

## Hydrogen inhalation therapy may ameliorate amyotrophic lateral sclerosis

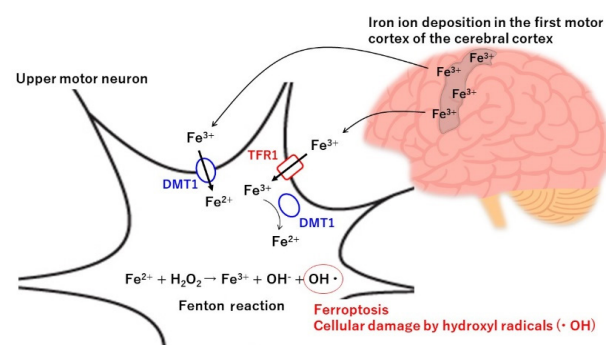
Amyotrophic lateral sclerosis (ALS) is a motor neuron disease, a neurodegenerative disorder characterized by sporadic and progressive degenerative loss of cell bodies of both the upper and lower motor neurons.<sup>1,2</sup> Clinical manifestations of ALS are known to include lower motor neuron symptoms, upper motor neuron symptoms, bulboparesis symptoms, cognitive dysfunction, and negative signs.<sup>3</sup> Dissociated small hand atrophy is also known as a characteristic symptom.<sup>4</sup> ALS is always progressive, and once a person has the disease, there is no relief from the symptoms.<sup>5</sup> No matter which part of the body the symptoms start in, eventually all the muscles in the body are affected, and finally the respiratory muscles also stop working, with a majority of people suffering from respiratory failure.<sup>6</sup> Without the use of a ventilator, the time from illness to death is roughly 3–5 years.<sup>5,6</sup> Since reactive oxygen species are known to be closely related to the onset of ALS, antioxidants are expected to contribute to the suppression of ALS onset and improvement of its symptoms, and a number of antioxidants have been developed as candidates for ALS treatment.<sup>7,8</sup> However, all of these antioxidants have been used only as a coping strategy, and there is no antioxidant that has been found to fundamentally improve ALS.<sup>7,8</sup>

It has been proposed that molecular hydrogen may inhibit chronic inflammation by scavenging hydroxyl radicals generated within cells and mitochondria, which may have an effect on many diseases caused by chronic inflammation.<sup>9–11</sup> However, there are no reports of prevention or amelioration of ALS or ALS-related symptoms.

This perspective describes the mechanism of action in the development of ALS, touches on the possibility of ALS amelioration by hydrogen, and presents a case in which ALS symptoms were ameliorated by inhalation of hydrogen gas.

**Mechanism of ALS pathogenesis:** Based on the mechanism of oxygen-induced damage, the pathogenesis of ALS can be explained. It is the excessive deposition of metal ions in the brain, rather than the lack of metal ions, that is the problem in the association between neurological disease and abnormal metal metabolism. In ALS patients, the first motor cortex of the cerebral cortex is also prone to excessive deposition of metal ions such as iron ions (**Figure 1**).<sup>12,13</sup> Trivalent iron ions ( $\text{Fe}^{3+}$ ) deposited into the brain are absorbed into upper motor neurons by transferrin receptor 1 and reduced to divalent iron ( $\text{Fe}^{2+}$ ) by divalent metal transporters (**Figure 1**).<sup>14</sup> On the other hand, leakage of electrons in the electron transfer system occurs inside mitochondria, which are known to produce the highest amount of reactive oxygen species in the cell, and 1–5% of the oxygen used for respiration is converted to hydrogen peroxide via superoxide.<sup>15</sup> Hydrogen peroxide produces hydroxyl radicals (Fenton reaction) by one-electron reduction, in which hydrogen peroxide receives an electron from the reducing  $\text{Fe}^{2+}$ .<sup>10,11,16</sup> Hydroxyl radicals have the strongest oxidative activity and indiscriminately attack neurons in the brain, destroying neurons and cellular constituents, resulting in ALS.<sup>11</sup> These are the so-called mechanisms of ferroptosis. Therefore, the key to preventing and improving ALS is how to eliminate hydroxyl radicals generated in the brain.

**Role of hydrogen in the living body:** Hydrogen is the smallest diatomic molecule and can freely penetrate cell membranes to reach the brain.<sup>16</sup> Hydrogen can also react with hydroxyl radicals



**Figure 1: Mechanism of cell damage by ferroptosis.**

Note: Hydroxyl radicals are generated by the Fenton reaction in the brain of healthy people. However, in the first motor cortex of the brain of ALS patients, metal ions such as iron ions are easily deposited. Metal ions deposited in the brain accelerate the Fenton reaction and generate more hydroxyl radicals, causing damage to cranial nerve cells (ferroptosis), which is thought to be a major factor in the pathogenesis of ALS. Therefore, how to eliminate hydroxyl radicals generated in the brain is an important issue for the prevention and improvement of ALS. Created with Microsoft PowerPoint 2019 MSO. ALS: Amyotrophic lateral sclerosis.

