Successful treatment of myalgic encephalomyelitis/chronic fatigue syndrome using hydrogen gas: four case reports

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is characterized by unexplained fatigue and malaise that persist for more than 6 months with neuropsychiatric symptoms, including slight fever, headache, weakness, impaired thinking, and depression.[1,2] The onset and severity of these symptoms vary and reduce the quality of life as well as social, occupational, and personal activities of those affected, with some becoming bedridden.[1,2] The number of ME/CFS patients in the United States is estimated to be between 836,000 and 2.5 million.[3]

Although it currently remains unclear whether there are objective and biological abnormalities in ME/CFS, recent neuroimaging, blood marker analyses, and energy metabolism and mitochondrial studies detected these abnormalities in ME/CFS patients.[4] ME/CFS may be caused by the activation of the immune system, both within and outside the brain, which induces the release of inflammatory cytokines. ME/CFS is presumed to cause abnormalities in the central and autonomic nervous systems, systemic energy metabolism, and immune system and also involve oxidative and nitrosative stress.[4-6] Dysfunctions in systemic energy metabolism may be related to abnormalities in the structure and function of mitochondria.[7-10]

Molecular hydrogen (H_2) is a gaseous molecule that selectively scavenges reactive oxygen and nitrogen species with strong oxidizing power, namely, hydroxyl radicals (·OH) and peroxynitrite, respectively.[11,12] H_2 easily crosses the blood-brain barrier and biological membranes, reaches mitochondria, and protects cells from ·OH-induced cell damage.[11,12] A recent literature review revealed that H_2 attenuated acute or chronic fatigue in animals and healthy subjects.[13] We also reported that the anti-fatigue effects of H_2 involved the protection of mitochondria, which may also ameliorate the pathogenesis of ME/CFS.[13] Therefore, we conducted this case study to test this hypothesis by examining the efficacy of H_2 gas inhalation in four patients with ME/CFS.

Case 1: We herein present a 58-year-old male patient with ME/CFS who successfully responded to H_2 gas inhalation therapy. The Canadian Consensus Criteria (CCC) are based on a score of 21 symptoms (no symptoms: 0, mild: 1, moderate: 2, severe: 3), including the typical symptoms of ME/CFS, such as post-exertional fatigue, sleep disturbance, impaired thinking, pain, autonomic disturbance, and chemical intolerance.[14] The score of each symptom and the total score of the 21 symptoms (a maximum score of 63) are used to establish whether symptoms improve or worsen.[14] To evaluate the efficacy of H_2 gas inhalation for this patient, we adopted a medical interview and CCC recorded by the patient every two weeks because there is currently no accurate method to evaluate substances that show efficacy against ME/CFS other than patients' symptoms.

The patient developed extreme fatigue, headache, and other symptoms in April 2012 and had difficulties thinking clearly and concentrating. He visited various hospitals in an attempt to diagnose and treat these symptoms, but was unsuccessful. He visited the National Center of Neurology and Psychiatry (NCNP) in 2019. Many examinations were performed and subjective symptoms met the ME/CFS criteria of CCC. Various treatments were conducted for approximately two years, but were unsuccessful.

The patient inhaled 6–7% H_2 gas (2 L/min, MHG-2000α, MiZ Company Limited, Kamakura, Japan) produced by water electrolysis between June 2021 and November 2021 for 3–5 hours per day. Severity scores before and after the H2 gas treatment are shown in **Table 1** and **Figure 1**.

Table 1: Severity scores of 21 symptoms in a patient with ME/CFS after hydrogen (H_2) gas inhalation

	H_2 gas treatment period (wk)									
Symptoms	**0**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**
Fatigue after exertion	3	2	2	2	2	3	2	2	2	2
Recovery time from exertion	2	1	1	1	1	2	1	1	1	1
Fatigue	3	2	0	1	1	2	1	1	1	1
Sleep disturbance	2	2	2	2	2	2	2	2	2	2
Pain (muscle pain, joint pain, and headache)	2	1	0	0	0	1	0	0	0	0
Memory impairment	1	1	1	1	1	2	1	1	1	1
Confusion and poor concentration	2	1	1	1	2	2	1	1	1	1
Difficulty with verbal retrieval	2	2	2	2	2	3	2	2	2	2
Gastrointestinal disorders	1	1	1	1	1	1	1	1	1	1
Recurrent sore throat	1	0	0	0	0	1	0	0	0	0
Influenza-like symptoms	0	0	0	0	0	0	0	0	0	0
Dizziness on standing up	1	1	1	1	0	1	0	0	0	0
Abnormal body temperature	1	1	0	0	0	0	0	0	0	0
Warmth and impatience	1	1	1	1	1	1	1	1	1	0
Red face and abnormal sweating	0	0	0	0	0	0	0	0	0	0
Weight change	1	1	0	0	0	0	0	0	0	0
Shortness of breath on exertion	2	2	1	1	1	2	1	1	1	0
Lymph node tenderness	0	0	0	0	0	0	0	0	0	0
Hypersensitivity to light, sound, and smell	3	3	1	1	1	3	1	1	1	1
Muscle weakness	0	0	0	0	0	0	0	0	0	0
Sensitivity to foods, drugs, and chemicals	1	1	1	1	1	1	1	1	1	1
Total severity score	29	23	15	16	16	27	15	15	15	13

