

**SHORT REPORT**

# Hyperbaric oxygen ameliorates cognitive impairment in patients with Alzheimer's disease and amnesic mild cognitive impairment

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**Abstract**

**Introduction:** It has been reported that environmental factors such as hypoxia could contribute to the pathogenesis of Alzheimer's disease (AD). Therapeutics like hyperbaric oxygen treatment, which improves tissue oxygen supply and ameliorates hypoxic conditions in the brain, may be an alternative therapy for AD and amnesic mild cognitive impairment (aMCI). The present work aims to investigate the potential therapeutic effect of hyperbaric oxygen treatment for AD and aMCI.

**Methods:** We recruited 42 AD, 11 aMCI, and 30 control AD patients in this study. AD and aMCI patients were treated with 40 minutes of hyperbaric oxygen once a day for 20 days and assessed by neuropsychiatric assessments including Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), and Activities of Daily Living (ADL) scale before and at 1-, 3-, and 6-month follow-up after treatment. Control AD patients who were not given hyperbaric oxygen treatment had similar clinical profile as hyperbaric oxygen treated AD. We examined 10 of the AD/aMCI patients with fluorodeoxyglucose positron emission tomography.

**Results:** In self-comparison study, one course of hyperbaric oxygen treatment significantly improved the cognitive function assessed by MMSE and MoCA in AD patients after 1-month follow-up; such treatment also significantly improved MMSE score at 3-month follow-up and MoCA score at 1- and 3-month follow-up in aMCI patients. The ADL scale was significantly improved in AD patients after 1- and 3-month follow-up. Compared to the control AD patients, the MMSE and MoCA in hyperbaric oxygen treated AD patients were significantly improved after 1-month follow-up. Hyperbaric oxygen treatment also ameliorated the reduced brain glucose metabolism in some of the AD and aMCI patients.

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**Conclusion:** Based on previous studies and our recent findings, we propose that hyperbaric oxygen treatment may be a promising alternative therapy for AD and aMCI.

**KEYWORDS**

Alzheimer's disease, hyperbaric oxygen treatment, hypoxia, mild cognitive impairment

## 1 | INTRODUCTION

Alzheimer's disease (AD) is the most common form of dementia in the elderly. It is generally considered that AD arises through the interactions between genetic and non-genetic factors.<sup>1</sup> Genic factors are dominantly inherited mutations in amyloid beta ( $A\beta$ ) precursor protein, presenilin 1, and presenilin 2; and there are several risk genes, including apolipoprotein E, which may contribute to the disease pathogenesis.<sup>2</sup> Non-genetic factors such as brain trauma, cerebrovascular diseases, type 2 diabetes, intellectual activity, sleep disorders, and hypoxia are thought to play an important role in sporadic AD.<sup>3,4</sup> Results from animal studies have indicated that hypoxia affects many aspects of AD-associated pathophysiology including  $A\beta$  and tau neuropathy, neuroinflammation, autophagy dysfunction, oxidative stress, and mitochondrial abnormality.<sup>5-8</sup> In AD patients, comorbidities such as stroke, cardiovascular diseases, obstructive sleep apnea syndrome, and chronic obstructive pulmonary disease (COPD) may cause acute and chronic hypoxic conditions.<sup>8-10</sup> A prospective study showed that women with sleep-disordered breathing were more likely to develop mild cognitive impairment or dementia.<sup>11</sup> Several studies have reported that high-altitude hypoxia exposure may cause deleterious effects on cognitive performance.<sup>12,13</sup> High altitude decreases brain oxygen saturation, reduces neural activity, induces immune response, and impairs cognitive functions.<sup>14</sup> These evidences imply that hypoxia may be an important culprit for cognitive decline. Hypoxia contributes to the pathogenesis of AD, anti-hypoxia treatment may be helpful to ameliorate the disease. Hyperbaric oxygen treatment is a well-established therapy used to treat neurological conditions by enhancing oxygen delivery to brain tissues and protect neurons.<sup>15,16</sup>

