Cognitive Decline in Patients with Long-Term Domiciliary Oxygen Therapy

Takashi Ohrui,* Kazunori Tanaka,* Kazue Chiba, Toshifumi Matsui, Satoru Ebihara, Mei He, Ichiro Tsuji, HIroyuki Arai and Hidetada Sasaki

Department of Geriatric and Respiratory Medicine, 1Division of Epidemiology, Department of Public Health, 2Department of Geriatric and Complementary Medicine, Tohoku University Graduate School of Medicine, Sendai, and 3Teijin Home Healthcare East Japan Limited, Saitama, Japan

OHRUI, T., TANAKA, K., CHIBA, K., MATSUI, T., EBIHARA, S., HE, M., TSUJI, I., ARAI, H. and SASAKI, H. Cognitive Decline in Patients with Long-Term Domiciliary Oxygen Therapy. Tohoku J. Exp. Med., 2005, 206 (4), 347-352 — Cognitive and psycho-physiological condition in patients with long-term domiciliary oxygen therapy (DOT) remains uncertain. A cross sectional analysis was performed to investigate the age-related changes in cognitive and psycho-physiologic functions in patients with chronic respiratory failure receiving long-term DOT. Two expert practitioners visited the patient’s home and examined them for analysis of cognitive function, emotional status, physical activity and degree of dyspneic sensation. One hundred and thirty-five patients completed the study. Control data from a cohort of 718 community dwellers were also included in this study. Male patients had significantly higher rates of chronic obstructive pulmonary disease (71% vs 47%, p = 0.001), lower values of forced expiratory volume in one second (FEV1.0 %) (49.7 ± 10.3 [standard deviation, S.D.] vs 66.0 ± 7.5% predicted, p = 0.002) and higher Borg score, an indicator of dyspneic sensation, during daily exercise (3.2 ± 0.8 [S.D.] vs 1.4 ± 0.6, p = 0.01) compared with female patients. Linear regression analysis based on mean Mini-Mental State Examination scores, an indicator of cognitive function, showed that age-related cognitive decline was more pronounced in female patients than in female controls (–0.524/year, R² = 0.426 vs –0.120/year, R² = 0.027, p < 0.0001), while there was no significant difference between male patients and male controls (–0.156/year, R² = 0.054, vs –0.077/year, R² = 0.016, p = 0.231). These results demonstrate that age-related cognitive decline is more exaggerated in female patients receiving long-term DOT which should be taken into consideration in caring for patients with chronic respiratory failure. ——— chronic respiratory failure; domiciliary oxygen therapy; long-term survivor; cognitive function; Borg scale

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Previous studies have reported that patients with chronic respiratory failure frequently suffer from neuropsychologic deficit and experience a disturbed mood, personality and life quality (Grant et al. 1982; Heaton et al. 1983; Incalzi et al. 1993). In a study assessing the neuropsychologic profile of patients with chronic obstructive pulmonary disease (COPD), diffuse mental deterioration characterized the study population with particular impairment of higher cognitive functions, and this was thought to be due to accelerated aging of the brain (Grant et al. 1982). To date, although long-term domiciliary oxygen therapy (DOT) has been proved to prolong survival of patients with chronic respiratory failure (The Medical Research Council Working Party 1981), its impact on cognitive function in long-term survivors remains uncertain.

In the present study, we, therefore, examined the cognitive and psychophysologic functions in patients receiving long-term DOT and compared them with those in age-matched community dwellers. We focused especially on the issue of the sex-related difference in cognitive function in patients with long-term DOT, because it remains unclear whether there is a gender difference in age-related cognitive decline in these subjects (Heaton et al. 1983; Scherr et al. 1988; Incalzi et al. 1993; Mortensen and Hogh 2001). We also aimed to identify possible contributing factors for the alteration in cognitive function in patients with long-term DOT.