Note: The patient recorded a 21-item severity score based on CCC. Each score was rated on a 4-point scale (0: no symptoms, 1: mild, 2: moderate, and 3: severe), and the total score (a score of 63) was calculated.[14] He was vaccinated against COVID-19 at weeks 8 and 11. The vaccination exacerbated the symptoms of ME/CFS, which returned to pre-vaccination levels after week 14. CCC: Canadian Consensus Criteria; COVID-19: coronavirus disease 2019; H_2: molecular hydrogen; ME/CFS: myalgic encephalomyelitis/chronic fatigue syndrome.

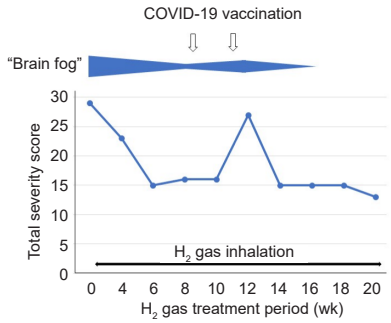

Figure 1: Changes in the total severity score and "brain fog" in a patient with ME/CFS after H_2 gas inhalation.
Note: The patient has been inhaling 6–7% H_2 gas produced by water electrolysis for 3–5 hours per day. Each severity score before and after the H_2 gas treatment was recorded based on CCC, and the total score (a score of 63) was calculated.[14] He was vaccinated against COVID-19 at weeks 8 and 11, and the vaccination exacerbated the symptoms of ME/CFS. However, symptoms recovered to the pre-vaccination level after 14 weeks of H_2 gas inhalation. CCC: Canadian Consensus Criteria; COVID-19: coronavirus disease 2019; H_2: molecular hydrogen; ME/CFS: myalgic encephalomyelitis/chronic fatigue syndrome.

The severity score decreased from 29 points before treatment to 23 points after four weeks, confirming the significant attenuation of both chronic severe fatigue and intense fatigue after exertion. The amelioration of headaches, post-exertional muscle pain, joint pain, poor concentration, and a recurrent sore throat was also noted. Further improvements were observed after 6 weeks. Severe fatigue, headache, and muscle aches following an increased intensity of exercise were markedly alleviated. Weight gain was noted as well as increased blood flow to the feet, and shortness of breath on exertion and sensitivity to sound decreased. Although not reflected in the severity score, "brain fog" was reduced; the severity score after 6 weeks decreased to 15. The severity score was 16 after 8 weeks, which was not significantly different from that at 6 weeks; however, the number of days without "brain fog" had increased.

The patient was vaccinated against coronavirus disease 2019 (COVID-19) at weeks 8 and 11. Five days after the first vaccination, ME/CFS symptoms temporarily worsened, but recovered after week 10 of H_2 gas inhalation with a severity score of 16. Eight days after the second vaccination (12 weeks after H_2 gas inhalation), ME/CFS symptoms worsened more than after the first vaccination with a severity score of 27. However, following vigorous H_2 gas inhalation, symptoms recovered to pre-vaccination levels after 14 weeks, and the severity score returned to 15. Although the COVID-19 vaccination exacerbated the symptoms of ME/CFS, this was temporary, and H_2 gas inhalation markedly attenuated these symptoms.

The severity score after 16 weeks was the same as that after 14 weeks, while daily activity levels significantly increased. Therefore, the patient was ready for rehabilitative training and a return to work. However, since his condition had not yet stabilized, the patient was only able to perform various activities to the same level as a healthy individual once every three days. Nevertheless, steady recovery was observed. Although fatigue after exertion still occurred, the patient was able to recover by resting for a few hours and inhaling H_2 gas. After 18 weeks, the severity score was the same as those after 14 and 16 weeks; however, he was able to perform the activities of daily living, such as housework, light work, and going out in the neighborhood, and his physical symptoms, which recurred after the COVID-19 vaccination, had completely resolved. Since the patient also had a greater range of activities after 20 weeks of treatment, he took a small trip. He felt tired and easily fell asleep after returning home, but recovered within a few days, suggesting the fatigue-attenuating effects of H_2 gas. Furthermore, the severity score decreased to 13 during this week.

