

Multiple sclerosis, inflammation in the brain, and mood

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In their study, “Neuroinflammation drives anxiety and depression in relapsing-remitting multiple sclerosis,” Dr. Rossi et al.¹ investigated the relationship between mood and inflammation. They did this by looking at a group of people who have multiple sclerosis (MS). It has long been observed that inflammation occurs in the brains and spinal cords of people with a specific kind of MS called relapsing-remitting MS.

The inflammation can be measured in several ways. First, it can be seen on an MRI scan of the brain. Areas of inflammation take up a contrast agent called gadolinium, and show up brightly on MRI. When inflammation occurs, there is an increase in certain kinds of molecules called cytokines. When inflammation occurs in the brain, these molecules can be measured in the liquid that surrounds the brain (called cerebrospinal fluid or CSF). Dr. Rossi and his group looked at MRI scans, and in some patients, measured the number of specific cytokines in the CSF. They carefully measured the patients’ anxiety and depression, and looked for an association between mood and inflammation in people with MS.

HOW WAS THE STUDY DONE? The study took place at Tor Vergata University Hospital in Rome, Italy. To be included, patients could not have had prior psychiatric illness like anxiety or depression. Further, they could not be taking medications or drugs that would affect their mood. A total of 405 people with relapsing-remitting MS met these criteria, and were included in the study. They were adults, ages 18–60.

The 405 people were divided into 2 groups: there were 78 patients who had active MS when they entered the trial. There were 2 main criteria for measuring who had active MS and who had inactive MS. First, if the person was experiencing worsening neurologic problems due to MS, the MS was labeled as active. Second, there were some people who had no physical signs of MS, but they had signs of active MS on their MRI. These patients also had active MS.

In the other people in the trial (327 people), the MS was quiet. These MS cases were called not active. The patients were not experiencing worsening neurologic problems. They also did not have signs of active disease on their MRI.

All people in the trial underwent a psychiatric assessment. They answered questions about depression (Beck Depression Inventory [BDI]) and about anxiety (State/Trait Anxiety Inventory [STAI]). Both tools are commonly used to assess the level or severity of a person’s depression and anxiety.

In this study, there were 111 people who had never had treatment for MS. It was in this group that measurements of CSF cytokines occurred. Of the 111 cases, 54 were active and 57 were not active.

WHAT WERE THE RESULTS? Overall, 33.5% of people in the study had anxiety and 11.6% had depression. Depression and anxiety scores were higher in people who had MS for longer periods of time. In addition, anxiety increased with higher disability scores.

In the 78 patients who had active MS, 29 were experiencing worsening neurologic symptoms. The other patients did not have neurologic symptoms, but showed active MS on their MRI scans. The patients with active MS had much higher anxiety and depression scores than did the patients with inactive MS. Interestingly, there was no difference in anxiety and depression between the people who were experiencing neurologic symptoms and those who were not but showed active disease on their MRI. In other words, the anxiety and depression did not correlate with neurologic symptoms: instead, it correlated with active disease. The authors proposed that the inflammation that was occurring in the patients with active disease was the reason for the increase in anxiety and depression.

The authors developed several lines of evidence to support this idea. First, 74 of the 78 patients had resolution of the inflammation 3 months later. A reassessment of their anxiety and depression occurred at that time. The anxiety and depression scores improved in this group, tracking the improvements in the inflammation.

Second, of the 29 patients with active MS at baseline, there were 20 who were treated with steroid medication (steroids are anti-inflammatory medicines). Anxiety scores improved in the group who received steroids. In the other 9, the anxiety scores did not change. This observation suggested that the anti-inflammatory treatment reduced the inflammation and therefore the anxiety scores.

Third, Rossi et al. measured the cytokines in 111 people with MS who had never been previously treated. Cytokine levels were higher in the active MS group. Certain cytokines were elevated in the people with higher anxiety. Other cytokines were increased in these with higher depression. In short, there was an association between higher cytokine levels and anxiety and depression in this group of patients.

Rossi et al. then wanted to see if the presence of anxiety might predict reactivation or a relapse of MS. There were 327 people whose MS was not active at the time they entered the trial. However, 40 of these people had a relapse during the trial: their MS went from not active to active. When the authors looked at the anxiety scores that were recorded before the relapse occurred, there were higher scores in the people who were going to relapse, suggesting that the presence of anxiety might predict later MS relapse.

