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Improvement in Long COVID Brain Fog After Benfotiamine and Methylcobalamin Supplementation: Case Report Series and Review of the Literature

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ABSTRACT

Long COVID, or post-acute sequelae of SARS-CoV-2 infection, is a complex and debilitating condition characterized by persistent symptoms affecting multiple organ systems, including neurological and musculoskeletal domains. With limited definitive treatments currently available, exploration of adjunctive therapies is critically needed. Emerging evidence suggests that deficiencies in thiamine (vitamin B1) or vitamin B12, or impaired metabolism of these vitamins, may be a contributing factor in symptomatology associated with COVID-19 disease. Here we present a case series in which three people suffering from Long COVID reported improvement in neurocognitive symptoms (brain fog) within one month following supplementation with a proprietary formulation of oral benfotiamine, a lipid-soluble thiamine derivative, and methylcobalamin (vitamin B12). No baseline thiamine or vitamin B12 biomarkers were obtained prior to initiation of vitamin supplementation, and no cognitive assessments were performed prior to supplementation, limiting the causal inference that can be derived from these cases. While these observations do not establish efficacy, they are consistent with the findings of other researchers in which the use of vitamin B1 and vitamin B12 was found to improve COVID symptomatology. These results support the need for controlled studies incorporating neurocognitive outcomes and biomarker characterization to further evaluate the usefulness of these vitamins in the treatment of Long COVID.

Introduction

Long COVID, or post-acute sequelae of SARS-CoV-2 infection (PASC), is an infection-associated chronic condition that occurs after SARS-CoV-2 infection and is present for at least 3 months as a continuous, relapsing and remitting, or progressive disease state that affects one or more organ systems.[1] Long COVID affects a significant number of individuals globally, with recent estimates indicating a pooled global prevalence of 36% among COVID-19-positive individuals.[2] Long COVID may affect multiple organ systems, and its symptoms may present with varying frequency and severity among individuals.[1] Studies have identified more than 200 symptoms associated with Long COVID. Common symptoms of Long COVID include fatigue, brain fog, neuropathy, memory loss, concentration difficulties, mood changes, and autonomic dysfunction.[1-3] The cause of Long COVID is likely multifactorial. Hypothesized pathophysiological mechanisms include sustained inflammation secondary to persisting reservoirs of SARS-CoV-2 in tissues, microbiota dysbiosis, endothelial dysfunction, dysfunctional neurological signaling, immune dysregulation, neuroinflammation, and mitochondrial dysfunction.[1-3] Current treatment and management strategies for Long COVID are insufficient and do not adequately address patient needs, underscoring the urgent need for more effective therapies.

Thiamine (vitamin B1) is a water-soluble, essential nutrient that plays a central role in energy metabolism and nervous system function.[4,5] As a coenzyme, thiamine is vital for key enzymes involved in glucose metabolism and the pentose phosphate pathway, supporting ATP generation, nucleic acid synthesis, and lipid metabolism. It is also critical for neurotransmitter production, cognitive function, memory, mood regulation, and the maintenance of myelin integrity. Thiamine contributes to gene expression, redox balance, immune system regulation, and cellular signaling processes. Additionally, by promoting the actions of the pentose phosphate pathway, it assists in the detoxification of harmful metabolic byproducts, such as advanced glycation end-products (AGEs), thereby promoting cellular health.[6,7] Thiamine has strong antioxidant and anti-inflammatory properties. It has been shown to enhance glutathione production, suppress pro-inflammatory cytokine production, reduce oxidative stress markers, and modulate immune responses.

Thiamine deficiency in humans can lead to a range of serious neurological and systemic effects.[4,5,8] In the nervous system, it contributes to neurodegeneration, characterized by damage to regions of the brain, such as the thalamus, cortex, cerebellum, and hippocampus, resulting in cognitive and motor impairments, memory loss, ataxia, and ophthalmoplegia. Thiamine deficiency also disrupts neurotransmitter balance, leading to excitotoxicity, oxidative stress, and neuroinflammation-ultimately impairing nerve conduction and myelin integrity. In severe cases, untreated thiamine deficiency can result in irreversible brain damage or death, underscoring the essential role of thiamine in nervoussystem health, energy metabolism, and cellular function.[8] As is the case in Long COVID, fatigue, brain fog, neuropathy, memory loss, concentration difficulties, mood changes, sleep disturbances, and autonomic dysfunction are common manifestations of thiamine deficiency. Thiamine supplementation has been used successfully in the treatment of many neurological diseases.[9-20]

