Medical Research Archives

ESMED
European Society of Medicine

OPEN ACCESS

Published: July 31, 2022

Citation: Ono H, Nishijima Y, et al., 2022. Long-Term Inhalation of Hydrogen Gas for Patients with Advanced Alzheimer's Disease: A Case Report Showing Improvement in Fecal Incontinence, Medical Research Archives, [online] 10(7). https://doi.org/10.18103/mra.v10i7.2951

DOI https://doi.org/10.18103/mra.v10i7.2951

ISSN: 2375-1924

CASE REPORT

Long-Term Inhalation of Hydrogen Gas for Patients with Advanced Alzheimer's Disease: A Case Report Showing Improvement in Fecal Incontinence

Hirohisa Ono*[1], Yoji Nishijima[1], Masaki Sakamoto[1], Soitirou Kitamura[1], Yuitiou Naitoh[1], Keiko Suzuki[1], Norio Fujii[1], Ryouta Kikura[1], Shigeo Ohta*[2]

[1]Department of Neurosurgery and Neurology, Nishijima Hospital, Ohoka, 2835-7, Numazu-city, Shizuoka-ken 410-0022, Japan, [2]Department of Neurology Medicine, Juntendo University Graduate School of Medicine, 2-1-1 Hongo, Bunkyo-ku, Tokyo 113-8421, Japan

* h.ono@shinwakai.or.jp or ohta@nms.ac.jp

ABSTRACT

Introduction: Molecular hydrogen (H_2) has emerged as a therapeutic medical gas that exerts multiple functions. H_2 inhalation has been approved as safe, and some clinical studies showed that it effectively improved conditions of patients with a variety of disorders such as stroke, heart infarction, chronic obstructive pulmonary disease, cancer, and COVID-19. Urinary and fecal incontinences are unavoidable symptoms of advanced Alzheimer's disease (AD) dementia. In particular, fecal incontinence increases the level of confusion for patients and caretakers suffer from increased workloads.

Materials and Methods: To assess the integrity of the neurons related to AD, the bundles of neurons passing through the hippocampus were visualized by modified diffusion tensor imaging (DTI) technology using advanced magnetic resonance imaging (MRI)

Results: A 79-year-old woman with advanced AD continued to inhale 3% H_2 gas containing 21% oxygen twice daily for 1 hour and maintained clinical observations for 2 years. After the long period of inhalation of H_2 gas, the patient went to the bathroom by herself for adequate excretion. She remained to be able to go to the bathroom for her bowel movements in time, afterwards. After the long-term inhalation of H_2 gas, her MRI of the brain to generate DTI images with an anisotropic (FA) value of 0.2 (FA = 0.2) showed improved integrity of the hippocampal neurons along with these clinical improvements.

Conclusion: This case report casts the question on the current understanding that the advanced and severe AD patients will never improve.

Keywords: Alzheimer's disease; diffusion tensor imaging; fecal incontinence; hydrogen gas; neuronal integrity; urinary incontinence

INTRODUCTION

Alzheimer's disease (AD) is the most common cause of dementia and significantly reduces cognitive ability, which can lead to memory loss and impaired daily activities. In the final stages of the disease, patients lose the ability to react to their environment, continue conversation, and control their movements. As memory and cognitive abilities continue to deteriorate, personality can change significantly and individuals require extensive care. The treatment currently under development for AD is aimed at improving the memory function[1,2] and does not evaluate the improvement of other symptoms of AD as factors determining the quality of life.[3] Urinary and fecal incontinences are unavoidable symptoms of advanced AD dementia. In particular, fecal incontinence increases the level of confusion for patients and workload of caregivers.[4] At this stage, caregivers may want to take advantage of support services, such as hospice care, that focus on providing comfort and dignity at the end of life.[5] However, with the increase in the number of patients, the lack of facilities providing such services adequately has become a serious problem.

