Microscopic Colitis Foundation

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What Causes the Brain Fog Often Associated with MC?

A microscopic colitis (MC) flare is typically associated with multiple symptoms, including diarrhea (or constipation), pain, fatigue, aching joints, lower back pain, and nausea, to name a few. Many, though not all, patients complain of weight loss. About half of MC patients have only diarrhea with none of the other symptoms, and this matches the original formal medical definition of MC. Consequently, for decades, most gastroenterologists have considered this to be the proper definition for MC, and so when patients complained of other symptoms, most doctors assumed that those symptoms were due to some other issue, not MC. Today, most gastroenterologists seem to realize that the disease can cause other symptoms, although many are not yet up-to-date in their understanding of the disease, as defined by more recent research.

But probably the most persistent symptom is brain fog.
One of the least understood symptoms of MC, among gastroenterologists and patients alike, is neurological issues, including long-term brain fog. Most gastroenterologists don't mention this problem, even if they realize that MC can cause neurological issues. Yet most of us seem to have the problem. And similar to what's known as Long Covid, brain fog for MC patients tends to be very persistent.

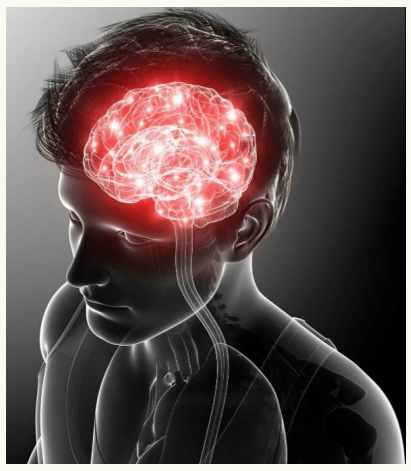
Unlike most other symptoms of MC, brain fog is rarely resolved when a patient reaches what's normally considered to be remission. Brain fog for MC patients seems to last for an average of about two years after normally defined remission is achieved, although this can vary greatly among individual patients. Patients often have memory problems, and their memory and cognizance problems are often so severe that they're unable to concentrate, or think clearly enough to be able to do their normal work. When combined with persistent fatigue, the combination can be debilitating.

Brain fog is not unique to MC.
Unfortunately, MC patients are not the only ones who are known to develop brain fog. Brain fog is a very common symptom reported by over half of multiple sclerosis (MS) patients, and it appears to be associated with all autoimmune diseases, including IBDs. And brain fog is often one of the symptoms reported by victims of Long Covid.

Brain fog is even associated with certain medications, and inadequate, or poor quality sleep. But in these cases, the problem can usually be promptly resolved by discontinuing the medication, or resolving the sleep problem.

New research provides some clues.
Fortunately, new research on brain fog has begun to appear in medical journals. Most of it appears to be focused on the neurological symptoms associated with Long Covid, but a careful analysis of the data, suggests that much of the research data may apply to autoimmune disease patients, and especially IBD patients, as well as Long Covid patients. For example, in July, an article was published in the journal Cell, that appears to define in detail how the neurological damage that results in brain fog occurs in Long Covid patients (Fernández-Castañeda et al., (2022)[1].

According to an article describing that research, published in Wired magazine, the project involved proving that the brains of mice with mild Covid 19 infections were left with inflammation that corrupted the normal functioning of certain types of brain cells called microglia (Chen, 2022, July 1)[2]. They also noticed that Covid 19 appeared to cause symptoms very similar to the brain fog associated with chemotherapy and certain other issues that resulted in patients complaining of brain fog. They then developed a mouse model that could closely mimic the human responses to the virus.