According to the epidemiological data in 2005, 24.2 million people worldwide suffer from dementia with 4.6 million new cases per year. By 2040, there will be >81 million people suffering from dementia, 70% of which are AD patients.<sup>17,18</sup> As the population ages, AD will undoubtedly bring significant social and economic burdens to the world. However, there is still no cure or effective treatment to reverse the pathological process of AD. Currently there are only a few anti-AD drugs in clinical use, such as cholinesterase inhibitors (ChEIs; donepezil, rivastigmine, and galantamine), and N-Methyl-D-aspartic acid (NMDA) receptor antagonist (memantine). These drugs have a limited therapeutic effect on symptoms and poorly affect the progression of the disease.<sup>19</sup> Despite great efforts to develop new anti-AD drugs aiming to stop the progression of AD, the therapeutic interventions predominantly targeting  $A\beta$  pathology have lim-

ited success.<sup>20</sup> Other novel therapeutics, including anti-tau and anti-inflammation interventions have not successfully yielded any good results.<sup>19,21</sup> Recent studies have indicated that dementia and stroke share some of the pathological risk factors resulting from small vessel degeneration; and dementia could be reduced through stroke prevention by using anticoagulation of atrial fibrillation and quit of smoking.<sup>22,23</sup> Microvascular flow impairment leading to tissue hypoxia has been demonstrated in AD and amnesic mild cognitive impairment (aMCI), and the degree of hypoxia correlates with the extent of cognitive decline.<sup>23</sup> Moreover, the hypoxia condition may cause energy failure resulting in dyshomeostasis of cytosol calcium ion concentration. The breakdown of the calcium ion signaling system is one of the common mechanisms of neurodegeneration.<sup>23</sup> Thus, hyperbaric oxygen treatment, which improves tissue oxygen supply and ameliorates hypoxic conditions, may be a potential therapeutic strategy for AD and aMCI.

In the present study, we recruited 42 AD and 11 aMCI patients for hyperbaric oxygen treatment and 30 AD patients without hyperbaric oxygen treatment as control. All the participants were tested with a battery of neuropsychiatric assessments before and at 1-, 3-, and 6-month follow-up after treatment. We aimed to investigate the potential therapeutic effect of hyperbaric oxygen treatment in patients with AD and aMCI.

## 2 | METHODS

### 2.1 | Patients

There were 42 AD and 11 aMCI patients enrolled in this hyperbaric oxygen study. All participants were from the First Affiliated Hospital of Dalian Medical University during 2015 to 2018. Another 30 AD patients who had similar clinical profile (age, sex, disease duration, and history of medication) but not undertaking hyperbaric oxygen treatment were recruited as control. The diagnosis of AD was made according to the criteria of the Diagnostic Statistical Manual of Mental Disorders IV (DSM IV) and National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association.<sup>24-26</sup> And the diagnosis of aMCI was referred to the DSM IV and Petersen 2005 diagnostic criteria.<sup>26-28</sup> Patients with the following conditions were excluded: gait imbalance, extrapyramidal signs, seizures, autonomic failures, severe psychiatric conditions (major depression, psychosis, bipolar disorders), toxic exposure, conditions

that affect intelligence (severe anemia, thyroid disorder, and vitamin B12 deficiency) and conditions that affect brain oxygen metabolism (cerebral vascular ischemic disease, anemia, and un-controlled hypertension and diabetes). In addition, the participants were ruled out with any of the following contraindications of hyperbaric oxygen treatment: pneumothorax, rib fracture, chest trauma, cavitary pulmonary tuberculosis, resistant hypertension, severe pneumonia, asthma, pulmonary heart disease, and COPD. AD and control patients in this study were contemporarily maintained with their medications including memantine (20 mg/d) and/or rivastigmine (6 to 12 mg/d) regularly. Patients with aMCI were not treated with any cognitive medications.

The study of hyperbaric oxygen treatment in AD and aMCI was approved by the Ethics Committee of the First Affiliated Hospital of Dalian Medical University before the study started. All enrolled patients and their legal guardians have been informed of the study procedure and the hazards that may result from the treatment, and they have agreed and signed the informed consent.

The demographic characteristics of patients enrolled in this study were summarized in Table S1 in supporting information. There were 42 AD patients (13 male/29 female). The mean age of AD patients was  $70.17 \pm 8.95$  years old, and the mean disease course was  $4.14 \pm 2.31$  years. All patients completed the 20-day hyperbaric oxygen treatment and 1- and 3-month follow-up. Two of the AD patients were dropped at the 6-month follow-up: one died of cardiovascular disease, and the other one left the original resident district and moved to another city. There were 11 aMCI patients enrolled in this study (7 male/4 female). The mean age of those patients was  $65.36 \pm 9.50$  years old, and the mean disease course was  $1.73 \pm 0.91$  years. All 11 aMCI participants completed the whole study. There were 30 control AD (12 male/18 female). The mean age of those patients was  $69.87 \pm 7.79$  years old, and the mean disease course was  $3.93 \pm 2.60$  years. There were no differences between hyperbaric oxygen treated AD and control AD in age, sex, age of onset, education level, disease course, and Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) scores at baseline level.