Molecular hydrogen (H_2) was first reported as a therapeutic anti-oxidant by one of the current authors.[6] Subsequent studies showed that H_2 has multiple functions to be effective against a variety of disease models.[7,8] We and others reported that inhalation of H_2 gas has various benefits for elderly patients with stroke,[9] heart infarction,[10] chronic obstructive pulmonary disease,[11] cancer,[12] and COVID-19.[13,14] Importantly, the safety of H_2 gas inhalation was approved by a Phase I clinical trial.[15] For dementia, a subgroup analysis of a randomized clinical trial reported that H_2 improved conditions of subjects with mild cognitive impairment (MCI) who carry the apolipoproten E4 (APOE4) genotype.[16]

As a more objective assessment, modified diffusion tensor imaging (DTI) as an advanced magnetic resonance imaging (MRI) technique can be applied to assess the neural integrity of AD patients.[17-19] A previous study by us showed that inhalation of H_2 gas for half a year led to improvement in patients with moderate AD. However, advanced AD patients with Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog)[20] above 50 showed no improvement with half a year of inhalation.[21]

This case report shows that two years of long-term inhalation of H_2 gas improved clinical symptoms as well as urinary and fecal incontinences. In addition, DTI analysis revealed the improvement of the neuronal integrity after the long-term inhalation of H_2 gas, along with clinical manifestations.

MATERIALS AND METHODS

Approval of this study

Inhalation of H_2 gas was carried out in accordance with the "Ethical Code of the World Medical Association (Declaration of Helsinki)". The protocol for this clinical trial was approved by the Nishijima Hospital Ethics Committee and pre-registered at URL: http://www.jmacct.med.or.jp Clinical Trial Registration – JMACCT ID: JMAIIA00308. We received written informed consent from the family.

The period of the approved study protocol was 6 months. However, if the patient's family hoped the continued inhalation of H_2 gas at the end of the clinical trial, resumption of the inhalation was allowed with the full understanding that this was a supplement therapy and that any related outcomes was the patient's family's responsibility.

Treatment

H_2 gas (3%) with 21% oxygen was produced using a portable H_2 generator (Nishijima / Enoagas Hydrogen Generator) as described.[9] Blood levels were confirmed to increase as described.[9] The patient inhaled 3% H_2 gas twice daily for 1 hour through a regular facial mask at the home where the patient lived. Patients with AD tend to remove the facial mask, so the family was asked to continue to observe the facial mask and inhalation with the patient for 1 hour. The gas generator was checked monthly assuming proper gas production.

Measurement of tube size by diffusion tensor image

Brain MRI was conducted in the radiology department. Staffs did not have information about whether the subject was a participant in this study or a general outpatient. These results were blindly reported to the physician via an electronic chart system.

Five seed points were set at the site where the bundle of neurons passed through the entire hippocampus. We performed digital tractographic imaging using Neuro3D with GRAPPA technology. DTI was obtained with anisotropy (FA) values of 0.1 and 0.2. The tract size was calculated from the number of pixels in the tract image, and the number of pixels in the tract was calculated using Image J software. DTI at FA=0.1 reflects visualization of the entire neuron, whereas DTI at FA=0.2 reflects the visualization of higher integrity of neurons because DTI strictly shows more one-directional H_2O diffusion along neuron fibers.

RESULTS

History of the patient

The patient, a 79-year-old woman, was first diagnosed with typical AD in 2011 and was treated with AD medications such as donepezil, galantamine, and lithium. She got worse and her ADAS-cog score reached 48/70.[20]

She was then referred to us in 2017. At that time, the patient could not remember her birthday, could not write her name or cook, but could go to the bathroom alone for her urination and defecation. However, as symptoms worsened rapidly and no other treatment was available, the patient's family agreed to participate in our clinical study designed for the treatment of AD with H_2 gas inhalation.[21] Patients have been participated in this clinical trial for 6 months starting in August 2017. The ADAS-cog score had deteriorated to 52 by the end of the clinical trial with H_2 gas inhalation in February 2018, but no rapid deterioration in other clinical conditions was observed. Brain MRI at that time also showed deterioration, and after 5 months, H_2 inhalation was stopped.

After the clinical trial was over, her ADAS-cog score began to deteriorate again. However, the patient's family wanted to resume H_2 inhalation because her family felt a slight but obvious improvement despite not matching her ADAS-cog scores. Since the clinical trial of H_2 gas inhalation treatment had been completed, additional H_2 inhalation was resumed as a supplement therapy. The H_2 gas inhalation began on April 19, 2019.

At that time, she could not flush the toilet with water or use the toilet paper. Her family noticed that her condition, including her bladder and bowel control, was gradually deteriorating. In January 2020, the frequency and severity of her fecal incontinence was not improved after 9-month inhalation.

In August 2020, she helped her husband in the kitchen and also helped washing the dishes, although this occurred only once. However, she continued to urinate involuntarily and show fecal incontinence.

