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Epidemiology of Dementia in Elderly Chronic Obstructive Pulmonary Disease Patients Living in China's Northwestern High-Elevation Area

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Background: The aim of this study was to investigate the effects of oxygen and cholinesterase inhibitor (donepezil) therapy on dementia in patients with age-exacerbated chronic obstructive pulmonary disease (COPD) in China's northwestern high-altitude area.

Material/Methods: A total of 145 patients with acute exacerbation of COPD admitted to the Gerontology Department of the First People's Hospital of Xining City were initially retrospectively screened. From among these 145 patients, we selected 33 cases with dementia and 33 patients without dementia through use of the Mini-Mental State Examination (MMSE), the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog), and Activities of Daily Living (ADL) Scale evaluated before, 7 days after, and at the end of the treatment after 3 months. Both patient groups received oxygen therapy for 7 days, but patients with dementia in the intervention group were medicated additionally with donepezil (5 mg/day for 1 week, followed by 10 mg/day for another 12 weeks).

Results: Mild dementia was found in 35 of the 145 COPD patients. ADL, MMSE, and ADAS-Cog scores were all significantly lower in the intervention group before treatment, improved after the first 7 days, and continued to improve significantly until week 12 in the intervention group, but were still significantly lower than in the control group.

Conclusions: Dementia in elderly COPD patients was mainly manifested as decreased executive function, attention, language, and delayed recall, while oxygen and donepezil therapy had beneficial effects on the symptoms.

MeSH Keywords: Acetylcholinesterase • Mild Cognitive Impairment • Pulmonary Disease, Chronic Obstructive

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Background

Chronic obstructive pulmonary disease (COPD) is characterized by continuous, incomplete, reversible airflow limitation and is associated with a chronic inflammatory response to harmful substances in the airway and lungs. Recent studies have shown that COPD is not only associated with lung and airway inflammation, but also with significant systemic reaction, especially in the central nervous system [1], which may be responsible for the occurrence of pulmonary encephalopathy [2]. In addition, various studies have found cognitive impairment in COPD patients [3–5], with an estimated incidence of 10% to 61% [6]. For example, Antonelli Incalzi et al. performed a comparative study of COPD patients with or without hypoxia and Alzheimer disease (AD) patients, reporting a correlation between anterior cerebral hypoperfusion and neuropsychological dysfunctions in hypoxemic COPD patients [7], and there is evidence that COPD can cause hypoxemia, which can be exacerbated by concomitant sleep-disordered breathing [8]. Another study has found an association between COPD and a decrease in cognitive performance at high altitudes [9]. In addition, the COPD mortality rate rose by 1/100 000 for each 95-meter altitude increase and was 3–4/10 000 greater at altitudes above 1000 meters compared to 100 meters [10].

Donepezil hydrochloride is the second FDA-approved acetylcholinesterase inhibitor with relative specificity, which plays a therapeutic role by enhancing the function of cholinergic nerves and is used as a cognition-enhancing medication. Several studies showed that acetylcholinesterase inhibitors can reverse the effects of hypoxia on cognitive functions [11–13]. Although there is currently no optimal therapy for cognitive impairment, early screening, prophylaxis, and treatment have been reported to be of some value [14]. Therefore, we retrospectively enrolled COPD patients admitted to the Gerontology Department of our hospital, which is located at an altitude of 2275 meters above sea level, between April 2014 and December 2016 (Figure 1). COPD patients with or without dementia were selected and we analyzed and compared the risk factors and the effects of oxygen uptake and drug (donepezil) therapy on cognitive impairment between the 2 groups. We hypothesized that donepezil would affect dementia in COPD patients.

Material and Methods

This study was approved by the Ethics Committee of our hospital. According to the diagnostic criteria of COPD formulated by the Chinese Thoracic Society Chronic Obstructive Pulmonary Disease group [15], 145 COPD patients admitted to the Gerontology Department of our hospital between April 2014 and December 2016 were screened. The following data were collected using a questionnaire: gender, age, level of education, occupation, marital status, fertility status, body mass index (BMI), newspaper and telephone use, using the internet, going outside alone, hypertension, diabetes, length of stay, diet, history of serious mental illness or surgery, history of stroke or malignancy, paralysis, smoking history, course of diseases, family history, medication history, preferred foods, exercise status, presence and duration of memory complaints, and whether the information was provided by the patient or a caregiver.