Benfotiamine is a lipid-soluble derivative of thiamine. It has been shown to achieve significantly higher plasma concentrations of thiamine than water-soluble forms, due to its superior absorption from the gut. Benfotiamine has greater bioavailability and enhanced tissue penetration when compared to water-soluble thiamine.[21,22] Loew et al. showed that benfotiamine elevated plasma thiamine levels about 5 times higher than thiamine hydrochloride.[23] Benfotiamine is converted in the gut to a lipid-soluble metabolite, S-benzoylthiamine, which diffuses into the intestinal epithelium and then enters the bloodstream.[4] It is further metabolized in the liver and red blood cells to thiamine. A portion is also converted to O-benzoylthiamine, another lipid-soluble form.[24] The lipid solubility of these thiamine derivatives is believed to enable efficient passive diffusion into cells, where they are then converted to thiamine, potentially bypassing the need for transporter-mediated uptake and mitigating the effects of impaired thiamine transporter production. Benfotiamine has demonstrated neuroprotective, antioxidant, and anti-inflammatory properties.[4] Benfotiamine improves mitochondrial function and immune function-desirable properties in the treatment of COVID-19 disease.

In 2022, Allowitz et al. published a comprehensive review detailing the therapeutic potential of benfotiamine, emphasizing its wide-ranging benefits in neurological and systemic diseases associated with oxidative stress, chronic inflammation, and impaired glucose metabolism.[25] Their review details how benfotiamine's lipid-soluble nature enhances cellular uptake, allowing it to bypass transporter limitations, especially relevant in inflammatory conditions including COVID-19 infection. Mechanistically, benfotiamine increases intracellular thiamine diphosphate levels, activates the Nrf2/ARE antioxidant pathway, reduces advanced glycation end products (AGEs), and suppresses pro-inflammatory signaling. Importantly, the authors proposed that thiamine and benfotiamine supplementation, with their potent anti-inflammatory actions, including inhibiting the generation of inflammatory cytokines, chemokines, growth factors, and arachidonic acid metabolites, could prevent the cytokine storm generally observed in patients with COVID-19 infections.

Vitamin B12 is essential for neurological and brain health, playing a pivotal role in myelin formation, neurotransmitter synthesis, the maintenance of neuronal function, and neuroprotection.[26,27] Its deficiency can lead to a wide array of neurological problems, including impaired cognition and peripheral nerve dysfunction.[28] As is the case in Long COVID and thiamine deficiency, vitamin B12 deficiency may cause fatigue, brain fog,

neuropathy, memory loss, concentration difficulties, mood changes, and autonomic dysfunction.[29]

Emerging evidence suggests that supplementation with vitamin B1 and vitamin B12 may be beneficial in the management of Long COVID, although a firmly established connection between vitamin B1 or vitamin B12 metabolism and Long COVID is yet to be supported by high-quality evidence.[30,31] Cited studies are preliminary or observational, and robust clinical evidence confirming a causal relationship between vitamin B1 and vitamin B12 status and Long COVID is not yet available. Here we present three case reports of patients with Long COVID-related cognitive dysfunction in which a combination of oral benfotiamine and methylcobalamin supplementation was self-reported by each patient to have led to significant improvement in neurocognitive symptoms commonly described as "brain fog". All patients provided informed consent for publication.

Case Presentation

Case 1: A 27-year-old Hispanic male claimed to have had persistent cognitive symptoms following two confirmed COVID-19 infections approximately 9 months apart. His past medical history was negative. During his first infection, the patient experienced a severe allergic reaction with widespread hives, requiring emergency medical attention. Following the second infection, he developed persistent cognitive difficulties, including brain fog, impaired concentration, and mental fatigue.

Soon after the second infection, the patient started a trial of amphetamine-dextroamphetamine extended-release 10 mg daily. This yielded temporary symptomatic relief but was ultimately discontinued after four months due to adverse effects, including rebound fatigue and low mood during off-medication periods. The patient also experimented with dietary strategies, including intermittent fasting and a meat-based diet. These provided partial but unsustainable improvement.