## 2.2 | Neuropsychiatric assessments

Neuropsychiatric assessments used in the study were MMSE, MoCA, and Activities of Daily Living (ADL) scale.<sup>29-32</sup> After the clinical history collection, physical examination, laboratory tests, and neuroimaging, the patients were examined with the neuropsychiatric assessments before the hyperbaric oxygen treatment and re-examined at 1-, 3-, and 6-month follow-up. The MMSE assesses the cognitive functions of orientation, registration, attention and calculation, recall, and language. The MoCA includes six sub-items of visuospatial abilities and executive functions, naming, memory, attention and calculation, language and abstract reasoning, and orientation to time and place. The ADL scale evaluates independence of daily activities (bathing, dressing, toileting, transferring, eating, and the use of incontinence materials) with 20 questions.

## RESEARCH IN CONTEXT

1. Systematic review: Hypoxia is one of the important environmental factors that could contribute to the pathogenesis of Alzheimer's disease (AD). Currently approved drug treatments for AD have a limited therapeutic effect on symptoms and poorly affect the progression of the disease. Non-pharmacological multi-targeted interventions like hyperbaric oxygen treatment targeting hypoxia may have potential in the future treatment of AD.
2. Interpretation: We recruited 42 AD and 11 amnesic mild cognitive impairment (aMCI) patients for hyperbaric oxygen treatment and 30 AD patients without hyperbaric oxygen treatment as control and performed a 6-month follow-up study. We found that hyperbaric oxygen treatment could improve cognitive functions and ameliorate the reduced brain glucose metabolism in AD and aMCI patients.
3. Future directions: Multi-center studies with larger numbers of participants with or without medications, multiple courses of treatments, and longer time of follow-up should be applied in future studies.

## 2.3 | Hyperbaric oxygen treatment

All 42 AD and 11 aMCI participants undertook one course of hyperbaric oxygen treatment once a day for 20 days. Each treatment included 20-minute pure oxygen inhalation ( $O_2 = 99.9\%$ , oxygen supply pressure 0.4 to 0.7 MPa, oxygen flow 10 to 15 L/h), 15 minutes interval, and then another 20-minute pure oxygen inhalation ( $O_2 = 99.9\%$ , oxygen supply pressure 0.4 to 0.7 MPa, oxygen flow 10 to 15 L/h) under the pressure of 0.22 MPa (0.12 MPa on pressure gauge) in hyperbaric oxygen chamber (Medical Oxygen Chamber, SY3200-8500, Yantai Hongyuan Oxygen Industrial Inc., Shandong, China).

## 2.4 | Fluorodeoxyglucose positron emission tomography

Six of the AD patients and four of the aMCI patients underwent fluorodeoxyglucose positron emission tomography (FDG-P) before and at 1 month after hyperbaric oxygen treatment. The  $^{18}F$ -FDG (radiochemical purity >95%) was synthesized by the Eclipse RD cyclotron and the FDG synthesizer Explora FDG4 (Siemens AG, Germany). All patients fasted for at least 6 hours, and the body weight and serum glucose level were determined before the injection. The fasting blood glucose <9 mmol/L was acceptable. Then a dose of 0.15 mCi/kg of FDG was injected via a peripheral cannula after resting for 30 to 40 minutes. After injection, the patients were instructed to stay awake, keep eyes open, and not vocalize in a quiet and darkened room for 40 minutes. The images were then acquired with Siemens Biograph 64 HD P/CT

**TABLE 1** Self-comparison of MMSE scores in AD and aMCI patients before and after hyperbaric oxygen treatment

Time	AD		aMCI	
	Mean ± SD	P value	Mean ± SD	P value
Baseline	15.19 ± 7.55	-	27.00 ± 2.19	-
1-month follow-up	16.43 ± 8.21	0.005*	28.00 ± 2.28	0.070
3-month follow-up	15.38 ± 8.05	0.750	28.45 ± 1.97	0.026*
6-month follow-up	13.95 ± 7.63	0.056	27.82 ± 2.34	0.136

Data of MMSE scores in AD patients were analyzed by paired *t* test; data of MMSE scores in aMCI patients were analyzed by Wilcoxon signed-rank test. \**P* < 0.05. Sample size: *n* = 42 in AD patients (*n* = 40 at 6-month follow-up); *n* = 11 in aMCI patients. The *P* values of 1-, 3-, and 6-month follow-up were compared with the baseline level.

