Impaired Efficacy of Cough in Patients With Parkinson Disease*

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Study objectives: Aspiration pneumonia, a leading cause of death in patients with Parkinson disease (PD), usually occurs at the advanced stages of the disease. We investigated both motor and sensory components of cough and induced-sputum substance P (SP) concentrations in patients with early and advanced stages of PD to assess whether cough efficacy is impaired in PD.

Subjects: Fifteen female patients with early stages of PD (Hoehn and Yahr stage II-III), 10 patients with advanced stages of PD (Hoehn and Yahr stage IV), and 15 age-matched female control subjects were investigated.

Measurements: The motor component of cough efficacy was assessed by monitoring voluntary maximal cough peak flow. The sensory component of cough efficacy was assessed by measuring cough reflex sensitivity to citric acid inhalation. Sputum SP concentrations were measured in sputum induced by hypertonic saline solution inhalation.

Results: The mean (± SD) cough peak flow rates in patients with both early PD (230 ± 74 L/min; \( p < 0.005 \)) and advanced PD (186 ± 60 L/min; \( p < 0.0001 \)) were significantly weaker than that in control subjects (316 ± 70 L/min). Cough reflex sensitivity in patients with advanced PD (46.7 ± 49.3 g/L) was significantly lower compared to control subjects (14.5 ± 16.6 g/L; \( p < 0.01 \)) and patients with early PD (11.2 ± 14.8 g/L; \( p < 0.005 \)). The sputum SP concentration was significantly lower in patients with advanced PD (11.2 ± 8.4 pg/mL) compared to that in control subjects (35.6 ± 15.4 pg/mL) and patients with early PD (28.5 ± 16.4 pg/mL).

Conclusion: In the early stages of the disease, mainly the motor component of cough was impaired. In advanced stages of the disease, both the motor and sensory components of cough were impaired. Sputum SP concentration significantly declined in patients with advanced PD. The results suggest that the combination of impaired motor and sensory components of cough may play an important role in the development of aspiration pneumonia in PD.

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Key words: cough; cough peak flow; cough reflex sensitivity; Parkinson disease

Abbreviations: PD = Parkinson disease; SP = substance P

Despite the progress in therapy for Parkinson disease (PD), PD is still associated with significant morbidity and mortality.\(^1\) Aspiration pneumonia is a leading cause of death in patients with PD.\(^1\) Airway protective mechanisms such as swallowing and cough may play a role in aspiration pneumonia. Although swallowing disorders in patients with PD are well-known,\(^2\) it has not been established whether the efficacy of cough in patients with PD is impaired.

Cough is an important defense mechanism, the main function of which is to remove mucus and/or foreign bodies from the airways by generating a high expiratory flow. The impairment of cough efficacy could be due to the dysfunction of either motor components (ie, cough intensity such as cough peak flow) or sensory components (ie, cough reflex sensi-
tivity) of cough. The risk of aspiration pneumonia is increased in stroke patients with a weak voluntary cough peak flow and impaired cough reflex sensitivity. In patients with motor neuron disease, declined cough peak flow was related to episodes of choking. Cough peak flow is also lower in patients with muscular dystrophy, amyotrophic lateral sclerosis, and spinal cord injury, who are susceptible to fatal aspiration pneumonia. Cough reflex sensitivity is diminished in patients after heart-lung transplantation, also making them highly susceptible to aspiration pneumonia.

The impaired motor component of cough in patients with PD has been shown by monitoring the electromyogram of abdominal muscles and maximal expiratory pressure. However, cough peak flow has not been measured in patients with PD. In terms of the sensory component of cough, previous studies have failed to detect the decline of cough reflex sensitivity in patients with PD. In these studies, however, the level of clinical disability was not taken into consideration when estimating cough reflex sensitivity. Since aspiration pneumonia usually occurs in patients in the advanced stages of PD, it is possible that this finding is not prominent in the early stages of the disease. Moreover, accumulating evidence shows that the cough reflex is more sensitive in women than in men, indicating that gender should be matched in a comparison of cough reflex sensitivities.

In the present study, we estimate both the motor and sensory components of cough efficacy by measuring the cough peak flow and sensitivity of cough reflex to citric acid in female patients with PD at different stages. In addition, we investigated sputum substance P (SP) concentration, which may play an important role in cough reflex.