On November 18, 2020, her husband noticed that the patient went to the bathroom on her own and showed adequate excretion. Since then, she has mostly been able to go to the bathroom for her bowel movements in time.

DTI measurement

Neuronal integrity was assessed by diffusion tensor imaging techniques using advanced brain MRI.[17-19] Figure 1 shows images with axial and lateral views, and the change in pixel count is shown in Figure 2.

Initial H_2 gas inhalation for 6 months (0-6 months) significantly improved conditions of moderate patients (ADAS-cog score <50), as previously reported, but did not improve the conditions of the current patient. These findings suggest that inhalation of H_2 gas for 6 months was effective for moderate patients, but not for advanced patients (ADS-cog score> 50), or it was not sufficient.

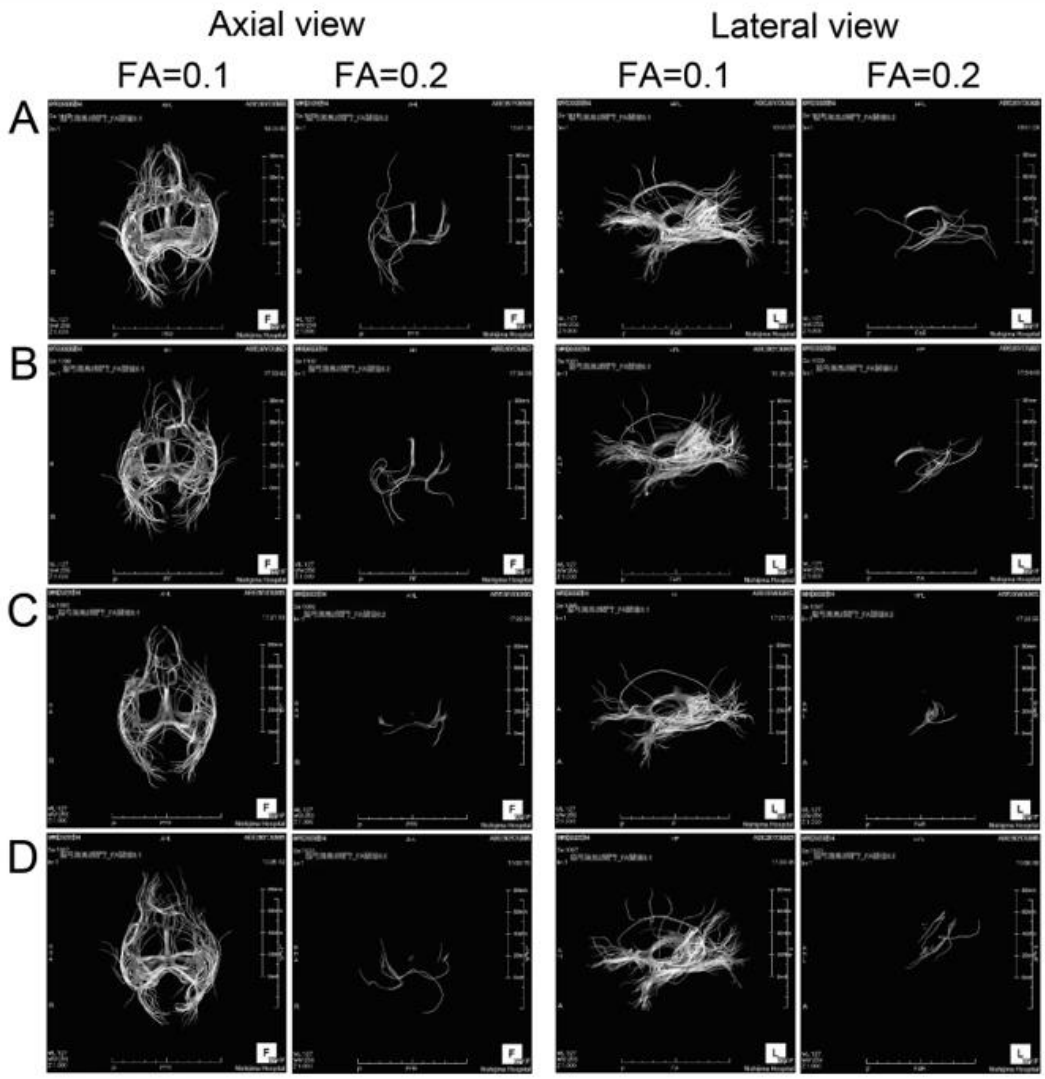

Figure 1. Diffusion tensor image of an advanced AD patient to assess neuronal integrity.
From axial and lateral views, neuronal bundles that pass through the hippocampal region of the five seed points at FA=0.1 were visualized to reflect the total number of neuron bundles. Diffusion of H2O along the neuron is manifested at FA=0.2 rather than FA=0.1, reflecting the integrity of the neuron. A, B, C, and D were taken with images at 0, 5, 29, and 54 months, respectively. During A-B and C-D periods, the patient inhaled H2 gas.