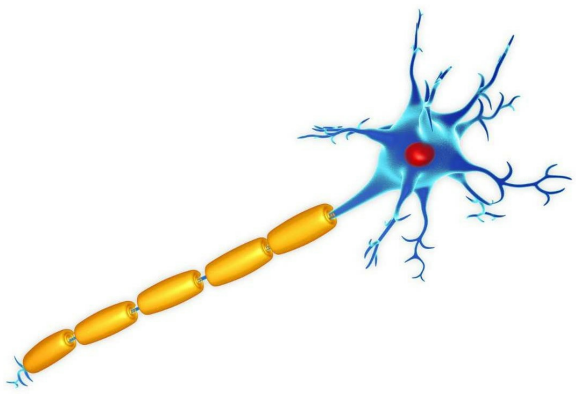


After the mice were infected with Covid 19, the cytokine levels in their blood and cerebrospinal fluid were measured after seven days, and again after seven weeks following the infection. There was an increase in the levels of certain cytokines for both intervals. They also saw increased microglia activity in the white matter of the brain, similar to what they had seen in the brains of patients receiving chemotherapy, both after seven days, and after seven weeks.

Among other things, microglia are garbage collectors.
Similar to the macrophages that the immune system uses to destroy unwanted cells and pathogens in other parts of the body, microglia in the brain help to clean up debris from dead or unwanted cells. A particular subset of microglia, known as axon tract microglia, are especially sensitive to insults (physical trauma) from inflammation or toxic substances. And when stimulated, they can become perpetually reactive, including an adverse habit of removing needed neurons or other brain cells by consuming them. Obviously, that causes additional disruption of the brain's normal functioning.

Memory is controlled by the hippocampus.
In the brain, the hippocampus region is associated with memory. Overactive microglia can prevent the production of new neurons that are needed to maintain a healthy memory, by producing more of an inhibitory protein called CCL11.

Increased levels of this protein were found in the infected mouse brains, not only at seven days, but also at seven weeks. A second group of uninfected mice were injected with CCL11. When tissue from the brains of these mice was examined, the researchers found that the microglia had reacted, and fewer new neurons had been produced in the hippocampus area of their brains.



Nerve fibers and neurons are protected by myelin sheaths.
In Alzheimer's disease patients, for example, progression of the disease is associated with a deterioration of the myelin sheaths covering nerve fibers in the brain, leaving the nerve fibers and neurons unprotected, and they slowly dry out and die, ending communications through those nerve channels in the brain. Myelin sheaths are produced by special cells known as oligodendrocytes.

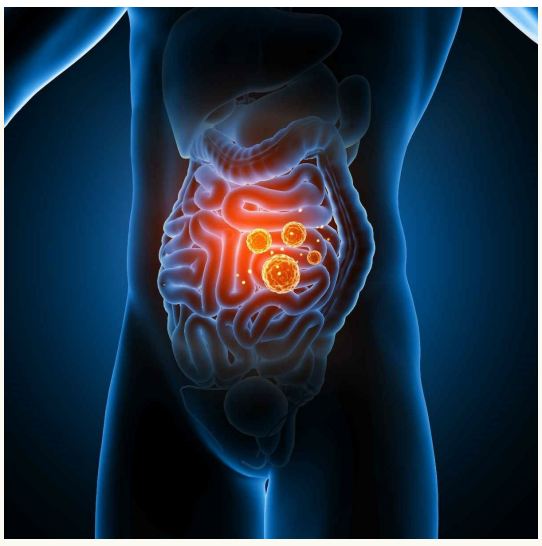
The research team had previously found that mice treated with chemo had myelin loss that resulted in the mice having compromised short-term memory and other brain issues. And now this research showed that a mild Covid infection caused the same pattern of myelin loss and this was still present at the seven-week point, confirming continued myelin loss.

Human Covid patients with cognitive symptoms show increased CCL11.
The researchers measured CCL11 levels in the plasma of people suffering from Long Covid. Compared with those who had Long Covid, but no cognitive issues, or brain fog, those who had cognitive symptoms also had elevated CCL11 levels. Interestingly, the researchers determined that patients who had a history of autoimmune disease, showed higher CCL11 levels.