Abbreviations: AD, Alzheimer's disease; aMCI, amnesic mild cognitive impairment; MMSE, Mini-Mental State Examination; SD, standard deviation

(Siemens AG, Germany). All images were compared with the template and analyzed with NeuroQ™ Brain Imaging Analysis (Syntermed Inc., Atlanta, GA, USA).

## 2.5 | Data analysis

Data were analyzed by SPSS 21.0 software (IBM Corporation, Armonk, NY, USA) and GraphPad Prism 8 (GraphPad Software Inc., La Jolla, CA, USA). The results were considered to be statistically significant when *P* value was <0.05.

**TABLE 2** Self-comparison of MoCA scores in AD and aMCI patients before and after hyperbaric oxygen treatment

	AD				aMCI			
	Baseline	1-month follow-up	3-month follow-up	6-month follow-up	Baseline	1-month follow-up	3-month follow-up	6-month follow-up
MoCA scores	10.86 ± 6.70	12.71 ± 7.39	11.38 ± 6.64	10.53 ± 6.69	21.91 ± 3.27	24.73 ± 4.31	24.64 ± 5.07	25.18 ± 4.24
<i>P</i> value	-	0.000*	0.280	0.799	-	0.007*	0.059	0.019*
Visuospatial abilities and executive functions	1.45 ± 1.43	1.74 ± 1.36	1.60 ± 1.42	1.65 ± 1.44	3.82 ± 0.87	4.00 ± 1.00	4.18 ± 0.98	4.36 ± 0.67
<i>P</i> value	-	0.032*	0.275	0.094	-	0.414	0.340	0.058
Naming	1.86 ± 1.14	2.00 ± 1.04	1.83 ± 1.15	1.75 ± 1.08	3.00 ± 0.00	3.00 ± 0.00	3.00 ± 0.00	2.91 ± 0.30
<i>P</i> value	-	0.326	0.837	0.572	-	1.00	1.00	0.317
Memory	0.48 ± 1.17	0.64 ± 1.34	0.48 ± 1.23	0.50 ± 1.20	1.00 ± 1.26	2.82 ± 2.09	2.73 ± 2.24	2.73 ± 2.05
<i>P</i> value	-	0.190	0.952	1.000	-	0.017*	0.024*	0.020*
Attention and calculation	3.00 ± 2.11	3.10 ± 1.96	3.21 ± 1.84	2.80 ± 1.90	5.64 ± 0.50	5.73 ± 0.47	5.64 ± 0.92	5.91 ± 0.30
<i>P</i> value	-	0.511	0.202	0.533	-	0.564	1.00	0.083
Language and abstract reasoning	1.81 ± 1.69	2.26 ± 1.86	1.50 ± 1.64	1.35 ± 1.59	3.33 ± 0.81	4.09 ± 0.30	3.73 ± 1.68	3.73 ± 1.74
<i>P</i> value	-	0.014*	0.040*	0.039*	-	0.033*	0.314	0.473
Orientation to time and place	2.40 ± 1.77	2.79 ± 1.96	2.36 ± 1.91	2.35 ± 1.73	5.00 ± 1.81	5.09 ± 1.22	5.36 ± 0.81	5.36 ± 1.21
<i>P</i> value	-	0.052	0.721	0.985	-	0.783	0.206	0.389

Data of MoCA scores in AD patients were analyzed by paired *t* test; data of MoCA scores in aMCI patients were analyzed by Wilcoxon signed-rank test; data of the six subitems of MoCA scores in AD and aMCI patients were analyzed by Wilcoxon signed-rank test.

\**P* < 0.05. Sample size: *n* = 42 in AD patients (*n* = 40 at 6-month follow-up); *n* = 11 in aMCI patients. The *P* values of 1-, 3-, and 6-month follow-up were compared with the baseline level.