**PATIENTS AND METHODS**

A total of 264 patients with COPD, sequelae of tuberculosis or chronic interstitial pneumonia, who were ex-smokers and had been followed as outpatients in the Pneumology Department for 9 to 16 years, were recruited from 34 medical institutions in Sendai, Japan. They were receiving continuous oxygen therapy (24 h/day) at home via nasal prongs sufficient to maintain a PaO\textsubscript{2} between 60 and 80 mmHg from the start of oxyhemoglobin desaturation. One hundred and sixty-seven of the 264 patients agreed to participate in this study in the period from March 2001 to July 2002.

Two expert nurses unaware of the findings at clinical examination visited the patient’s home and examined them for analysis of cognitive function, emotional status, degree of dyspneeic sensation and physical activity, by Mini-Mental State Examination (MMSE) score (Folstein et al. 1975), geriatric depression scale (GDS) (Sheikh and Yesavage 2000), Borg scale (Borg 1982) and functional/performance status (Katz index) (Katz et al. 1970), respectively. Cognitive impairment was present if total MMSE score was 23 or below. At the time of the study, patients were receiving a regular dose of oxygen. Patients were excluded from this study if they used sedative drugs or they had cardio- and cerebro-vascular diseases, major psychiatric disorders, and acute infectious diseases.

Control data from a cohort of community dwellers were also included in this study. These data were obtained from the Tsurugaya Aging Study comprised of several studies of the biomedical and psychological determinants of cognitive ageing conducted in July 2002 in Sendai, Japan. The control group included 718 subjects (male 301) of comparable age, sex, duration of education and socio-economic status to patients receiving long-term DOT. This study was approved by the Tohoku University Ethical Committee and informed consent was obtained from each subject.

Student’s t-test or chi-square test for independent samples was performed to determine whether clinical variables and cognitive and psycho-physiological functions of patients with long-term DOT differed from those of control subjects and whether there was a gender difference among these parameters. Linear regression analysis was used to evaluate the relation between age and cognitive function in male and female patients with long-term DOT vs control subjects. The strength of the relations was quantified by partial correlation coefficients. SPSS version 10.0 (SPSS, Chicago, IL, USA) statistical packages were used. A p value of < 0.05 was regarded as significant.

**RESULTS**

Of the 167 participating patients, 8 subjects refused to complete all subsets of examinations because of fatigue, 10 subjects were admitted to other hospitals and 14 died during the study period. Finally, 135 subjects (male 101) completed the study. Clinical characteristics of control subjects and patients with long-term DOT are described in Table 1. The mean duration of DOT was 4.2 yr (4.3 yr and 3.6 yr for male and female
patients, respectively) and the mean oxygen flow was 1.2 l/min (1.1 l/min and 1.4 l/min for male and female patients, respectively). There were no significant differences between male and female patients among these values. However, male patients had a significantly higher rate of COPD (71% vs 47%, *p* = 0.001) and lower values of forced expiratory volume in one second (FEV₁) (49.7 ± 10.3 [standard deviation, s.d.] vs 66.0 ± 7.5% predicted, *p* = 0.002) compared with female patients (Table 1).

The proportion of patients with cognitive impairment (MMSE, lower than 23 points) was significantly higher in female patients than in male patients with long-term DOT (14[41%] vs 15[15%], respectively; *p* = 0.01, after correction for differences in age, education, and disease duration). In contrast, there were no significant differences between male and female controls in these data (Table 2). The relation between MMSE score and age is illustrated in Fig. 1. There were significant negative correlations between MMSE (Table 1). The proportion of patients with cognitive impairment (MMSE, lower than 23 points) was significantly higher in female patients than in male patients with long-term DOT (14[41%] vs 15[15%], respectively; *p* = 0.01, after correction for differences in age, education, and disease duration). In contrast, there were no significant differences between male and female controls in these data (Table 2). The relation between MMSE score and age is illustrated in Fig. 1. There were significant negative correlations between MMSE