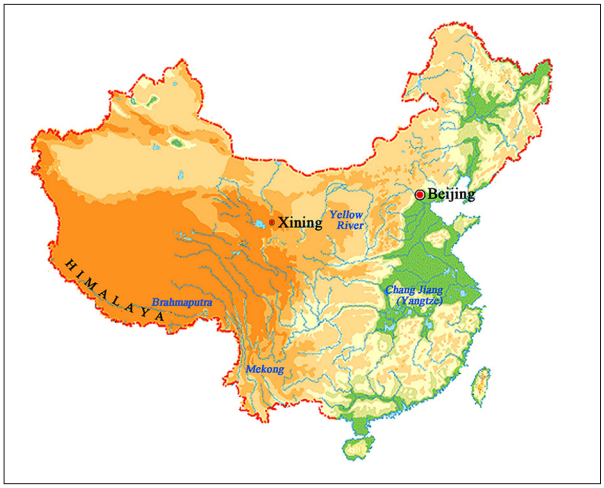

Figure 1. Location of the Xining area from which the COPD patients were recruited.

Cognitive impairment was diagnosed according to the criteria by Albert et al. (2011) [16]. Patients with anxiety and depression according to the Hamilton Anxiety and Depression Scale were excluded. Finally, 33 cases with cognitive impairment and 33 patients without cognitive impairment were selected and evaluated using the Mini-Mental State Examination (MMSE), ADAS-Cog, and Activities of Daily Living (ADL) scales (Figure 2).

Inclusion criteria

We included patients with acute exacerbation of COPD, complete clinical data, without mental and psychological diseases, without serious lesions of major organs, and without drug dependence. Data on blood gas analysis, pulmonary CT, electrocardiogram, and lung function were recorded before the treatments.

Exclusion criteria

We excluded patients who were unable to think clearly or express themselves, or who had: 1) severe dementia; 2) history of cerebrovascular disease; 3) central nervous system injury or brain damage caused by other diseases such as brain tumors or intracranial infection, or 4) history of CO poisoning or demyelinating disease of the central nervous system.

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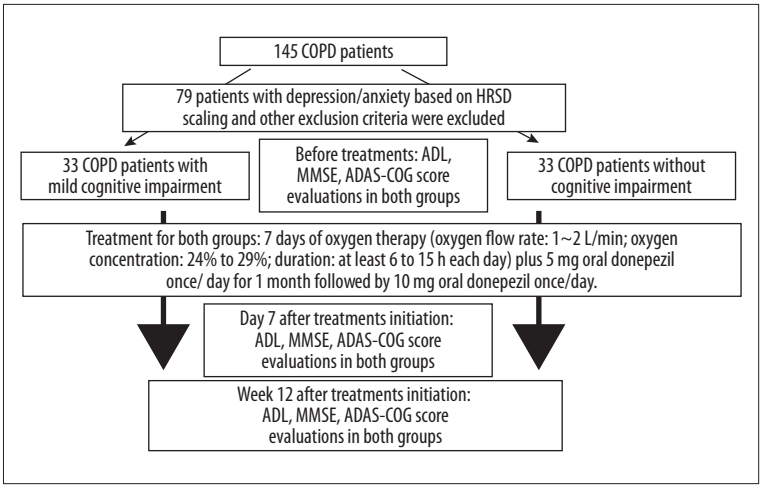

Figure 2. Flow chart of the present study. HRSD – Hamilton Rating Scale for Depression; COPD – chronic obstructive pulmonary disease; ADL – activities of daily living; MMSE – mini-mental state examination; ASAS-COG – Alzheimer's Disease Assessment Scale-Cognitive Subscale.