Abbreviations: AD, Alzheimer's disease; aMCI, amnesic mild cognitive impairment; MOCA, Montreal Cognitive Assessment

## 3 | RESULTS

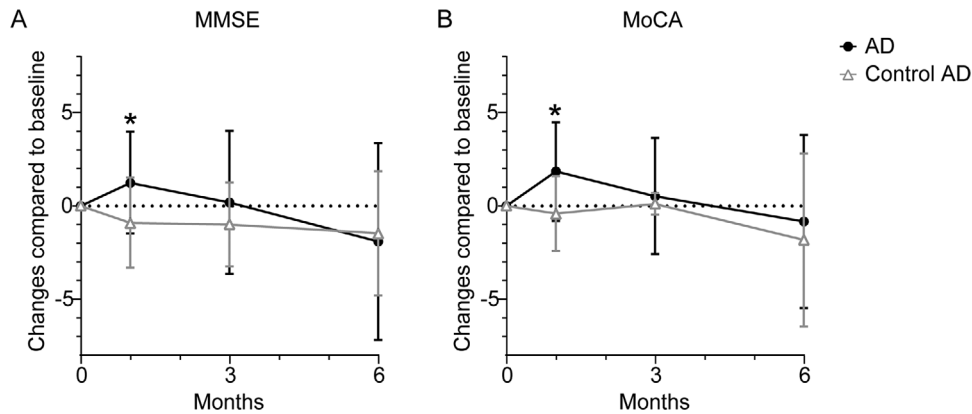
### 3.1 | Cognitive assessments of AD and aMCI patients before and after hyperbaric oxygen treatment

#### 3.1.1 | MMSE score before and after treatment

Compared to the baseline level, the MMSE score was significantly improved at 1-month follow-up in AD patients (Table 1) and at 3-month follow-up in aMCI patients after hyperbaric oxygen treatment (Table 1). Compared to control AD, the hyperbaric oxygen treated AD patients got significant improvement in MMSE score at 1-month follow-up.

#### 3.1.2 | MoCA score before and after treatment

The MoCA score was improved significantly at 1-month follow-up in AD patients and at 1-month and 6-month follow-up in aMCI patients after hyperbaric oxygen treatment compared to the baseline level (Table 2). The six subitems of MoCA scores are summarized in Table 2. The visuospatial abilities and executive functions were significantly improved at 1-month follow-up and the language and abstract reasoning were significantly improved at 1-, 3-, and 6-month follow-up in AD patients after hyperbaric oxygen treatment compared to baseline level (Table 2). In aMCI patients, the language and abstract reasoning were improved at 1-month follow-up after hyperbaric oxygen treatment.



**FIGURE 1** Neuropsychiatric assessments at 1-, 3-, and 6-month follow-up in hyperbaric oxygen treated Alzheimer's disease (AD) and control AD patients. A and B, Changes of Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) scores at 1-, 3-, and 6-month follow-up in AD after hyperbaric oxygen treatment versus control AD compared to baseline, respectively. Data were presented as mean  $\pm$  standard deviation. Data of MMSE score in 1- and 6-month follow-up and MoCA score in 1-, 3-, and 6-month follow-up were analyzed by Mann-Whitney test; data of MMSE score in 3 months was analyzed by *t* test. Sample size:  $n = 10$  in 1-month follow-up,  $n = 9$  in 3-month follow-up, and  $n = 11$  in 6-month follow-up in control group;  $n = 42$  in 1- and 3-month follow-up,  $n = 40$  in 6-month follow-up in AD. \* $P < 0.05$

Memory function of aMCI patients was ameliorated at 1-, 3-, and 6-month follow-up after hyperbaric oxygen treatment compared to baseline level (Table 2). Compared to control AD, the hyperbaric oxygen treated AD patients got significantly higher MoCA score at 1-month follow-up (Figure 1).

### 3.2 | ADL in AD and aMCI patients before and after hyperbaric oxygen treatment

Compared to the baseline level, the daily living activities of AD patients were significantly improved at 1-month and 3-month follow-up after hyperbaric oxygen treatment (Table 3). There were no significant differences in ADL scores of aMCI patients after the hyperbaric oxygen treatment (Table 3).

### 3.3 | MMSE, MoCA, and ADL scores in different stages, medications, and sexes in AD patients after hyperbaric oxygen treatment

The difference of MMSE, MoCA, and ADL scores in disease stages, medications, and sexes AD patients was further analyzed. As shown in Table S2 in supporting information, the MMSE score was increased significantly at 1-month follow-up after hyperbaric oxygen treatment in mild AD patients, the MoCA score was improved significantly at 1-month follow-up after hyperbaric oxygen treatment in mild and moderate AD patients, and the ADL score was increased significantly at 1-month follow-up after hyperbaric oxygen treatment in moderate AD patients. The difference of MMSE, MoCA, and ADL scores in AD patients with medications is shown in Table S3 in supporting information. The MMSE score was increased significantly at 1-month follow-up after hyperbaric oxygen treatment in AD patients maintained with ChEIs. And the MoCA score was improved significantly at