### Table 1. Clinical characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Controls</th>
<th>Patients</th>
<th><em>p</em> value&lt;sup&gt;*&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male (n = 301)</td>
<td>Female (n = 417)</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>77.4 ± 8.2</td>
<td>78.3 ± 9.2</td>
<td>0.96</td>
</tr>
<tr>
<td>Education (yr)</td>
<td>11.4 ± 2.7</td>
<td>10.8 ± 2.1</td>
<td>0.08</td>
</tr>
<tr>
<td>COPD diagnosed - No. (%)</td>
<td>36(12)</td>
<td>25(6)</td>
<td>0.001</td>
</tr>
<tr>
<td>FEV₁ (% predicted)</td>
<td>82.7 ± 19.6</td>
<td>87.5 ± 24.6</td>
<td>0.002</td>
</tr>
<tr>
<td>Blood gas analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PaO₂ (mmHg)</td>
<td>85.2 ± 3.6</td>
<td>84.4 ± 5.3</td>
<td>0.23</td>
</tr>
<tr>
<td>PaCO₂ (mmHg)</td>
<td>42.8 ± 2.7</td>
<td>41.2 ± 3.4</td>
<td>0.44</td>
</tr>
<tr>
<td>PH</td>
<td>7.41 ± 0.2</td>
<td>7.42 ± 0.1</td>
<td>0.88</td>
</tr>
</tbody>
</table>

Plus-minus values are means ± s.d. *Comparisons were made between male patients and female patients with long-term DOT.

Blood gas data refer to the patient breathing oxygen at the usual therapeutic concentration via nasal prongs. COPD and FEV₁ denote chronic obstructive pulmonary disease and forced expiratory volume in one second.

### Table 2. Clinical outcomes

<table>
<thead>
<tr>
<th>Variable</th>
<th>Controls</th>
<th>Patients</th>
<th><em>p</em> value&lt;sup&gt;*&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male (n = 301)</td>
<td>Female (n = 417)</td>
<td></td>
</tr>
<tr>
<td>MMSE score</td>
<td>27.0 ± 3.0</td>
<td>26.4 ± 3.4</td>
<td>0.02</td>
</tr>
<tr>
<td>≤ 23 No. (%)</td>
<td>18(6)</td>
<td>29(7)</td>
<td>0.01</td>
</tr>
<tr>
<td>&gt; 24 No. (%)</td>
<td>283(94)</td>
<td>388(93)</td>
<td></td>
</tr>
<tr>
<td>GDS score</td>
<td>4.4 ± 2.8</td>
<td>4.2 ± 2.9</td>
<td>0.16</td>
</tr>
<tr>
<td>Functional/performance status</td>
<td>6.2 ± 1.8</td>
<td>6.2 ± 2.1</td>
<td>0.17</td>
</tr>
<tr>
<td>Borg score</td>
<td>1.1 ± 1.0</td>
<td>1.2 ± 1.1</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Plus-minus values are means ± s.d. *Comparisons were made between male patients and female patients with long-term DOT.

MMSE and GDS denote Mini-Mental State Examination and Geriatric depression scale.
score and age in both controls and patients receiving long-term DOT. There was no significant difference in declining rate of MMSE score between male controls and patients (−0.077/year, $R^2 = 0.016$ vs −0.156/year, $R^2 = 0.054$, respectively, $p = 0.231$) (Fig. 1). By contrast, a significant difference in declining rate of MMSE score was observed between female controls and patients (−0.120/year, $R^2 = 0.027$ vs −0.524/year, $R^2 = 0.426$, respectively, $p < 0.0001$). Furthermore, although there was no significant difference in declining rate of MMSE score between male and female controls, a significant difference was observed between male and female patients (−0.156/year, $R^2 = 0.054$ vs −0.524/year, $R^2 = 0.426$, respectively, $p = 0.021$), which demonstrated age-related cognitive decline was more pronounced in female patients receiving long-term DOT (Fig. 1). Male patients had a significantly higher Borg score during daily exercise compared with female patients ($3.2 \pm 0.8$ [s.d.] vs $1.4 \pm 0.6$, $p = 0.01$, respectively) (Table 2). There seemed to be a positive correlation between the MMSE score and the Borg score in both male and female patients, whereas it was not statistically significant (data not shown). There were no correlations between the MMSE score and the FEV$_1$, GDS score, Katz index, PaO$_2$, PaCO$_2$ or the duration of DOT by multi-regression analysis in male and female patients with long-term DOT (Table 2).