At FA = 0.1, which reflects the entire neuron, the number of pixels gradually decreased (5 - 29 months) before inhaling H_2 gas (Fig. 2A and B). At FA = 0.2, which reflects the higher integrity of the neuron, and a decrease in the number of pixels suggests a decrease in nerve function. The tract with high FA values (FA=0.2) was the most sensitive to change. It was clearly reduced from FA = 0.1 (Fig. 2C-F).

After inhalation for 2 years, the number of pixels increased slightly at FA = 0.1 and FA = 0.2, and the increase was more apparent at FA = 0.2 over FA = 0.1 (29-53 months) (Fig. 2). These results suggest an improvement in the neuronal integrity after long-term inhalation of H_2 gas, which may require a prolonged period such as 2 years or more.

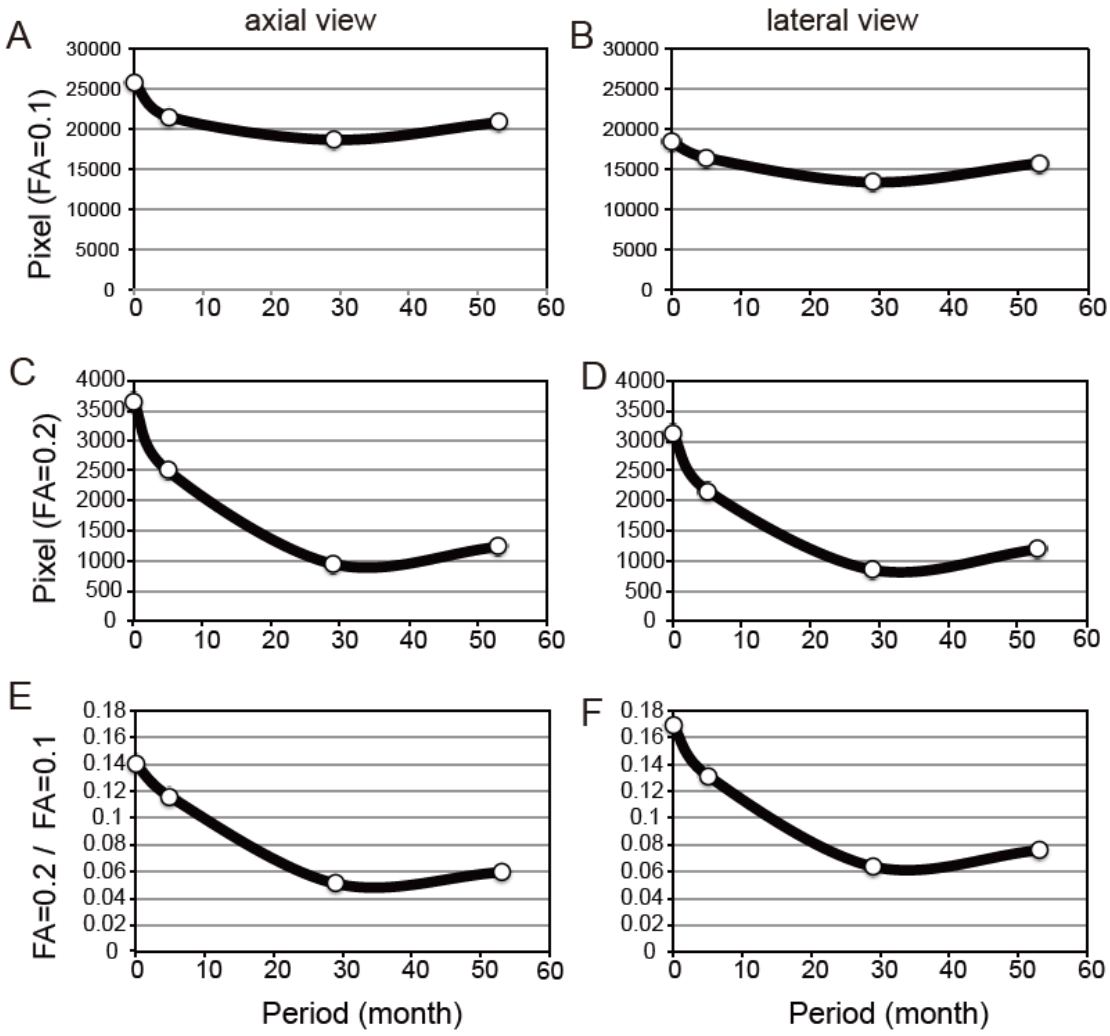

Figure 2. Time-course of diffusion tensor image.
Time-course of changes in the number of pixels in the neuron bundle visualized at FA=0.1 and FA=0.2. A and C (axial view) and B and D (lateral view) show the number of pixels at FA=0.1 and FA=0.2, respectively. For normalization, FA=0.2 / FA=0.1 are shown by E (axial view) and F (lateral view).

DISCUSSION

Ageing is the strongest risk factor for AD, suggesting multiple factors are involved in the etiology of AD in a complex manner. Most AD drug developments to date have focused on targeting a single mechanism according to conventional strategies. Multifactorial mechanisms and multi-target strategies have been considered to develop disease-modifying drugs.

H_2 was first reported as a therapeutic antioxidant by one of the present authors.[6] Subsequent studies have shown that H_2 exerts multiple functions such as anti-oxidation, anti-inflammation, anti-cell death and stimulation of energy metabolism.[7,8] Thus, H_2 may have the potential for a multi-functional drug by itself. H_2 inhalation has actually been applied in several clinical areas. The most important feature of H_2 is the safety for the human body without cytotoxicity, as approved in a Phase I clinical trial.[15] Moreover, H_2 has the characteristics of crossing the blood brain barrier by gaseous diffusion without a specific drug delivery system to the brain.[22]