Arterial blood gas analysis method and pulmonary function test

For arterial blood gas analysis, we used the PHOX automatic blood gas analyzer (NOVA Biomedical, Waltham, MA USA). Radial arterial blood of patients was drawn to measure oxygen (PaO2), carbon dioxide (PaCO2) pressures, and oxygen saturation (SaO2%). Pulmonary function testing was performed with a spirometer (SensorMedics, Los Angeles, CA, USA). We used the flow-volume curve method to determine the maximum forced expiratory volume in the first second (FEV1) and Forced Vital Capacity (FVC) tested 3 times in parallel. The tests should have a deviation of less than 5%. The data in the table indicate FVC values/normal values ×100% and FEV1/FVC x 100%. Normal ranges for PaO2 (1.5–13.5 kPa), PaCO2 (4.5–6 kPa) and SaO2 (95–97%) are 20% lower in Xining.

Intervention methods and evaluation of therapeutic effect

In addition to anti-inflammatory and cough-suppressant drug treatment, patients in the 2 groups were given 7 days of oxygen therapy (general oxygen flow rate: 1–2 L/min; oxygen concentration: 24–29%; duration: at least 6–15 h each day). Intervention patients with dementia also received oral donepezil 5 mg/day for 7 days, which was increased to 10 mg/d for another 12 weeks. Therapeutic effects were evaluated using the MMSE, ADL, and ADAS-Cog scales before, 7 days after treatment initiation, and after another 12 weeks of treatment.

Assessment scales

The Hamilton Rating Scale for Depression (HRSD), first compiled by Hamilton in 1960, is the most widely used rating scale for depression. We used the 24-item version, in which a score of ≥20 means that the patient "may have depression (mild or moderate)", while a score of <8 refers to normal. According to the data provided by the China Scale Collaboration Group, a score of ≥29, ≥21, ≥14, ≥7, and <7 points refer to possible serious anxiety, obvious anxiety, anxiety, possible anxiety, and no anxiety, respectively.

We used the Chinese version of the 20-item Activities of Daily Living scale (ADL) by Lawton and Brody [17], which has 2 parts: One is the physical Self-Maintenance Scale, which includes using the toilet, feeding, dressing, grooming, physical ambulation, and bathing. The other is the Instrumental Activities of Daily Living Scale, which includes using the telephone, shopping, preparing food, doing housework, washing laundry, using transportation, taking medicine, and handling finances. For each item, 1, 2, 3, and 4 points are given for being able to do it alone without difficulty, with some difficulty, with help, and not being able to do it, respectively. A total score of 20 points means 'completely normal,' while a score of >23 points refers to various levels of functional decline.

The Mini-Mental State Examination (MMSE) scale, first published by Folstein in 1975 [18], was used in the evaluation of space and time orientation, attention, computing power, memory, and language ability, with a maximum full score of 30 points, and a higher score indicating better cognitive function. The MMSE is the most widely used tool for cognitive evaluation, with advantages of simplicity and good sensitivity, which can be used in epidemiological surveys or for determining the severity of cognitive function decline. The scores for cognitive impairments were severe (less than 9), moderate (10–18), mild (19–23) and no impairment (24 and above) [19].

A modified Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) was used to evaluate cognitive impairments. The maximum score is 85, with higher scores indicating greater dysfunction, with a score of 26–30 indicating mild cognitive impairment, >30–35 indicating mild AD, 35–39 indicating moderate AD, and 40–45 indicating severe AD [20].

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Table 1. Baseline characteristics of COPD patients in the 2 groups.

		Control group (33 cases)	Intervention group (33 cases)	t/χ^2	*P*-value
Gender	Male	24	17	3.879	0.076
	Female	9	16		
Age	≤ 75	15	12	2.182	0.140
	> 75	18	21		
Level of education	Illiteracy	9	13	0.253	0.553
	Primary	10	6		
	Middle/high school	10	11		
	College degree or above	4	3		
Course of disease	~10 years	12	12	0.766	0.945
	~15 years	18	17		
	More than 20 years	3	4		

Statistical analysis

All analyses were performed with SPSS Statistics for Windows (Version 17.0. Chicago; SPSS Inc.). The chi-square test was used for comparison of numerical data. The data are displayed as $\bar{\chi}$±SD and the independent-samples t test was used for their comparison. A paired t test was used for comparing the data collected 7 days after admission with data collected 12 weeks after discharge. A result of P<0.05 was considered to be statistically significant.