Summarizing the findings of this research.
Corrupt microglial hyperactivity, a demyelinating effect, and increased cerebrospinal fluid cytokines, especially CCL11, all of which compromise memory and cognizance capabilities, were found in the brains of mice following a mild Covid 19 infection, and in the brains of human patients suffering from Long Covid who had brain fog. These findings closely matched those previously found in the brains of patients who were suffering from brain fog due to cancer treatments involving chemotherapy.

But this research leaves us craving more facts.
Why is this happening? Reflecting on this research article is somewhat reminiscent of the old saying about eating Chinese food — 30 minutes later, you're hungry again. We are left to wonder, “What is the mechanism by which Covid 19 causes these changes in the brain?” Nowhere in the article is this mentioned. Clearly, the virus has to be capable of crossing the blood-brain barrier, in order to make changes inside the brain. But that's not particularly surprising, since many viruses are capable of crossing the blood-brain barrier.

And published research verifies this connection.
A better understanding of this mechanism would allow us to more easily understand why other diseases are capable of causing brain fog, and other neurological issues. IBDs are associated with increased intestinal permeability (a.k.a. "leaky gut"), and increased intestinal permeability allows pathogens and assorted intestinal contents to get into the bloodstream, and some of these are then able to cross the blood-brain barrier. Although not necessarily valid scientific proof, evidence of this phenomenon can be found in an article published in Frontiers in Bioscience Elite (Kociszewska, and Vlajkovic, 2022)[3]. Therefore, it's not surprising that IBDs are capable of causing brain fog.



Gluten sensitivity is notorious for causing neurological problems.
Professor Marios Hadjivassiliou and his associates published their findings on this issue over 20 years ago (Hadjivassiliou, Grünewald, and Davies-Jones. 2002)[4]. Hadjivassiliou and his team noted that in many celiac cases, gluten sensitivity can cause neurological issues before it causes gastrointestinal issues, and in some cases, it causes neurological issues despite the fact that gastrointestinal issues never develop. And although at the time this was published, most authorities considered it to be associated only with celiac disease (and not IBD), that certainly doesn't rule out the possibility that this may also apply to IBD patients.

Are IBD patients gluten sensitive?
Numerous medical research articles have been published, citing an association between gluten sensitivity and IBD (other than celiac disease). But most such articles only show that the association is common, and their research typically shows only a limited percentage of IBD patients who are actually gluten sensitive. For example, an article published in the Scandinavian Journal of Gastroenterology found that 23.6% of Crohn's disease patients, and 27.3% of ulcerative colitis (UC) patients were gluten sensitive (Limketkai et al., 2017)[5].

But note that the *“Results” section of that article states that … There was no difference in these symptoms when comparing patients with and without GS (gluten sensitivity) …*". Furthermore, the ”Methods” section of that article reveals that … "*Descriptive analyses estimated the prevalence of GS….*" Presumably, that infers that each patient's gluten sensitivity status was based on their own (the patients' own) assessment of whether or not they were gluten sensitive (not on the results of any medical test).

Do such articles grossly understate gluten sensitivity among IBD patients?
Epidemiological evidence found in the archives of our own MC discussion and support forum indicate that most newly diagnosed MC patients initially deny that they are gluten sensitive (and yet we're all aware that carefully following a gluten-free diet is capable of bringing remission for the vast majority of us). Why would Crohn's disease and UC patients be any different? And even if researchers wanted to check for gluten sensitivity in IBD patients, they have no officially approved diagnostic test by which they can detect non-celiac gluten sensitivity, despite the fact that it appears to be far more prevalent than celiac-associated gluten sensitivity (Igbinedion et al., 2017)[6]. And despite its relatively widespread prevalence, physicians can't even agree on an official name for non-celiac gluten sensitivity, let alone decide on any diagnostic criteria.

The statement in the previous paragraph indicating that there was no difference in symptoms between IBD patients who were were found in the study to be gluten sensitive, and those who were not, suggests that they all were probably gluten sensitive, despite the lack of medical verification. If their symptoms were all identical, how could they all have not had a similar neurological status?