Approximately two years after the initiation of the patient's symptoms, the patient independently began self-administering a proprietary supplement containing benfotiamine 150 mg and methylcobalamin 500 mcg (two capsules at 7:00 a.m. and two capsules at 2:00 p.m., approximately four times per week). Within three days of initiating supplementation with benfotiamine and methylcobalamin, he reported a marked improvement in energy and mental clarity, with resolution of brain fog on days when the supplement was taken. No other medication or supplement changes occurred within the first six weeks of starting benfotiamine and methylcobalamin. He reported no adverse effects and did not experience the energy fluctuations previously associated with amphetamine use. As of the writing of this paper he continues benfotiamine and methylcobalamin supplementation and claims to have sustained benefit.

Case 2: A 65-year-old Caucasian male claimed to have had a decade-long history of progressive forgetfulness, which worsened substantially following two separate COVID-19 infections. Following the infections, he reported persistent brain fog, difficulty sustaining coherent conversations, significantly impaired reading comprehension, and social withdrawal related to reduced confidence. His past medical history was negative.

The patient independently began self-administering supplementation with a proprietary formulation of benfotiamine 300 mg and methylcobalamin 1,000 mcg twice daily. No other medication or supplement changes occurred within the first six weeks of starting benfotiamine and methylcobalamin. Within six weeks of initiating this supplementation regimen, he reported significant improvements in mental clarity, executive function, and confidence. He was able to successfully lead a business meeting-an achievement he had not felt capable of in several years.

Approximately six months after starting supplementation, the patient traveled for five weeks without access to the supplement. During this period, his cognitive dysfunction recurred, including brain fog and impaired concentration. Upon resuming supplementation, he reported a return of improved cognitive function within four to six weeks. As of the writing of this paper, he remains on benfotiamine and methylcobalamin therapy, with continued subjective symptomatic improvement.

Case 3: A 71-year-old Caucasian female with a history of both long-standing physical and emotional trauma and chronic fatigue syndrome/myalgic encephalomyelitis became infected with SARS-CoV-2 in 2021. Post-infection, she noted an increase in the level of her chronic fatigue. Her symptoms persisted unchanged for the next three years. In 2024 she reported being infected once again with SARS-CoV-2. She reported a marked worsening of symptoms, including fatigue, sleep disturbances, joint pain, dizziness, vertigo, brain fog, digestive issues, and radicular pain in an ulnar distribution affecting both arms. At that time, she sought nutritional counseling and treatment. Genomic testing revealed a homozygous MTHFR mutation. Additional findings included hypothyroidism, hypercholesterolemia with low HDL, elevated high-sensitivity C-reactive protein, and vitamin D insufficiency. The patient was started on glutamine, vitamin D, probiotic, quercetin, magnesium threonate, and B12 methylfolate. These led to partial symptom relief, but brain fog, dizziness, and radicular pain persisted. After six months of treatment on these nutrients, and noting no additional improvement for many weeks, a proprietary formulation of benfotiamine (300 mg twice daily) with methylcobalamin (12 mcg per day) was introduced into her supplementation regimen by her nutritional counselor. No other medication or supplement changes occurred within the first six weeks of starting benfotiamine and methylcobalamin. Within 10 days of starting benfotiamine and methylcobalamin, the patient reported improvement in brain fog and joint pain. After 30 days, radicular pain resolved and dizziness improved by approximately 85%. As of the writing of this paper, she continues to take benfotiamine and methylcobalamin and self-reports sustained benefit.

Case Series Analysis

All patients in this case series reported neurocognitive issues consistent with Long-COVID. Although they differed in age, comorbidities, illness duration and dosing regimen, each patient described a noticeable benefit within a brief period–ranging from several days to several weeks–after the initiation of supplementation with benfotiamine and methylcobalamin. No serious adverse effects were reported by any of the patients. In one case, discontinuation of supplementation was associated with recurrence of symptoms and re-initiation was followed by improvement, suggesting a temporal association between ongoing supplementation and perceived benefit. These observations, while limited to a self-evaluation, are consistent with the hypothesis that benfotiamine and methylcobalamin may ameliorate neural cognitive symptoms in a subset of patients with Long-COVID.