Sample size calculation

We anticipated that the score change of MMSE from baseline is 5.5±3.0 after 12 weeks of intervention, and the score change of MMSE from baseline is 3±3.0 in the control group. With a P-value of 0.05, a test power of 90% and anticipating losses of 10% in follow-ups, we established a target sample size of 34 participants in each group.

Results

Baseline characteristics

Cognitive impairment was found in 35 of the 145 enrolled patients, and 33 COPD patients without cognitive impairment were selected as the control group. During the trial, 1 patient withdrew from the study and 1 patient died in the intervention group, so a total of 66 patients were followed up (Figure 2).

There were 24 males and 9 females in the control group, with an average age of 70.6 years, while there were 17 males and 16 females in the intervention group, with an average age of 78.1 years. There was no significant difference in gender, age, course of disease, and level of education between the 2 groups (Table 1).

Data about arterial blood gas and pulmonary function were derived at baseline as well as 1 week and 2 weeks after treatment initiation during the hospital stay (Table 2). All parameters other than FEV1% were comparable between the 2 groups at baseline.

MMSE, ADAS-Cog scale, and ADL scores for COPD patients in the 2 groups

Significant differences were found between the 2 groups in all items of the ADL scale (*P*<0.001), except for taking medicine (*P*=0.354), putting on and taking off clothes (*P*=0.507), combing and brushing hair (*P*=0.265), walking on a flat interior floor (*P*=0.153), using the telephone (*P*=0.911) and handling finances (*P*=0.658) (Tables 3, 4).

There were also significant differences in MMSE scores between the 2 groups (*P*<0.001), and cognitive impairment in the intervention group was mainly manifested as impairment of orientation (*P*<0.001), attention (*P*<0.001, computational power (*P*<0.001), recall (*P*<0.001), and language abilities (*P*<0.001) (Tables 5, 6).

ADAS-Cog scales also showed significant differences between the 2 groups (*P*<0.001) in all tested items (*P*<0.001) (Table 7).

Assessment of therapeutic effect

After oxygen and drug (donepezil) therapy, ADL scores improved significantly in the intervention group between day 7 days and week 12 of the intervention, and there was no

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Table 2. Arterial blood gas and pulmonary function comparisons of the control and intervention groups (mean ±SD).

	Control group	Intervention group	*P*-value
Baseline			
PaO2 (kPa)	5.27±2.41	5.41±2.80	0.8284
PaCO2 (kPa)	7.66±2.90	7.60 ±2.82	0.9324
After 1 week of treatment			
PaO2 (kPa)	5.93±2.87	5.87±2.63	0.9297
PaCO2 (kPa)	7.55 ±2.61	7.48±3.12	0.9216
After 2 weeks of treatment			
PaO2 (kPa)	6.88±2.32**	6.79±3.11	0.8944
PaCO2 (kPa)	7.44 ±3.17	7.41 ±2.96	0.9684
Baseline			
FVC%	43.3±11.6	47.4±13.1	0.1830
FEV1%	51.94±3.56	54.2±3.68	0.0137
After 1 week of treatment			
FVC%	46.4±11.6	47.76±12.7	0.6512
FEV1%	54.28±2.39**	55.16±4.03	0.2847
After 2 weeks of treatment			
FVC%	46.56±12.7	48.8±11.4	0.4536
FEV1%	54.89±2.74 ***	55.99±4.03	0.1994
Baseline			
SaO2 (%)	84.52±3.77	85.23±3.28	0.4174
After 1 week of treatment			
SaO2 (%)	86.15±4.12	87.09±4.34	0.3702
After 2 weeks of treatment			
SaO2 (%)	90.12±5.67 ***	91.22±5.02 ***	0.4071

FVC%=FVC values/normal values ×100%; FEV1%=FEV1/FVC ×100%. PaO2 – alveolar oxygen partial pressure; PaCO2 – arterial partial pressure of carbon dioxide; FVC – forced vital capacity; FEV1 – forced expiratory volume in one second; SaO2: arterial oxygen saturation; ** P<0.01 compared to the baseline; *** P<0.001 compared to the baseline.