WHAT DOES THIS MEAN? The relationship between anxiety, depression, and MS has long been

observed. For a long time, the mood problems have been thought to be due to the level of disability and the awareness of having a neurologic disease. However, this study suggests that the relationship between mood and MS is more complicated. The inflammation that occurs in MS causes not only visible changes in the brain (on MRI) but also changes in the levels of cytokines in the CSF. This study suggests that the inflammation itself may be responsible for the mood changes. If true, this may be important in developing treatments for the mood changes that occur in inflammatory illnesses.

In addition, Rossi et al. saw that anxiety predicts MS relapses. The explanation of this is unclear. If true, this would suggest that treating the anxiety, along with treating the MS, might help to change the course of this illness.

Further study is needed. Scientists are just beginning to understand the role of inflammation and how it relates to mood. As more is learned, better and more focused treatments may be developed.

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About multiple sclerosis

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WHAT IS MS? MS is an inflammatory disease that affects the central nervous system (the brain and spinal cord). It affects women about twice as often as men. It usually is diagnosed around age 30.

The cause of MS is unknown. However, there are several clues about how MS begins. For instance, MS occurs more often in people who live in northern latitudes. Some have proposed that northerners are exposed to an infection in childhood. The immune system forms antibodies to the infectious agent (it could be a bacteria or virus).

Later in life, for reasons that are unclear, the antibodies attach to a protein in the myelin coating of the axons. The body becomes confused, and begins destroying the much-needed myelin. Without myelin, nerve cell signals travel much more slowly. This results in weakness, numbness, and other neurologic symptoms.

Something in our genes may be responsible for MS. For instance, MS is more likely to occur in first-degree relatives (mother, father, brother, or sister) than in distant relatives or unrelated individuals. Twenty-five percent of identical twins, who have identical genetic makeup, develop MS. In comparison, only 2% of fraternal twins, whose genetic makeup is like that of a brother or sister, develop MS.

Some genetic research in MS focuses on how our bodies can recognize foreign substances. For instance, in organ transplantation, the immune system may see the transplanted organ as foreign and reject it. Research into the genetics of MS may show how some people's bodies become confused. This would help us to identify who is more likely to develop illnesses like MS, where the body attacks its own myelin.

HOW MS AFFECTS THE BRAIN Most people think MS is an illness that mostly affects white matter. Studies show that MS affects gray matter as well. When MS affects gray matter, the nerve cells die. Nerve cell death causes a decrease in the volume of the gray matter. A reduction in volume is called atrophy. Years ago, before MRI, an autopsy might show atrophy. Today, MRI can identify atrophy in the living brain. Newer MRIs can detect subtle changes even more easily.

If MS primarily affects the white matter, why do nerve cells die? Some scientists believe that an attack

on myelin also affects the axon. Some nerve cells cannot live without their axons. When a nerve cell dies due to axonal injury, it is called Wallerian degeneration.

Others have proposed that MS affects the nerve cell body directly. In other words, the nerve cell body is destroyed first. Which is correct? Is it the axon first, or is an attack on the cell body the beginning of what we call MS? The answer to this question could lead to a cure of this illness.

As MS affects different parts of the brain, neurologic symptoms appear. Depending on the brain region, these symptoms can be weakness or numbness, or can manifest as changes in vision or balance. Often, the symptoms come and go (relapsing-remitting). In other people, the symptoms appear, and gradually worsen over time (progressive). The treatments for MS are designed to prevent new symptoms, slow or halt the progression of disease, and to reverse, if possible, the injury that has occurred.

Most textbooks describe 2 types of MS. In one, the symptoms come and go. In between the symptoms, the person may feel fine. This type of MS is called relapsing-remitting MS. The other main type is called progressive MS. This type slowly worsens, resulting in a gradual loss of neurologic function. Some have observed that white matter is more involved in the relapsing-remitting type, while gray matter may be more involved in the gradually progressive form.

More recent literature has made the distinction between these 2 types less clear. Are they separate illnesses? Does one type turn into the other? How do they overlap? The answers to these questions remain unclear.

REFERENCE

1. Rossi S, Studer V, Motta C, et al. Neuroinflammation drives anxiety and depression in relapsing-remitting multiple sclerosis. *Neurology* 2017;89:1338–1347.

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