

## Depression in Autoimmune Encephalitis

Major depressive disorder, commonly called depression, is a disorder that affects more than 168 million people worldwide<sup>1,2</sup>. Symptoms include depressed mood, lack of energy, loss of interest/pleasure, sleep disturbances, significant weight changes, and thoughts of suicide<sup>3</sup>. While depression can occur on its own, which is known as primary depression, it can also be caused by other diseases or medical conditions. This form of depression, called secondary depression, is relatively common in patients diagnosed with chronic illnesses, and is one of the key factors resulting in an impaired quality of life experienced by patients with chronic diseases<sup>4</sup>.

Research has shown that patients with autoimmune diseases involving the brain and spinal cord, such as multiple sclerosis (MS), Hashimoto encephalopathy, and autoimmune encephalitis (AE), are at increased risk for depression and other mood disorders<sup>5,6</sup>. One study found that depressive symptoms occur in up to half of all patients with MS<sup>7</sup>, and another showed that prior hospitalization for an autoimmune disease increases the risk of developing a major mood disorder by 45%<sup>8</sup>. Some of this increase is likely a reaction to the diagnosis itself and the impairments caused by the disease. However, increased rates of depression are seen in MS patients up to 2 years before they are diagnosed with MS. These findings suggest that there is a biological link between autoimmune disease and depression that increases the risk of developing depression, independent of any reaction to the diagnosis or resulting lifestyle changes.<sup>9,10</sup> Research over the last 2 decades supports this idea, with increasing evidence linking the immune system and inflammation to a number of psychiatric disorders, including depression.

### A link between the immune system and depression?

One indicator that the immune system can affect mood and behavior is the phenomenon of cytokine-induced sickness behavior. During an illness, cells in the immune system release small proteins called cytokines to help regulate and synchronize the immune system's response to an invading bacteria or virus. Some examples of cytokines include interleukins (IL), tumor necrosis factors (TNF), and interferons (IFN). This increase in cytokines leads to specific behaviors many of us have experienced before while sick, including decreased activity, loss of energy, and even depressed mood<sup>11</sup>.

Based on the observation that increased cytokines during sickness can lead to depression-like symptoms, researchers began to examine cytokine levels in patients diagnosed with depression and other psychiatric disorders. Many studies have found that patients with depression, who were otherwise medically healthy, showed signs of immune system activation, with increased levels of IL-6 and, in some cases, TNF-alpha<sup>12</sup>. Another study examined brain tissue from patients diagnosed with depression and found increased levels of many types of interleukins as well as IFN-gamma<sup>13</sup>. Additionally, mice treated with cytokines or drugs that increase levels of cytokines show depression-like behaviors, further linking the immune system and inflammatory response to depression<sup>14</sup>. This effect is also seen in humans, with one study finding that 17% of patients treated with IFN-alpha developed psychiatric side effects, including depression, and that these side effects improve once the cytokine treatment is stopped<sup>15</sup>.

Just as increases in cytokine levels are linked to an increased risk of depression, research suggests that decreasing cytokines and inflammation can improve depression symptoms. A number of antidepressant therapies, including selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, and even psychotherapy have anti-inflammatory effects, lowering levels of certain pro-inflammatory cytokines<sup>16-19</sup>. Taking this even further, there is evidence that anti-inflammatory drugs can improve depression symptoms<sup>20</sup>. However, anti-inflammatory treatments can sometimes interfere with the anti-depressant effects of SSRIs, so adding an anti-inflammatory drug (including drugs such as aspirin or ibuprofen) to a depression treatment plan should only be done after careful discussion with your doctor<sup>21</sup>.

### Depression in autoimmune encephalitis

Given this link between immune system activation and depression, it is not altogether surprising that depression and other psychiatric symptoms are common in AE and other autoimmune disorders. For reasons that are still not understood, patients with autoimmune



encephalitis with antibodies directed against cell surface antigens (especially anti-NMDA receptor encephalitis) are more likely to experience psychiatric symptoms compared to patients with antibodies directed against intracellular antigens (such as anti-Hu or anti-Ma encephalitis)<sup>22</sup>. In fact, between 65-80% of patients with anti-NMDA receptor encephalitis experience psychiatric symptoms, with depression being among the most common<sup>23,24</sup>. This has also been demonstrated in a mouse model of AE, where mice received infusions of cerebrospinal fluid into their brains containing antibodies from patients with NMDA receptor encephalitis. As the anti-NMDA receptor antibodies attacked their NMDA receptors, the mice developed depressive-like behaviors and lost interest in things they had previously found pleasurable (in this case, a sugary drink). Once the infusions stopped and the NMDA receptor levels returned to normal, these depressive-like behaviors improved<sup>25</sup>.

In NMDA receptor encephalitis, psychiatric symptoms often appear before any neurologic symptoms<sup>26</sup>. As a result, it can be difficult to distinguish the initial phases of the disease from psychiatric disorders such as depression or schizophrenia. This leads many patients to assume they have a purely psychiatric disorder and to seek help from a psychiatrist first. One study found that this occurred in 76% of patients ultimately diagnosed with NMDA receptor encephalitis<sup>27</sup>!

This becomes problematic when psychiatrists are not aware that early stages of autoimmune encephalitis can mimic psychiatric disorders. Rather than ordering antibody tests to examine a potential autoimmune disorder, they may assume the patient has major depressive disorder or another psychiatric disorder. Based on this assumption, they may attempt to treat the patient with anti-depressant therapies rather than treatments aimed at the underlying autoimmune condition. This is unfortunately not a hypothetical scenario. In a study examining a group of 464 people with NMDA receptor encephalitis, nearly 10% were initially diagnosed with a psychiatric disorder, including depression, before the correct diagnosis of NMDA receptor encephalitis was reached<sup>6</sup>.

A timely diagnosis is critical in treating autoimmune encephalitis, since earlier administration of immunotherapies is associated with better patient outcomes<sup>28</sup>. A delay in a correct diagnosis and treatment plan can be especially harmful given that an estimated 10% of patients with NMDA receptor encephalitis experience suicidal thoughts<sup>29</sup>. Luckily, as more is learned about AE, psychiatrists are becoming increasingly educated and aware of the psychiatric symptoms of the disease. An improved awareness of AE will allow for faster and more accurate diagnoses, leading to faster treatment and improved outcomes for patients suffering from this disease.

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