Table 3. Comparison of ADL scores between intervention and control groups before treatments (mean ±SD).

	n	ADL score	t	*P*-value
Intervention group	33	35.24±2.75	21.470	<0.001
Control group	33	28.36±2.08		

significant difference in ADL scores between the intervention and the control group at 12 weeks after treatment initiation (*P*=0.247). MMSE and ADAS-Cog scores significantly improved in the intervention group after 12 weeks, but were still inferior to the control group (*P*=0.003), (*P*=0.002) (Table 8).

Adverse effects

Donepezil adverse effects were mild diarrhea in 4 patients, dizziness in 2 patients, and anorexia in 1 patient.

Discussion

A study of global disease burden predicted that by 2020, COPD would be the third leading cause of disease death in the world, and the World Bank and Health Organization forecast at a large epidemiological statistical meeting that by 2020, COPD would rank fifth in global disease burden [21,22].

Severe cognitive dysfunction often occurs in COPD patients, manifested by decreased alertness, delayed reaction time, and

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Table 4. ADL assessment of patients in the 2 groups according to Lawton and Brody before treatments (mean ±SD).

Items	Intervention group (n=33)	Control group (n=33)	*t*	*P*-value
Taking a bus	3.03±0.78	2.03±0.68	5.551	<0.001
Ambulation (walking distance)	3.98±0.30	3.32±0.34	8.362	<0.001
Cooking	3.96±0.21	3.83±0.27	2.183	0.033
Doing housework	3.96±0.21	2.38±0.32	23.714	<0.001
Taking medicine	3.29±0.72	3.12±0.76	0.933	0.354
preparing food	3.86±0.67	2.5±0.58	8.297	0.001
Putting on and taking off clothes	3.49±0.92	3.12±0.83	0.671	0.507
Combing and brushing hair	3.89±0.86	3.78±0.83	1.125	0.265
Doing the laundry	3.72±0.46	3.32±0.32	4.101	0.001
Walking on flat interior floor	3.96±0.73	3.68±0.84	1.445	0.153
Walking up and down stairs	3.69±0.21	2.32±0.41	17.085	<0.001
Getting in and out of bed, sitting down or standing up	3.96±0.22	3.36±0.36	8.169	<0.001
Preparing water to cook and bathe	3.49±0.78	1.42±0.64	11.786	<0.001
Bathing (water has been prepared)	3.92±0.21	3.42±0.64	4.264	<0.001
Cutting toenails	3.83±0.23	3.32±0.28	8.085	<0.001
Shopping	3.89±0.22	3.54±0.35	4.861	<0.001
Going to the toilet at regular times	3.88±0.26	2.36±0.36	19.663	<0.001
Using the telephone	3.89±0.28	3.88±0.43	0.112	0.911
Handling finances	3.96±0.49	3.89±0.76	0.447	0.658
Staying at home alone	3.92±0.73	3.12±0.59	4.896	<0.001

Table 5. Comparison of MMSE scores between intervention and control groups before treatments (mean ±SD).

	n	MMSE score	t	*P*-value
Intervention group	33	16.67±1.44	25.361	<0.001
Control group	33	24.36±0.98		

Table 6. MMSE assessment for patients in the 2 groups before treatments (mean ±SD).

Items	Intervention group (n=33)	Control group (n=33)	*t*	*P*-value
Orientation	7.40±0.38	8.43±0.46	9.917	<0.001
Memory	2.00±0.46	2.96±0.72	6.455	<0.001
Attention and computational power	3.68±0.61	4.78±0.75	6.536	<0.001
Recall ability	2.34±0.59	2.96±0.76	3.702	<0.001
Language ability	6.36±0.63	8.76±0.58	16.100	<0.001

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Table 7. Comparison of ADAS-Cog score between intervention and control groups before treatments (mean ±SD).