**TABLE 3** Self-comparison of ADL scores in AD and aMCI patients before and after hyperbaric oxygen treatment

Time	AD		aMCI	
	Mean $\pm$ SD	<i>P</i> value	Mean $\pm$ SD	<i>P</i> value
Baseline	38.19 $\pm$ 13.90	-	21.00 $\pm$ 1.26	-
1-month follow-up	36.40 $\pm$ 13.89	0.008*	21.00 $\pm$ 1.41	1.000
3-month follow-up	35.07 $\pm$ 14.14	0.004*	21.18 $\pm$ 1.78	0.655
6-month follow-up	38.12 $\pm$ 14.21	0.678	20.73 $\pm$ 0.90	0.180

Data of ADL scale in AD and aMCI patients were analyzed by Wilcoxon signed-rank test.

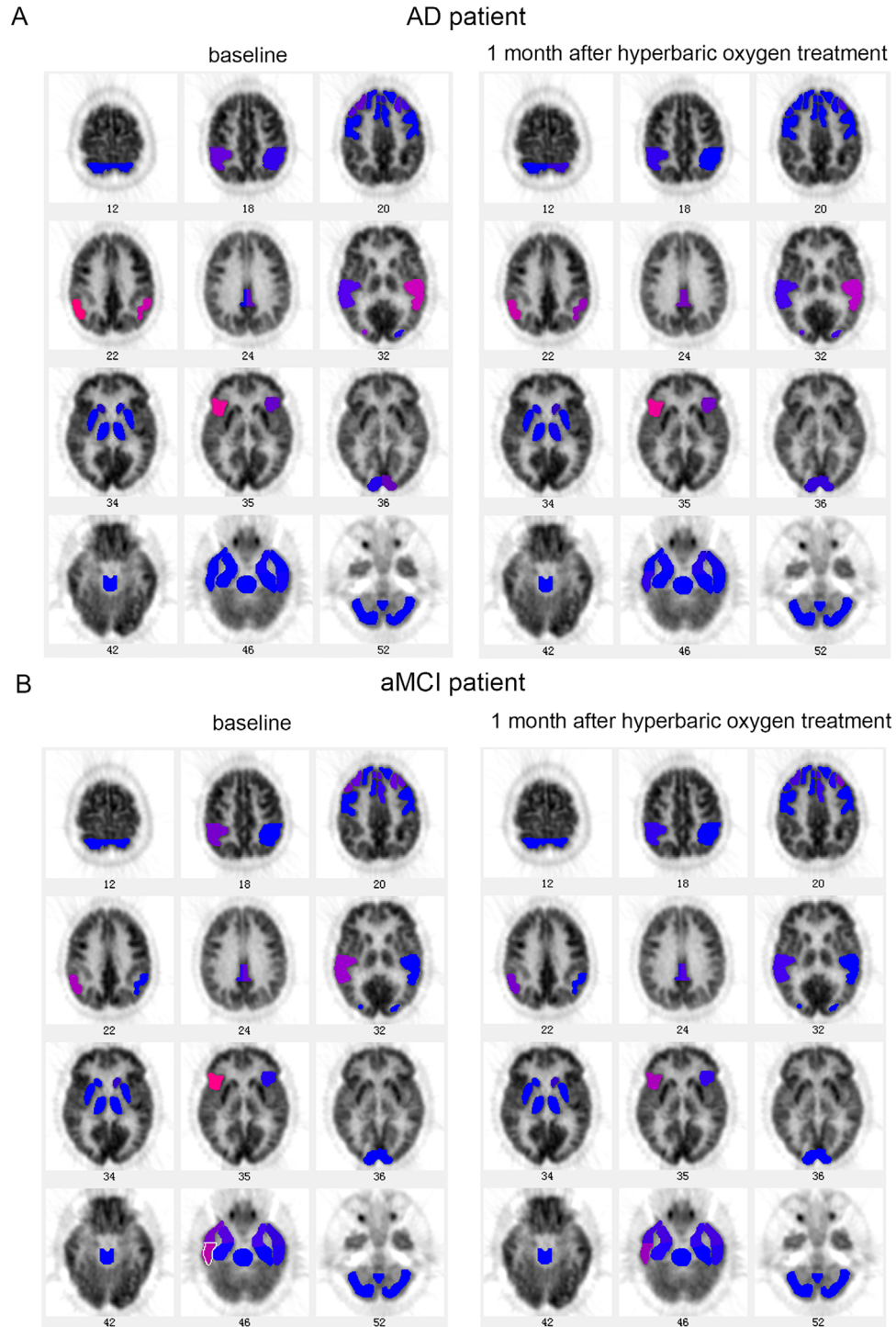
\* $P < 0.05$ . Sample size:  $n = 42$  in AD patients ( $n = 40$  at 6-month follow-up);  $n = 11$  in aMCI patients. The *P* values of 1-, 3-, and 6-month follow-up were compared with the baseline level.