Regarding the molecular mechanism, H_2 suppresses the nuclear factor of activated T cell (NFAT) transcription pathway through modifying oxidized phospholipids, and regulates various gene expression patterns.[23,24] NFAT signaling plays an important role in promoting amyloid β-mediated neurodegeneration.[25] Moreover, the NFAT transcriptional cascade affects amyloid β synaptotoxicity.[26] Therefore, the beneficial effects of H_2 on AD may be explained by the suppression of NFAT transcriptional regulation.

The number of patients with AD is increasing rapidly around the world. Incontinence, especially loss of bowel control, is the most common reason for these patients to enter a facility. It is hoped

that if fecal incontinence in patients with advanced AD can be improved by some new treatments, AD patients might be able to be cared for in their own home. A notable advantage of H_2 inhalation is its low cost. Using an H_2 gas generator that utilizes distilled water costs only $ 1 a month after purchasing a generator for about $ 6,000.

This case report describes improvement in only one case, and it is not clear whether the improvement is actually due to H_2 gas. The disadvantage is that it can take a very long time to observe the effects of treatment, so it is necessary to create a comfortable device or system for actual long-term application.

CONCLUSION

The current case report is valuable even as a single case because the current general understanding that advanced and severe AD patients will never improve can be dispelled. Further studies will be needed involving more AD patients to confirm the current results.

CONFLICT OF INTEREST

The author has no financial connection to this study.

FINANCING STATEMENT

This study is not specifically funded by a commercial or non-profit sector funding agency.

ACKNOWLEDGMENTS

We are grateful to the staffs for MRI examination at Nishijima Hospital.