	ADAS-Cog score		*P*-value
	Intervention group (n=33)	Control group (n=33)	
Items	33.03±5.75	17.76±4.64	<0.001
Word memory	5.46±0.48	3.23±0.21	<0.001
Naming	3.98±0.42	2.62±0.32	<0.001
Instructions	2.98±0.46	2.48±0.64	<0.001
Structural practice	2.69±0.57	1.98±0.41	<0.001
Intentionality	2.84±0.86	1.52±0.72	<0.001
Orientation	3.68±0.32	2.43±0.26	<0.001
Word recognition	4.23±0.56	1.87±0.36	<0.001
Recall of testing instructions	2.63±0.64	1.82±0.63	<0.001
Oral ability	2.86±0.78	1.69±0.66	<0.001
Finding words	2.82±0.36	1.76±0.47	<0.001
Language comprehension	3.97±0.38	2.12±0.52	<0.001
Attention	2.88±0.49	1.82±0.67	<0.001

Table 8. Comparison of therapeutic effects between the 2 groups 7 days and 12 weeks after treatment initiation (mean ±SD).

Group	N	Time points		*P*-value
		7 days	12 weeks	
ADL				
Intervention group	33	33.55±2.51	28.37±3.44	<0.001
Control group	33	28.64±3.92	27.42±3.08	0.872
P-value		<0.001	0.247	
MMSE				
Intervention group	33	17.34±3.5	23.14±2.70	<0.001
Control group	33	24.36±2.78	22.91±2.21	0.750
P-value		<0.001	0.003	
ADAS-Cog				
Intervention group	33	33.02+4.51	27.12+4.17	<0.001
Control group	33	16.23+4.23	15.93+6.07	0.956
P-value		<0.001	0.002	

abnormal logical thinking [23]. In the present study, cognitive impairment was diagnosed in 24.2% of the initially screened COPD patients living in the Xining region with 25% reduced atmospheric O_2 content. However, since 54.5% of the initially screened COPD cases were excluded in this study, the overall dementia incidence might have been underestimated due to the presence of more serious depression and/or anxiety symptoms in the excluded patients. It has been proposed that hypoxemia is a crucial factor for cognitive impairment in COPD patients [24,25]. Furthermore, some researchers have suggested that cognitive impairment is prone to occur in COPD patients with hypoxemia, while the risk of subclinical cognitive dysfunction would not be increased in COPD patients without hypoxemia, and the degree of cognitive impairment in COPD patients with hypoxia is closely related to the degree of hypoxia. This is supported by the clinical finding that cognitive function can be improved by long-term oxygen therapy in COPD patients [26,27]. A proposed reason for the correlation between hypoxia and cognitive impairment is the shortage of cholinergic transmitters, since hypoxemia affects oxygen-dependent enzymes for the synthesis of acetylcholine [28]. In our study, oxygen treatment for 1 week, in combination

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with low-dose donepezil, significantly improved ADL scores, and there was some improvement in ADAS-Cog scores in the intervention group, whereas the control group did not show significant changes. However, there were still significant differences between the groups regarding ADL, MMSE, and ADAS-Cog scores at day 7 after treatment initiation. After 12 weeks of treatment, ADL scores showed no difference between the groups, but MMSE and ADAS-Cog scores were still significantly inferior in the intervention group, although they were significantly improved compared to before treatment. These results indicate that high doses of the acetylcholinesterase inhibitor donepezil improve the cognitive impairment in COPD patients, even without oxygen therapy. The cognitive impairment screening used in the current study employed a variety of clinical neuropsychological scales, and could be used to assess the overall state of cognitive function, as well as specific cognitive domain status, identifying some cognitive impairments that would be harder to detect by routine examination [29]. A limitation of our study is the small sample size, and further large-scale studies are necessary to confirm the findings.

Conclusions

Dementia developed in a large percentage of COPD patients from China's northwestern region, mainly manifested as symptoms of decreased performance on executive function, attention, language, and delayed recall. Regular cognitive impairment screening and intervention should be available to COPD patients, particularly those living in high-altitude areas. Oxygen and donepezil therapy had a distinct beneficial effect on cognitive impairment in COPD patients with dementia.

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