or cancerous) may generate the antibody.<sup>9</sup>

## Diagnosing AE

In patients whose symptoms are consistent with AE, testing used to aid in its diagnosis has historically included MRI of the brain with contrast, electroencephalogram (EEG), blood and cerebrospinal fluid (CSF) analysis for markers (autoantibodies) of inflammation. However, because criteria for AE relied on antibody detection and response to immunotherapy, which could delay accurate diagnosis, a team of researchers published a position paper in 2016 establishing three levels of clinical evidence for AE: possible and probable for which the autoantibody status is not needed in most cases, and definite for which the autoantibody status is often needed.<sup>12</sup>

For instance, for possible AE, diagnosis can be made when all three of the following criteria have been met:

- 1) Subacute onset (rapid progression of less than three months) of working memory deficits (short-term memory loss), altered mental status (defined as decreased or altered level of consciousness, lethargy or personality change, or psychiatric symptoms);

### Organizations Supporting Autoimmune Encephalitis

#### Autoimmune Encephalitis Alliance

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Durham, NC 27701  
aealliance.org

#### Encephalitis Society

32 Castlegate  
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+44 (0)1653 699599  
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www.encephalitis.info

#### International Autoimmune Encephalitis Society

11417 Sarasota Court  
Fredericksburg, VA 22407  
admin@autoimmuneencephalitis.net  
www.autoimmuneencephalitis.net/

#### American Autoimmune Related Diseases Association

22100 Gratiot Avenue  
Eastpointe, MI 48021  
(800) 598-4668  
(586) 776-3900  
aarda@aarda.org  
www.aarda.org

2) At least one of the following:

- New focal central nervous system findings
  - Seizures not explained by a previously known seizure disorder
  - CSF pleocytosis (elevated white blood cell count of more than five cells per mm<sup>3</sup>)
  - MRI features suggestive of encephalitis; and
- 3) Reasonable exclusion of alternative causes.

For probable and definite AE diagnoses, the researchers published additional criteria. According to the researchers, in these patients “diagnosis of a definite autoimmune encephalitis greatly depends on the results of autoantibody tests. By contrast, disorders exist in which the clinical syndrome and MRI findings allow for classification as probable or definite autoimmune encephalitis before the autoantibody status is known.” Diagnostic criteria for these are extensive and can be found in their position paper titled “A Clinical Approach to Diagnosis of Autoimmune Encephalitis” published in the April 1, 2016, issue of *The Lancet*.<sup>12</sup>

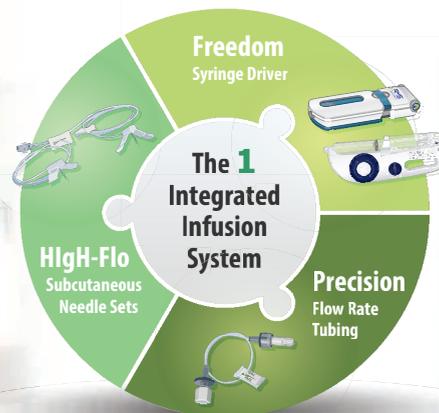
## Treating AE

First-line treatment for AE includes removal of the tumor (if identified), high-dose corticosteroids (anti-inflammatory), intravenous immune globulin (IVIG) (immunomodulatory and anti-inflammatory) or plasmapheresis (removal of harmful autoantibodies). If a cell-surface or synaptic antibody has been detected and symptoms are suggestive of AE, immunotherapy is initiated in various sequences. However, if it is not known whether the cause is due to a tumor or infection, steroid therapy can complicate matters in the case of a cancerous tumor, whereas IVIG and plasmapheresis will not exacerbate the infectious condition.

If a tumor is identified, removal is essential to remove the source of the antibodies and improve the prognosis of the tumor. One study showed 50 percent of patients with a specific AE (anti-NMDAR) improved with first-line treatment and, when tumor removal was present, there was almost full recovery of 97 percent after two years.<sup>13</sup>

When a synaptic or cell-surface antibody has been detected,

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first-line therapy is given aggressively and early with escalation if improvement is not satisfactory, meaning it leads to better outcomes and fewer relapses. Unfortunately, in approximately 50 percent of cases, first-line therapy fails to reverse symptoms, so second-line therapy is required. This includes rituximab, CellCept and cyclophosphamide. Rituximab is a monoclonal (which destroys B-cells that produce antibodies including harmful ones) anti-CD20 antibody given weekly for four weeks to rapidly deplete CD20/CD19 B cells from the blood to undetectable levels. Cyclophosphamide, which suppresses the immune system, is an antimetabolite used in chemotherapy regimens. CellCept is an oral immunosuppressant that interferes with the formation of DNA in certain immune system cells that become overactive in cases of autoimmune disorders.

## RECOVERY FROM AE IS DIFFERENT AND UNIQUE FOR EACH PATIENT.

Approximately 20 percent to 50 percent of patients with AE show inadequate responses to second-line therapies. In these cases, readministration of first-line immunotherapeutic agents, extended use of second-line immunotherapy and long-term maintenance of prednisolone or steroid-sparing agents such as azathioprine and mycophenolate mofetil are options. Mycophenolate mofetil (CellCept), in particular, has better results for inducing remission and a more favorable side effect profile than cyclophosphamide in other autoimmune disorders, supporting its use as a safer alternative to cyclophosphamide. A small number of studies reported a more targeted therapy with monoclonal antibodies such as Tocilizumab or direct infusion of immune mediators such as low-dose IL-2 therapy, Treg modulation and Bortezomib.<sup>14</sup>

Patients who respond to first- and second-line therapies often recover well or at least partially, but then show acute worsening (relapse) of symptoms that mirror the initial attack but may be milder. Approximately 12 percent of patients relapse over the first two years, but patients who receive second-line treatment have the lowest rate of relapse. Relapse treatment is typically with second-line therapy, but first-line treatment may be tried first.<sup>13</sup>

Recovery from AE is different and unique for each patient. Early diagnosis with early and aggressive treatment is the best

path to quicker recovery. According to studies, about half of patients with AE have substantial improvement within a month of starting treatment and continue to show improvement after getting discharged from the hospital. In addition, more than half of patients with AE will slowly have partial or complete recovery, but the average time toward recovery is about 14 months.<sup>15</sup>

### Clinical Outlook

There are many forms of AE, which is difficult to diagnose due to its shared symptoms with other disorders. Fortunately, because earlier criteria for AE often resulted in a delay of diagnosis, researchers have developed improved diagnostic guidelines, and it is now known that early and aggressive first- and second-line treatments ensure the best outcomes.

In a 2013 study of 577 anti-NMDA-receptor AE patients, 53 percent who received immunomodulation therapy showed improvement within four weeks. Eighty-one percent of patients showed substantial or complete recovery. On average, patients continued to improve for 14 months after onset of acute AE. And, while 12 percent of patients who recovered from a first acute episode had at least one relapse in the next two years, overall mortality associated with the disease was approximately 6 percent,<sup>16</sup> which is a hopeful outlook for those afflicted with this life-threatening disease. ■

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