Cases 2–4: Due to the efficacy of H_2 gas for ME/CFS in Case 1, three more case studies were conducted. We provided the same type of hydrogen gas inhaler used in Case 1 to three patients referred by NCNP. The efficacy of H_2 gas was assessed twice, after 3 weeks and after 8 to 9 weeks, by an interview and the recording of general symptoms because patients were not able to perform self-scoring by CCC.

Case 2: A 43-year-old woman diagnosed with probable ME/CFS by NCNP in 2017 attempted various treatments, but did not respond well. Prior to H_2 gas inhalation, she was unable to maintain standing, erect, and seated postures due to significant reductions in upper and lower extremity and trunk functions. The patient spent most of her time in bed during the day and used a wheelchair for indoor mobility. She also exhibited general pain, weakness, malaise, fatigue after exertion, and sleep disturbance as well as slight fever, bradycardia, and hypotension, which were diagnosed by testing at NCNP. The patient inhaled H_2 gas for 6 hours per day from the end of August 2021 to early November 2021. Sleep disturbance and daily headaches and migraines, which occurred several times a day, were attenuated after 3 weeks of inhalation. Nine weeks later, sleep disturbance, headaches, and migraines continued to be ameliorated by H_2 gas inhalation.

Case 3: An 18-year-old woman diagnosed with probable ME/CFS by NCNP in April 2020 had attempted various treatments, but did not respond well. She spent most of the day in bed. She began inhaling H_2 gas for 5 hours per day from the end of August 2021 to the end of October 2021. Approximately 3 weeks after inhalation, she noted a decrease in fatigue, improved bowel movements, and increased motivation. At the end of 8 weeks, she was not sleeping as much during the day and had more time for physical activity, but still felt tired.

Case 4: An 18-year-old man who was diagnosed with probable ME/CFS and fibromyalgia by NCNP in August 2020 attempted various treatments, but did not respond well. Prior to H_2 gas inhalation, the patient exhibited fatigue, headache, muscle weakness, general aches and pains, sleep disturbance, impaired thinking, concentration, and memory, tinnitus, and "brain fog". He began inhaling H_2 gas for 6 hours per day from the end of August 2021 to early November 2021. The attenuation of headache and general pain was noted after approximately 3 weeks of treatment, and the ameliorating effects of H_2 gas inhalation on these symptoms continued after 9 weeks, with a decrease in the use of analgesics. In addition, "brain fog" improved.

Substances that attenuate the pathogenesis of ME/CFS are being developed. Clinical studies investigated the efficacies of the antibody drug rituximab, nicotinamide adenine dinucleotide hydrogen, coenzyme Q10, and acetyl L-carnitine for the treatment of ME/CFS, but found that they were ineffective or their effects were limited.[15-18] Therefore, the development of therapeutic substances that are curative rather than symptomatic for ME/CFS is needed.

In this case study, we examined the efficacy of H_2 gas in four patients with ME/CFS. Case 1, a patient diagnosed with ME/CFS 2 years ago who did not respond to various therapies, was treated with H_2 gas inhalation for 20 weeks. H_2 gas inhalation significantly attenuated post-exertional fatigue, the recovery time from exertion, shortness of breath on exertion, headache, sore throat, poor concentration, abnormal body temperature, and sensitivity to sound. Cases 2–4 were also patients who did not respond to various treatment attempts. After 8 to 9 weeks of H_2 gas inhalation, headache, general aches and pains, sleep disturbances, bowel movements, decreased motivation, and brain fog improved in all three patients. These four cases are the first in which H_2 gas inhalation has been shown to attenuate the symptoms of ME/CFS.

COVID-19 results from infection with severe acute respiratory syndrome coronavirus 2. Although acute symptoms resolve within 2–3 weeks, some patients continue to have "sequelae" for months after the initial infection. A number of symptoms have been reported as these "sequelae," which are termed "long COVID" or "post COVID" and are similar to those of ME/CFS.[19,20] However, despite these similarities, it remains unclear whether COVID-19 infection is a trigger for the development of ME/CFS.[19,20] Botek et al.[21] recently conducted a single-blind randomized trial on 50 "post COVID" patients and reported that 14 days of H_2 gas inhalation improved physical and respiratory functions in the acute phase of infection. Although further large-scale studies are needed, if we assume that "long COVID" or "post COVID" develops via the same mechanism as ME/CFS, the results of our case study are supported by the findings of Botek et al.[21]

In conclusion, since this was a case study based on self-assessments by a small number of patients and not a clinical study in the form of a randomized controlled trial, there are some limitations to the present results. Nevertheless, the results obtained suggest the potential of H_2 gas as a therapeutic gas for ME/CFS. Further large-scale clinical studies are needed to evaluate the efficacy of H_2 gas as a therapeutic agent for ME/CFS and the underlying mechanism of action.

Ethical approval was waived for this study because it is not a research study. Written informed consent was obtained from the subjects for the publication of data included in this article.

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