Abbreviations: AD, Alzheimer's disease; ADL, Activities of Daily Living; aMCI, amnesic mild cognitive impairment; SD, standard deviation

1-month follow-up after hyperbaric oxygen treatment in AD patients with combined medications (ChEIs + NMDA receptor antagonist). The ADL score was improved significantly at 1- and 3-month follow-up after hyperbaric oxygen treatment in AD patients with ChEIs. The difference of MMSE, MoCA, and ADL scores in AD patients male and female is shown in Table S4 in supporting information. The MMSE and MoCA scores were improved significantly at 1-month follow-up after hyperbaric oxygen treatment in both sexes. And the ADL score was increased significantly at 1- and 3-month follow-up after hyperbaric oxygen treatment in female AD patients.

### 3.4 | Fluorodeoxyglucose positron emission tomography imaging before and after hyperbaric oxygen treatment

The representative images of AD and aMCI patients are shown in Figure 2. Compared to the images at the baseline, as the disease,



**FIGURE 2** Representative images of fluorodeoxyglucose positron emission tomography. A, images of Alzheimer's disease (AD) patients before and 1 month after hyperbaric oxygen treatment; (B) images of amnesic mild cognitive impairment (aMCI) before and 1 month after hyperbaric oxygen treatment

AD patients showed a reduction of glucose metabolism in brain regions including right medial frontal gyrus, right posterior cingulate cortex, parietotemporal cortex, superior lateral temporal cortex, and left inferior frontal gyrus, but the hyperbaric oxygen treatment ameliorated the reduced glucose metabolism in brain regions including left medial frontal gyrus, right middle frontal gyrus, right

inferior parietal lobule, left anterior cingulate gyrus, right associative visual cortex, left Broca area, and left inferior lateral anterior temporal cortex. Moreover, aMCI patients showed more brain regions with improved glucose metabolism including middle frontal gyrus, right inferior parietal lobule, right anterior cingulate gyrus, right Broca region, left parietotemporal cortex, superior lateral temporal cortex, left

inferior frontal gyrus, right inferior lateral anterior temporal cortex, anterior medial temporal cortex, and left inferior lateral posterior temporal cortex after the hyperbaric oxygen treatment.

## 4 | DISCUSSION

Increasing evidence has shown that non-pharmacological interventions have promising roles in the treatment of AD.<sup>33</sup> Non-pharmacological therapies, such as transcranial magnetic stimulation, transcranial direct current stimulation, light therapy, regular and long-term exercise, acupuncture, musical interventions, aromatherapy, and vagus nerve stimulation might have beneficial effects on cognitive and non-cognitive functions.<sup>34-41</sup> In the present study, we applied one course of 20-day hyperbaric oxygen treatment on AD and aMCI patients, showing that hyperbaric oxygen treatment could improve cognitive function at 1-month follow-up in AD patients. However, these improvements were not found 3 or 6 months after treatment, indicating that one course of hyperbaric oxygen treatment may temporarily ameliorate cognitive impairment in AD patients, but the effect was not permanent. In addition, the ADL score was improved in all 1-, 3-, and 6-month follow-up, implying that hyperbaric oxygen treatment could improve the patients' daily living abilities with a longer benefit. Compared to control, one course of hyperbaric oxygen treatment significantly improved cognition in AD patients at 1-month follow-up, but the improvement was decreased with time. In aMCI patients, the hyperbaric oxygen treatment enhanced the cognitive function with longer beneficial effect. The results of MMSE, MoCA, and ADL scores in different stages of AD patients indicate that one course of hyperbaric oxygen treatment could improve cognitive impairment in AD patients with early stages. Compared to the currently approved drug donepezil that improved cognition by 0.7 in MMSE score up to 24 weeks,<sup>42</sup> in our study, one course of hyperbaric oxygen treatment can significantly enhance AD patients' functions by 1.24 for at least 1 month, indicating that such treatment is a promising alternative therapy for AD, and it is possible that multiple courses of such therapy might have significantly longer benefits to AD patients. The images showed that hyperbaric oxygen treatment improved the glucose metabolism of AD patients in medial frontal gyrus associated with executive function,<sup>43</sup> and Broca area related to language processing,<sup>44</sup> which were consistent with the results of the MoCA scores. Thus, hyperbaric oxygen treatment may ameliorate cognitive function, delay the disease progress, and improve daily living activities in patients with AD in a limited duration. More interestingly, the MMSE scores in aMCI patients were significantly improved at 3-month follow-up, and the MoCA scores were significantly improved at 1-month and 6-month follow-up. Images also showed improvement of glucose metabolism in brain regions associated with language function in aMCI patients, such as Broca area, inferior frontal gyrus, and superior lateral temporal cortex, and in brain regions linked to memory, such as anterior medial temporal lobe. The improvement of glucose metabolism seemed to be greater in aMCI patients than that in AD patients. The therapeutic effects in aMCI patients indicate that hyperbaric oxygen treatment