Discussion

Fatigue, brain fog, neuropathy, memory loss, concentration difficulties, mood changes, and autonomic dysfunction are hallmark symptoms of Long COVID.[1-3] These symptoms are also hallmarks of vitamin B1 deficiency, as well as vitamin B12 deficiency.[4,5,8,26-29] This commonality in symptoms may suggest that individuals with underlying deficiencies in these vitamins are possibly more susceptible to contracting COVID-19 or that the infection may exacerbate these deficiencies, or both. Furthermore, elderly individuals, diabetics, those with alcohol use disorder, ulcerative colitis/inflammatory bowel disease, or chronic kidney disease-groups already predisposed to both vitamin B1 and vitamin B12 deficiency or their impaired metabolism-appear to face higher risks of severe COVID-19 and its lingering complications.[26,30-40] However, common symptom overlap alone does not establish a shared etiology. Instead, it raises the hypothesis that low levels of vitamin B1 and/or vitamin B12, their impaired metabolism, or an increased functional demand for these vitamins, could contribute to persistent symptoms in a subset of post-COVID patients. This hypothesis remains preliminary and requires further study.

Adequate vitamin B12 levels are essential for proper neurological function, and its deficiency is a well-known cause of neurological dysfunction.[26,28] There is accumulating evidence linking low vitamin B12 levels to higher odds of COVID-19 infection, more severe disease and inflammatory response, as well as worse overall prognosis.

Batista et al. published a comprehensive review establishing the role of vitamin B12 as adjunct therapy for the persistent symptoms of COVID-19, focusing on symptoms related to the muscle-gut-brain axis.[41] They presented data from randomized clinical trials and meta-analyses that indicate vitamin B12 in the forms of methylcobalamin and cyanocobalamin may decrease pain intensity, memory loss, and impaired concentration. Goderidze et al. found that 85% of 312 patients with confirmed Long COVID were vitamin B12 deficient.[42] Common symptoms included memory issues, poor concentration, mood changes, tingling, and muscle weakness-none of which had significantly affected patients before becoming infected. Treatment involved daily oral vitamin B12 for two months, with some patients initially receiving vitamin B12 injections. Upon completing the treatment, all patients reported a significant reduction or complete disappearance of their symptoms. In a 2022 retrospective study of 408 Long COVID-19 patients in Turkey, Aslaner et al. found that 60% of these patients were vitamin B12 deficient. The authors also found clinical progression to be worse in COVID-19 patients with vitamin B12 deficiency than those who had no deficiency.[43] Inflammatory markers of the patients with vitamin B12 deficiency were found to be higher. They suggest that vitamin B12 supplements in COVID-19 patients may have a positive effect. In a 2023 case-control study, Sezgin investigated the relationship between vitamin B12 levels, homocysteine levels (a marker of vitamin B12 deficiency), and COVID-19 infection by analyzing data from 152 patients-76 with confirmed COVID-19 and 76 controls.[44] He found that COVID-19 patients had substantially lower serum vitamin B12 levels than the control group and that patients with low vitamin B12 levels and high homocysteine levels were more severely affected by COVID-19 infection. Clemente-Suárez et al. reported that deficiency in vitamin B12 (as well as in vitamins C and D, selenium, iron, and fatty acids) is associated with an increased risk of hospitalization and mortality from COVID-19.[45]

Emerging evidence suggests that thiamine deficiency or its impaired metabolism may be a contributing factor in symptomatology associated with COVID-19 disease. Several cases in the medical literature report the onset of Wernicke's encephalopathy (WE), an acute neurological emergency resulting exclusively from thiamine deficiency, following SARS-CoV-2 infection in individuals who had no predisposing risk factors for thiamine deficiency.[46-50] Branco de Oliveira et al. described three mechanically ventilated ICU patients with COVID-19 presenting with full or partial WE treated with intravenous thiamine.[51] All patients responded with immediate neurologic improvement, and two of them had accelerated ventilatory weaning. Branco de Oliveira et al. also reported on a retrospective case series involving 15 severe COVID-19 patients with encephalopathy, two-thirds of whom exhibited additional signs of WE.[52] After receiving intravenous thiamine (500 mg three times daily), all patients demonstrated marked neurological recovery within 2-5 days. A two-center retrospective cohort study by Al Sulaiman et al. evaluated the impact of thiamine as adjunctive therapy in critically ill COVID-19 patients admitted to intensive care units.[53] Thiamine administration was associated with a significant reduction in both in-hospital mortality and 30-day mortality. Additionally, patients in the thiamine group had an 81% lower risk of thrombosis during ICU stay. Tehrani et al. conducted an open-label, randomized, controlled trial evaluating the efficacy of thiamine in treating Long COVID.[30] Sixty-six patients with persistent symptoms following COVID-19 infection were assigned

to receive either vitamin B1 (600 mg daily) along with supportive therapy or supportive therapy alone. Over a nine-week follow-up, the group receiving thiamine demonstrated significantly faster symptom improvement, with notable effects observed within the first two weeks. By week five, symptoms such as myalgia, anosmia, ageusia, fatigue, and sleep disturbances had improved in the intervention group, and from week seven onward, their recovery rate was double that of the control group.