REFERENCES

1. Olloquequi J, Ettcheto M, Cano A, Sanchez-Lopez E, Carrasco M, Espinosa T, et al. Impact of New Drugs for Therapeutic Intervention in Alzheimer's Disease. *Front Biosci* (Landmark Ed). 2022; 27(5): 146. ISNN: 2768-6698 (Electronic) 2768-6698 (Linking) DOI: 10.31083/j.fbl2705146
2. Sang Z, Wang K, Dong J, Tang L. Alzheimer's disease: Updated multi-targets therapeutics are in clinical and in progress. *Eur J Med Chem*. 2022; 238: 114464. ISNN: 2768-6698 (Electronic) 2768-6698 (Linking) DOI: 10.31083/j.fbl2705146
3. Honig LS, Mayeux R. Natural history of Alzheimer's disease. *Aging* (Milano). 2001; 13(3): 171-82. ISNN: 0394-9532 (Print) 0394-9532 (Linking) DOI: 10.1007/BF03351476
4. Warshaw GA. New perspectives in the management of Alzheimer's disease. *Am Fam Physician*. 1990; 42(5 Suppl): 41S-7S. ISSN: 0002-838X (Print) 0002-838X (Linking) PMID: 2239649
5. AlAmeel T, Andrew MK, MacKnight C. The association of fecal incontinence with institutionalization and mortality in older adults. *Am J Gastroenterol*. 2010; 105(8): 1830-4. ISSN: 1572-0241 (Electronic) 0002-9270 (Linking) DOI: 10.1038/ajg.2010.77
6. Ohsawa I, Ishikawa M, Takahashi K, Watanabe M, Nishimaki K, Yamagata K, et al. Hydrogen acts as a therapeutic antioxidant by selectively reducing cytotoxic oxygen radicals. *Nat Med*. 2007; 13(6): 688-94. ISSN: 1078-8956 (Print) 1078-8956 (Linking) DOI: 10.1038/nm1577
7. Ohta S. Molecular hydrogen as a preventive and therapeutic medical gas: initiation, development and potential of hydrogen medicine. *Pharmacol Ther*. 2014; 144(1): 1-11. ISSN: 1879-016X (Electronic) 0163-7258 (Linking) DOI: 10.1016/j.pharmthera.2014.04.006
8. Ohta S. Development of Hydrogen Medicine and Biology: Potential for Various Applications in Diverse Fields. *Curr Pharm Des*. 2021; 27(5): 583-4. ISSN: 1873-4286 (Electronic) 1381-6128 (Linking) and DOI: 10.2174/1381612827052102111445l5
9. Ono H, Nishijima Y, Ohta S, Sakamoto M, Kinone K, Horikosi T, et al. Hydrogen Gas Inhalation Treatment in Acute Cerebral Infarction: A Randomized Controlled Clinical Study on Safety and Neuroprotection. *J Stroke Cerebrovasc Dis*. 2017; 26(11): 2587-94. ISSN: 1532-8511 (Electronic) 1052-3057 (Linking) DOI: 10.1016/j.jstrokecerebrovasdis.2017.06.012
10. Katsumata Y, Sano F, Abe T, Tamura T, Fujisawa T, Shiraishi Y, et al. The Effects of Hydrogen Gas Inhalation on Adverse Left Ventricular Remodeling After Percutaneous Coronary Intervention for ST-Elevated Myocardial Infarction- First Pilot Study in Humans. *Circ J*. 2017; 81(7): 940-7. ISSN: 1347-4820 (Electronic) 1346-9843 (Linking) DOI: 10.1253/circj.CJ-17-0105
11. Zheng ZG, Sun WZ, Hu JY, Jie ZJ, Xu JF, Cao J, et al. Hydrogen/oxygen therapy for the treatment of an acute exacerbation of chronic obstructive pulmonary disease: results of a multicenter, randomized, double-blind, parallel-group controlled trial. *Respir Res*. 2021; 22(1): 149. ISSN: 1465-993X