might be a preventive strategy by blocking the conversion of aMCI to AD.

Hyperbaric oxygen treatment is a safe and routinely used medical procedure. Common complications of hyperbaric oxygen treatment include headache, claustrophobia, reversible myopia, and seizure. Most of those complications are mild and reversible when the treatment is stopped.<sup>45</sup> Some severe complications, such as oxygen toxicity and irreversible nuclear cataracts, are extremely rare.<sup>46,47</sup> In our study, only two patients experienced ear discomfort occasionally and the symptom was relieved when the procedure ended. Thus, hyperbaric oxygen treatment under 1.2 standard atmospheres and <1 hour per day is safe.

A $\beta$  and tau pathologies are the two main hypotheses in AD onset and progression. Our previous study reported that chronic hypoxia can increase A $\beta$  deposition and cause learning and memory deficits in AD mice.<sup>5</sup> Moreover, we found that chronic hypoxia can enhance the  $\gamma$ -secretase activity to promote A $\beta$  production through the downregulation of the DNA methyltransferase 3b to reduce the methylation at CpG sites in promoter region of genes of  $\gamma$ -secretase components, indicating that chronic hypoxia can aggravate AD pathology through epigenetic modifications.<sup>5</sup> On the other hand, chronic hypoxia may upregulate protein kinases, including GSK-3 $\beta$  and CDK5, and suppress phosphatase, PP2A, leading to an enhanced tau phosphorylation.<sup>48,49</sup> Because hypoxia is involved in AD pathogenesis, hyperbaric oxygen treatment targeting hypoxia may be helpful to delay or ameliorate the progression of AD. Studies have shown that hyperbaric oxygen treatment can improve cognitive behavioral performance, reduce A $\beta$  load and tau hyperphosphorylation, and alleviate neuroinflammation in AD mouse models.<sup>50</sup> Studies have also shown that hyperbaric oxygen decreased lipid peroxidation, inhibited leucocyte activation, and restored the functional blood-brain barrier.<sup>16</sup> Hyperbaric oxygen treatment might be a multi-targeted non-pharmacological intervention for AD. The underlying mechanisms need further investigation.

Hyperbaric oxygen treatment was occasionally studied in vascular dementia, showing that such therapy could improve the cognitive function and enhance the activities of daily living assessed by MMSE and ADL, respectively.<sup>51,52</sup> There was only a case report that hyperbaric oxygen treatment could reverse the patient's symptomatic decline and increase global brain metabolism assessed by.<sup>53</sup>

In the present study, considering the ethic issue, approved drug treatment was maintained in hyperbaric oxygen treated AD and control AD. It is not known if the therapeutic effect of hyperbaric oxygen treatment is directly acting on brain functions or indirectly influencing the efficacy of the medications undertaken by AD patients. Multiple-center studies with larger numbers of participants with or without medications, multiple courses of treatments, and longer time follow-up, should be applied in the future study. Moreover, more measurements of AD progression in addition to neuropsychiatric assessments, such as A $\beta$  levels and neuroimaging, should be performed. Furthermore, earlier application of hyperbaric oxygen treatment in aMCI or in the early stage AD is mostly needed to validate if the procedure can block the conversion from aMCI to AD and reduce the cognitive decline in AD.

## ACKNOWLEDGMENTS

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## CONFLICTS OF INTEREST

All the authors have no conflicts of interest to declare.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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