and protect the brain from hydroxyl radical attack by converting hydroxyl radicals to water molecules.<sup>16</sup> Given the mechanism of action of ALS, it is thought that the progression of ALS can be inhibited and improved if antioxidants can be delivered to the areas of the brain where metals are deposited and hydroxyl radicals can be scavenged; however, attempts to use antioxidants have failed.<sup>7,8</sup> For example, edaravone, a radical scavenger known as a therapeutic agent for ALS, has a large molecular weight, making it difficult for it to reach deep into the brain. There is also a limit to how much of the reaction byproduct of edaravone can be expelled from the brain, and it is associated with serious side effects. Therefore, edaravone cannot stop the progression of ALS.<sup>12,17</sup> In addition to edaravone, other drugs targeting cranial nerve diseases face the following problems.

- Problem 1: Must penetrate the blood-brain barrier.
- Problem 2: Must target the affected part of the brain. It is particularly difficult to reach the deep brain. It is also difficult to penetrate intracellular organelles such as mitochondria.
- Problem 3: Metabolites must be removed from the brain to the outside of the brain.
- Problem 4: The drug itself has side effects.

On the other hand, hydrogen, unlike other antioxidants, has the following advantages.

- Advantage 1: It is an inert substance and does not react with biological substances other than hydroxyl radicals
- Advantage 2: Because it is a diatomic molecule at minimum, it can penetrate cell membranes and reach deep into the brain. Furthermore, it can not only enter the cytoplasm, but also reach the inside of cell organelles such as mitochondria and nucleus, and can scavenge hydroxyl radicals generated inside intracellular organelles.
- Advantage 3: Since the reaction product is a water molecule, there are no side effects caused by pharmaceutical byproducts.
- Advantage 4: Excess hydrogen is naturally released from the body by diffusion.

Hydrogen can protect the brain with these advantages without any side effects. Hydrogen can easily overcome all the problems of pharmaceuticals. Because of this mechanism of action, hydrogen may be effective against neurological diseases such as ALS and Parkinson's disease, and we decided to confirm the effect of hydrogen on ALS symptoms by recommending one patient with ALS to inhale hydrogen gas. Care must be taken when handling



hydrogen because it is explosive, so hydrogen gas inhalers that produce less than 10 volume hydrogen, which is under the explosive concentration, should be used.<sup>18,19</sup>

**Case of ALS improvement by hydrogen gas inhalation:** A 64-year-old Japanese man felt something wrong with his left calf in the spring of 2021, and when he went to the hospital in August of the same year, he was diagnosed with ALS. Doctors declared that there was no treatment for ALS and that he had 3 to 4 years to live. The paralysis in his left leg progressed, and the calf of his left leg became noticeably thinner than his right leg, which could be seen just by looking at it. Walking became difficult, and he could not walk straight without the use of a cane. The patient began inhaling hydrogen gas in October 2022. The hydrogen gas inhaler used was a product named Jobs- $\alpha$  (trademark registered as Jobs) from MiZ Company Limited (Kamakura, Kanagawa, Japan). The hydrogen concentration of Jobs- $\alpha$  is 4% to 5% and the hydrogen volume is 200 mL/min as 100% hydrogen generates. The inhalation time was 7 to 8 hours per day, mainly during sleep. On November 10, 2022, muscle tone in the left calf returned at a visually noticeable level. In early December 2022, the patient went on a business trip to Europe. His family was concerned about whether he could go on a business trip with his ALS, but he decided to go on the trip because his health condition had not deteriorated and he had been able to work energetically despite his difficult schedule due to inhalation of hydrogen gas. He had no problems walking, despite the cold weather and cool temperatures in Europe. Although he still uses a cane for safety, he has seen a definite improvement in his ability to walk. Other positive results include increased appetite and good bowel movements, and he has seen improvements in his blood pressure, blood sugar, and liver function. The study has obtained written informed consent from the patient.

**Conclusion:** In view of the mechanism of conversion of hydroxyl radicals to water molecules by hydrogen as described above, hydrogen may have the potential to prevent ferroptosis in motor neurons, thereby inhibiting ALS progression. In this study, we succeeded in suppressing the paralysis and degeneration of the calf muscles, a symptom of ALS, and even improved the difficulty in walking by having one ALS patient actually inhale hydrogen. Until now, no drug has been able to halt the progression of ALS symptoms, and the disease has been so intractable that patients have had no choice but to wait for death. Although this is only one case, future clinical trials with multiple patients should confirm the effectiveness of this treatment.

*The authors are grateful to Ms. Yoko Satoh (MiZ Company Limited) for her excellent advice in the writing of this manuscript.*

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doi: 10.4103/2045-9912.390249

**How to cite this article:** Ichikawa Y, Sato B, Hirano S, Takefuji Y, Satoh F. Hydrogen inhalation therapy may ameliorate amyotrophic lateral sclerosis. *Med Gas Res* 2024;14(3):149-150.

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Date of submission: February 7, 2023

Date of decision: September 10, 2023

Date of acceptance: October 21, 2023

Date of web publication: March 20,

2024