Compromised neurological status causes neurological symptoms. That's prima facie evidence that the study cohort were all gluten sensitive (since we know that at least about 1/4 of them

acknowledged gluten sensitivity). That issue may prove to be very relevant to this situation, since we know that the mechanism that causes neurological issues for IBD patients is leaky gut, and gluten sensitivity is not only commonly associated with leaky gut, but it's also commonly associated with brain fog.

Is gluten sensitivity a primary player in the majority of brain fog cases?
Data regarding that possibility are unavailable in the published medical literature, because the gluten sensitivity status of patients is always ignored in the respective studies, whether the studies involve brain fog in Long Covid patients, MS patients, cancer patients who receive chemotherapy treatments, or IBD patients. None of the studies consider gluten sensitivity.

A Beyond Celiac blog describes a study showing that 90% of survey respondents reported brain fog. 89% of celiac patients had brain fog, and 95% of those who had non-celiac gluten sensitivity reported brain fog (Beyond Celiac, n.d.)[7]. Obviously, brain fog is highly prevalent among patients who are gluten sensitive, regardless of the etiology of their gluten sensitivity.

Note that many Long Covid patients are gluten sensitive.
Covid has been shown to trigger mast cell activation syndrome, resulting in excessive histamine production. Because of this, many Long Covid patients find themselves with new food sensitivities, among which wheat gluten is the most common (Afrin, Weinstock, and Molderings, 2020)[8].

Following that publication, a research group even predicted an increase in celiac prevalence following the Covid pandemic (Trovato, Montuori, Pietropaoli, and Oliva, 2021)[9]. Their published article contains this conclusion, "*Genetically predisposed patients could be more likely to develop celiac disease following SARS-CoV-2 infection, making COVID-19 a candidate culprit for a potential outbreak of celiac disease in the forthcoming future.*"

What does this all tell us?
As noted above, published research shows that the brain fog reported by many IBD patients is probably due to the same cerebrospinal cytokines, microglial hyperactivity, and demyelinating issues attributed to the brain fog associated with chemotherapy treatments, and Long Covid. It appears that brain fog may be a product of increased intestinal permeability in virtually every case, accompanied by food sensitivities, especially gluten sensitivity, in many cases. But research proving these associations remains to be done, and is urgently needed, in order to close the loop.

Can brain fog be treated?
Conventional treatments follow a general pattern that usually includes brain exercises such as solving puzzles, reading and learning about a new topic, repetitive memory exercises, getting plenty of sleep, going to bed at a regular time, avoiding screens prior to going to bed, staying physically active, eating a good diet, etc. Like most healthcare-based treatments, most of these recommendations address the clinical symptoms, rather than the cause of the problem. But until now, advice such as this has been the only treatment approach available.

Low dose naltrexone seems to help in some cases.
Some doctors are experimenting with low dose naltrexone (LDN) treatments to help relieve brain fog among their patients who are suffering from Long Covid. LDN has been successfully used to treat certain autoimmune diseases, although MC patients who have tried LDN have not experienced any improvements in their MC symptoms, other than a reduction of pain, in some cases.

LDN hasn't shown a capability to relieve all the symptoms of Long Covid, but early treatment trials have indicated that about half the patients in these trials appear to gain significant resolution of their brain fog problems. An online article describes a Long Covid patient whose brain fog and other symptoms began during the spring of

2020[10]. In June of 2021, her doctor prescribed LDN for her to try, to see if it might bring relief from her symptoms. Although it hasn't resolved all her symptoms, it has allowed her to lead a much more normal life. Numerous clinical trials based on LDN treatments are planned, and others are currently underway.

The bottom line is: Treatment appears to be a work in progress.

We have to conclude that the medical community is still undecided about the best methods for treating brain fog. Eventually, it may become obvious that every case is different, and must be treated on its own merits, by an individualized treatment that's custom tailored for each patient, much as we've found to be true for successfully treating MC. But if that should turn out to be the case, would the medical community be willing and able to adopt such a treatment policy? So far, it appears that in this case, at least, they might be.

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