



Behavior Change from Autoimmune Encephalitis

Autoimmune encephalitis (AE) is a disorder that can be hard to diagnose. Typically, early symptoms are flu-like, making it difficult to distinguish from many other illnesses. Psychiatric symptoms and behavior changes are often among the first signs of autoimmune encephalitis, especially NMDAR encephalitis, and a majority of patients are seen first by psychiatrists upon entering the emergency room¹. Other neurological symptoms of AE, such as seizures and problems with movement and memory typically develop later than the psychiatric symptoms¹. However, AE is not usually diagnosed until the appearance of these neurological symptoms since the early psychiatric symptoms are often misdiagnosed as a psychiatric disorder, which leads to a delay in treatment for AE¹. Understanding the psychiatric symptoms and behavior changes that often signal the onset of AE can lead to quicker detection, earlier treatment, and better outcomes for patients.

One study of AE found that 77% of patients with anti-NMDAR encephalitis initially came to the hospital due to psychiatric symptoms². Usually, the psychiatric symptoms caused by AE include agitation, aggression, irritability, hallucinations, delusions, and depressed mood³. The most common symptom was agitation or irritability, appearing in 59% of adults and 66% of children². Psychotic symptoms such as hallucinations were the second most common². These psychiatric symptoms are often misdiagnosed as a psychiatric disorder rather than being investigated as early symptoms of AE.

An additional challenge in diagnosing AE from psychiatric symptoms is that the pattern of symptoms often differs between adults and children. Adults are more likely than children to experience psychotic symptoms like hallucinations². Children, unlike adults, are likely to have temper tantrums as a symptom⁴. Children also often have some early neurological symptoms like seizures in addition to the behavior changes, while adults usually begin with psychiatric but not neurological symptoms⁶. The differences in type and timeline of symptoms between children and adults could be explained by different underlying causes of AE. For example, in adults AE is often the result of a tumor, but tumors are usually not the cause of AE in kids⁷.

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How might AE affect behavior?

While the exact mechanisms by which AE causes behavior changes are not well understood, anti-NMDAR encephalitis research provides some potential insights into processes in the brain that might lead to these symptoms. Anti-NMDAR encephalitis, as the name suggests, involves antibodies against a type of neurotransmitter receptor called NMDARs. These NMDARs bind a neurotransmitter called glutamate. Several conditions must be met for NMDARs to become active: glutamate must bind to the NMDAR and the electrical voltage of the cell must reach a certain level⁸. When NMDARs are active, they allow charged ions to cross the cell membrane, which can then send a signal to other cells. NMDAR activation is involved in processes like learning, memory, and behavior.

In anti-NMDAR encephalitis, antibodies in the immunoglobulin G (IgG) subclass target the NMDA receptors⁹. These IgG antibodies bind to part of the NMDA receptor and make it so they are not able to signal as usual. Neurons from rats that were treated with IgG from AE patients had a decreased number of NMDARs on the cell surface. When the antibodies were removed, the NMDARs returned back to normal levels¹⁰. This indicates that IgG antibodies can cause removal of NMDARs from the surface of the cell, where they can no longer interact with neurotransmitters. Many NMDARs are found on a type of cell called GABAergic neurons⁹. These neurons typically suppress activation of nearby neurons and help to regulate levels of activity in the brain. The attack on NMDARs in AE may lead to reduced activity of GABAergic neurons, which in turn causes too much activity in other parts of the brain.

How does this change in glutamate signaling that is mediated by NMDARs relate to psychiatric symptoms? One theory about the mechanisms underlying schizophrenia, a psychiatric disorder characterized by hallucinations and delusions, also includes reduced availability of NMDARs¹¹. The subsequent deactivation of GABAergic neurons is believed to produce too much activity that leads to many of the psychiatric symptoms of schizophrenia. Drugs that block NMDARs, such as ketamine, are known to cause psychosis, agitation, and difficulties with memory¹¹. All of these are also common symptoms of anti-NMDAR encephalitis. The progressive loss of NMDARs due to antibody attack could create these same psychiatric symptoms in people with AE.

How are psychiatric symptoms addressed?

Getting a better handle on understanding and treating the behavioral symptoms of AE requires improved diagnosis and intervention. When someone arrives in the hospital with significant behavioral changes or psychiatric symptoms, it would be beneficial if doctors could screen for and diagnose AE even before some of the more severe neurological symptoms begin to appear.

Many patients receive medications that target the psychiatric symptoms that are later diagnosed as related to AE¹². These medications include antipsychotics for people who are having symptoms of psychosis. However, in some cases, antipsychotic

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medications have been shown to cause adverse effects such as catatonia and coma in AE patients, so doctors need to give these medications with care². Earlier diagnosis of AE can prevent patients from getting incorrect diagnoses and psychiatric treatments that can actually worsen their AE. Importantly, while medications may help to manage the psychiatric symptoms, they do not target the underlying causes of AE and patients will still need standard treatments like immunotherapy or tumor removal to treat the AE itself.

Typically once patients receive immunotherapy, the behavior symptoms of AE begin to go away. Most patients recover fully and no longer have any psychiatric symptoms after recovery. However, approximately 30% of patients may have lasting neuropsychiatric deficits after treatment for AE¹³. In patients who have psychiatric symptoms after immunotherapy, continued use of antipsychotic medications such as clozapine can help to alleviate symptoms¹⁴.

In children who recover from AE, behavioral symptoms may continue and pose particular challenges for parents⁷. Some children were reported to have academic difficulties after recovering from AE¹⁵. Parents and caregivers dealing with bad behavior from a child who had AE can learn behavior management techniques to help address these behavioral difficulties. These strategies, as well as early screening of psychiatric symptoms and behavioral changes, could help to improve diagnosis, treatment, and recovery from AE.

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