Although not clinically validated and requiring further study, preliminary in silico and molecular modeling studies by multiple authors suggest that vitamins B1 and B12 may inhibit SARS-CoV-2 replication and entry into host cells.[54-57]

The foregoing literature raises the possibility that COVID-19 and its post-acute sequelae may be associated with abnormalities in vitamin B1 and/or vitamin B12 status or metabolism in some individuals. Although vitamin B1 and vitamin B12 biomarkers were not measured in the three patients in this series and no standardized cognitive outcomes were assessed, the temporal association between supplementation and self-reported improvement observed in these three cases is consistent with, but does not confirm, the hypothesis that vitamin B1 and/or vitamin B12 related factors could contribute to neurocognitive symptoms in a subset of Long COVID patients. It should be noted that these observations are preliminary and hypothesis generating rather than evidence of therapeutic efficacy. They support the need for prospective, randomized placebo-controlled trials incorporating, objective neurocognitive outcomes, and biomarker evaluation to characterize altered vitamin B1 and vitamin B12 status or metabolism.

Conclusions

Long COVID is a complex and multifaceted condition characterized by persistent symptoms following SARS-CoV-2 infection and is widely attributed to chronic inflammation, immune dysregulation, metabolic disturbances, and neurological dysfunction. The biological actions of thiamine and methylcobalamin-including their roles in mitochondrial function, neuroinflammation, myelin maintenance, and cytokine modulation-provide a plausible mechanistic basis for their potential relevance to post-COVID conditions. Populations disproportionately affected by COVID-19, such as the elderly, individuals with diabetes, alcohol use disorder, inflammatory bowel disease, or chronic kidney disease, are also known to be at increased risk for deficiencies in these vitamins. Prior reports describing symptomatic improvement with thiamine and vitamin B12-based therapies in SARS-CoV-2 infection are consistent with the favorable clinical response observed in the three case studies presented here; however, these observations are at best hypothesis-generating and cannot establish causality.

The case series described in this paper suggests that further study of benfotiamine and methylcobalamin in the treatment of Long COVID is warranted, particularly given their long-standing safety record, low cost, and wide availability. Definitive evaluation of their therapeutic potential will require randomized, double-blind, placebo-controlled trials, using objective neurocognitive, metabolic, and neurological outcome measures. Future studies should also aim to clarify whether specific subgroups of patients may be more likely to respond to supplementation. Additional mechanistic research examining how these nutrients might influence viral entry pathways, neuroinflammatory cascades, or mitochondrial function may further elucidate their potential role.

The study presented here has significant limitations. It describes observations on improvement in Long COVID symptomatology, which were self-reported by a small sample size of three subjects. It lacks a control group. It lacks objective testing of symptoms. There is the potential for a placebo effect as well as possible unaccounted-for confounders. More formalized double-blind placebo randomized studies are needed to explore the possibility of the contributory role of vitamin B1 and vitamin B12 deficiency or their impaired metabolism in the symptomatology of Long COVID.

Author Details

Dr. Mann is an independent researcher on the use of nutrients to improve patients' central and peripheral neurological function. He is a key opinion leader and has given lectures at over a hundred domestic and international medical conferences. In June 2023, he authored and published a scientific peer-reviewed article entitled "Impaired Thiamine Metabolism in Amyotrophic Lateral Sclerosis and Its Potential Treatment with Benfotiamine: A Case Report and a Review of the Literature" (10.7759/cureus.40511). In May 2025 he co-authored and published a scientific peer-reviewed article entitled "The Beneficial Effects of a Combination Therapy of Oral Benfotiamine and Methylcobalamin in the Treatment of Parkinson's Disease: Case Reports and Review of the Literature. Medical Research Archives, [online] 13(5). https://doi.org/10.18103/mra.v13i5.6580

Disclosures and Conflict of Interest

Dr. Richard H. Mann holds a financial interest in Zobria Labs, LLC and Realm Labs, LLC, companies that distribute nutritional supplements, including benfotiamine and methylcobalamin. Dr. Mann serves as the Chief Scientific Officer at Zobria Labs, LLC and Realm Labs, LLC.

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