**DISCUSSION**

Oxyhemoglobin desaturation is reported to be an important determination of mental deterioration (Heaton et al. 1983; Incalzi et al. 1993). A previous study has shown that 6 months oxygen treatment is associated with small but definite improvement in brain functioning among patients with hypoxemic COPD (Heaton et al. 1983). However, cognitive function in patients receiving long-term oxygen treatment and its gender differ-
ence has not been studied. The present study demonstrated that age-related cognitive decline was more pronounced in female patients receiving long-term DOT, while cognitive function in male patients was fairly preserved compared with control subjects of the same age. To the best of our knowledge, there are no published data concerning interactions between sex and cognitive outcome after long-term DOT. There were no significant differences among several clinical parameters except the Borg score, probably due to the difference in the lung function, between male and female patients. Despite the lack of clear knowledge of the mechanism for the interaction of sex and cognitive outcome after long-term DOT, a possible explanation for this finding might be a contribution of substance P (SP) in the CNS. Several findings indicate involvement of tachykinins in stress-related anxiety and depressive states (Megens et al. 2002). Especially, SP plays a role in dyspnea perception and in some autonomic reflexes and behaviors (Megens et al. 2002). SP release is suggested in stressful situations in the CNS (Culman and Unger 1995) and the NK1 receptor antagonist has been shown to improve anxiety and depression rating scales in depressed patients (Rupniak and Kramer 1999). SP might be released significantly in the CNS in male patients with long-term DOT and an increased release of SP might up-regulate neprilysin (Stefano et al. 1992), a major amyloid-β peptide degrading enzyme in the brain, leading to protection against cognitive decline in male patients (Iwata et al. 2000).

That continuous oxygen therapy did not provide a complete protection against the deteriorating cognition in both male and female patients is not surprising, since several factors related chronic respiratory failure other than hypoxemia are known to affect cognition. Among these factors, hypercapnia, acidosis, and hypocapnia resulting from hypoxemia-induced hyperventilation should be taken into consideration (Heaton et al. 1983; Incalzi et al. 1993).

The limitation of the present study should be discussed. First, we did not conduct a longitudinal but a cross-sectional analysis of the cognitive and psychologic functions in patients receiving long-term DOT. A longitudinal study for a long-term period may provide more detail information about the age-related cognitive decline in each subject. Second, the absolute number of the female patients with long-term DOT is limited, which is pointed out in other previous reports (Heaton et al. 1983; Incalzi et al. 1993). This is probably due to a gender difference in the prevalence of pulmonary diseases such as COPD, which require DOT in the case of disease progression. Third, although a significant negative correlation between MMSE scores and age in both controls and patients with long-term DOT was found, the correlation coefficient values were low in individual groups. A further study with a large number of patients is needed to translate the present findings to patients with DOT in general. However, we believe that our data provide sufficient grounds for a reexamination of the effect of long-term DOT on cognitive function in those patients.

In conclusion, the current study demonstrates that the effect of long-term DOT on cognitive outcome differs between men and women. The increased life expectancy of patients with chronic respiratory failure after the introduction of the oxygen therapy implies that a growing fraction of physically disabled and to a various extent mentally impaired patients can be alive until old age especially in female patients (Sasaki et al. 1998; Kubo et al. 2005). Thus, end-stage pulmonary diseases will become a growing geriatric problem, and health care systems should be prepared to deal with it.

Acknowledgments

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