(Electronic) 1465-9921 (Linking) DOI: 10.1186/s12931-021-01740-w

12. Akagi J, Baba H. Hydrogen gas restores exhausted CD8+ T cells in patients with advanced colorectal cancer to improve prognosis. *Oncol Rep*. 2019; 41(1): 301-11. ISSN: 1791-2431 (Electronic) 1021-335X (Linking) DOI: 10.3892/or.2018.6841
13. Botek M, Krejci J, Valenta M, McKune A, Sladeckova B, Konecny P, et al. Molecular Hydrogen Positively Affects Physical and Respiratory Function in Acute Post-COVID-19 Patients: A New Perspective in Rehabilitation. *Int J Environ Res Public Health*. 2022; 19(4): 1992. ISSN: 1660-4601 (Electronic) 1660-4601 (Linking) doi: 10.3390/ijerph19041992.1992
14. Luo P, Ding Y, He Y, Chen D, He Q, Huang Z, et al. Hydrogen-oxygen therapy alleviates clinical symptoms in twelve patients hospitalized with COVID-19: *A retrospective study of medical records*. *Medicine* (Baltimore). 2022; 101(9): e27759. ISSN: 1536-5964 (Electronic) 0025-7974 (Linking) DOI: 10.1097/MD.0000000000027759
15. Cole AR, Sperotto F, DiNardo JA, Carlisle S, Rivkin MJ, Sleeper LA, et al. Safety of Prolonged Inhalation of Hydrogen Gas in Air in Healthy Adults. *Crit Care Explor*. 2021; 3(10): e543. ISSN: 2639-8028 (Electronic) 2639-8028 (Linking) DOI: 10.1097/CCE.0000000000000543
16. Nishimaki K, Asada T, Ohsawa I, Nakajima E, Ikejima C, Yokota T, et al. Effects of Molecular Hydrogen Assessed by an Animal Model and a Randomized Clinical Study on Mild Cognitive Impairment. *Curr Alzheimer Res*. 2018; 15(5): 482-92. ISSN: 1875-5828 (Electronic) 1567-2050 (Linking) DOI: 10.2174/1567205014666171106145017
17. Chua TC, Wen W, Slavin MJ, Sachdev PS. Diffusion tensor imaging in mild cognitive impairment and Alzheimer's disease: a review. *Curr Opin Neurol*. 2008; 21(1): 83-92. ISSN: 1350-7540 (Print) 1350-7540 (Linking) DOI: 10.1097/WCO.0b013e3282f4594b
18. Amlien IK, Fjell AM. Diffusion tensor imaging of white matter degeneration in Alzheimer's disease and mild cognitive impairment. *Neuroscience*. 2014; 276: 206-15. ISSN: 1873-7544 (Electronic) 0306-4522 (Linking) DOI: 10.1016/j.neuroscience.2014.02.017
19. Toniolo S, Serra L, Olivito G, Caltagirone C, Mercuri NB, Marra C, et al. Cerebellar White Matter Disruption in Alzheimer's Disease Patients: A Diffusion Tensor Imaging Study. *J Alzheimers Dis*. 2020; 74(2): 615-24. ISNN: 1875-8908 (Electronic) 1387-2877 (Linking) DOI: 10.3233/JAD-191125
20. Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. *Am J Psychiatry*. 1984; 141(11): 1356-64. ISSN: 0002-953X (Print) 0002-953X (Linking) DOI: 10.1176/ajp.141.11.1356
21. Ono H, Nishijima Y, Sakamoto M, Hirikosi T, Tamaki M, Oishi W, et al. Pilot study on Therapeutic Inhalation of hydrogen gas for improving patients with Alzheimer's disease assessed by cognitive subscale scores and magnetic resonance diffusion tensor umaging. *Int J Alzheimers & Neuro Disorder*. 2018; 1(1): 004. https://bioaccent.org/alzheimers-neurological/alzheimers-neurological04.pdf
22. Wood KC, Gladwin MT. The hydrogen highway to reperfusion therapy. *Nat Med*. 2007; 13(6): 673-4. ISSN: 1078-8956

(Print) 1078-8956 (Linking) DOI: 10.1038/nm0607-673

23. Iuchi K, Imoto A, Kamimura N, Nishimaki K, Ichimiya H, Yokota T, et al. Molecular hydrogen regulates gene expression by modifying the free radical chain reaction-dependent generation of oxidized phospholipid mediators. *Sci Rep*. 2016; 6: 18971. ISSN: 2045-2322 (Electronic) 2045-2322 (Linking) DOI: 10.1038/srep18971
24. Ohta S. Direct Targets and Subsequent Pathways for Molecular Hydrogen to Exert Multiple Functions: Focusing on Interventions in Radical Reactions. *Curr Pharm Des*. 2021; 27(5): 595-609. ISSN: 1873-4286 (Electronic) 1381-6128 (Linking) DOI: 10.2174/1381612826666200806101137
25. Abdul HM, Sama MA, Furman JL, Mathis DM, Beckett TL, Weidner AM, et al. Cognitive decline in Alzheimer's disease is associated with selective changes in calcineurin/NFAT signaling. *J Neurosci*. 2009; 29(41): 12957-69. ISSN: 1529-2401 (Electronic) 0270-6474 (Linking) DOI: 10.1523/JNEUROSCI.1064-09.2009
26. Hudry E, Wu HY, Arbel-Ornath M, Hashimoto T, Matsouaka R, Fan Z, et al. Inhibition of the NFAT pathway alleviates amyloid beta neurotoxicity in a mouse model of Alzheimer's disease. *J Neurosci*. 2012; 32(9): 3176-92. ISSN: 1529-2401 (Electronic) 0270-6474 (Linking) DOI: 10.1523/JNEUROSCI.6439-11.2012