Material and Methods

Subjects

Because gender differences in the cough peak flow and cough reflex sensitivity are known, we focused on female subjects in this study. Twenty-five female outpatients with idiopathic PD were recruited from our neurologic clinics at Tohoku University Hospital and National Nishitaga Hospital in Sendai City. The diagnosis of idiopathic PD was based on the consensus of two neurologists. The age at onset of PD was defined as the appearance of the first symptom estimated by medical interview, and the severity of PD was classified on a scale from I to V, as stage II (8 patients), stage III (7 patients), and stage IV (10 patients), according to Hoehn and Yahr. Here, we defined the patients with stage II or III disease as early PD, and stage IV as advanced PD. All patients had a Mini-Mental State Examination score of >24 and had been stable for at least 3 months before entering the trial. All patients responded to and their conditions were being maintained with a combination of levo-

dopa and carbidopa. Sixteen healthy volunteers, who were age-matched and height-matched, were recruited from the community by advertisement. All subjects were nonsmokers and had no history of chronic respiratory disease or acute respiratory problems during the previous 6 months. Patients taking angiotensin-converting enzyme inhibitors were excluded from the study. The studies were performed on two consecutive days at the same time of the day (around 2 h after taking the dopaminergic medication). On the first day, spirometry (model OST 80A; Chest Co; Tokyo, Japan), cough intensity, and cough reflex sensitivity were measured. On the second day, the spumon for SP measurement was collected. All measurements were performed by a laboratory technician who did not know the purpose of the study. The experimental protocol adhered to the Recommendations of the Declaration of Helsinki for Human Experimentation. The protocol was approved by the Tohoku University Ethics Committee. Individual informed consent was obtained after a detailed explanation of the procedure, but not of the purposes, of the study. Studies were conducted after the patients gave informed consent, according to the Declaration of Helsinki for Human Experimentation.

Cough Reflex Sensitivity

Cough reflex sensitivity to citric acid was evaluated with tidal breathing of a nebulized solution that was delivered by ultrasonic nebulizer (model MU-32; Sharp Co Ltd; Osaka, Japan). The nebulizer generated particles with a mean mass median diameter of 5.4 μm at an output of 2.2 mL/min. Citric acid was dissolved in saline solution, providing a twofold incremental concentration from 0.07 to 36%. Cough was recorded on a Fleisch pneumotachograph mounted at the expiratory ports of the valve. The cough threshold was defined as the concentration at which the patients coughed at least five times during 1 min of breathing the citric acid aerosol. Each nebulizer application had a 2-min interval.

Cough Intensity

Cough intensity was estimated by measuring the cough peak flow during voluntary maximal cough. To measure the cough peak flow, the sitting subjects were instructed to take a full inspiration and to cough into the face mask connected to a peak flowmeter (mini-Wright; Clement Clarke International; Harlow, UK) as forcefully as possible. The values obtained by a peak flowmeter are known to be quite close to the value obtained by a pneumotachometer. The presented values are the mean of the three highest values from five attempts.

Sputum SP Concentration

Induced sputum was collected the day after measurements of cough reflex sensitivity, spirometry, and cough peak flow were made. Capsaicin-containing meals were not allowed for 12 h before sputum collection. Around 2 h after the intake of their regular dopaminergic medication, the sputum collection was performed. A 3% saline solution was administered via an ultrasonic nebulizer for 15 to 30 min until the sputum volume was approximately 1 mL. Because the sample contained saliva, we eliminated this contamination by visual inspection and inverted microscopy examination. The SP was quantified using modification of a previously described method. The collected 1-mL sputum samples were immediately mixed with 0.5 U/mL aprotinin and 3 mmol/L ethylenediaminetetraacetic acid, and was stored at −70°C until assay. For radioimmunoassay, the samples were mixed with 2 vol (vol/vol) acetone using a mixer at room temperature for 5 min. The precipitate was pelleted by centrif-
Cough is an important defense mechanism functioning to remove mucus and foreign bodies from the respiratory tract by generating a high expiratory flow. In our study, we showed impaired efficacy of cough in patients with PD, with more pronounced impairment in patients with advanced PD compared to those with early PD. In the early stages of the disease, the motor component of cough was impaired. In advanced stages of the disease, both motor and sensory components of cough were impaired. Since dysphagia and the risk of aspiration worsen with the progression of PD, it is of importance to elucidate the factors involved in the impaired efficacy of cough in the advanced stage of PD.

Several measurements have been reported to be useful in the assessment of the motor component of the cough (ie, cough intensity), as follows: cough noise; electromyogram of abdominal muscles; and peak expiratory pressure. These measurements of the intensity of cough require special equipment and skills to measure, whereas it is quite simple to measure the cough peak flow by flowmeter. Using electromyogram and peak expiratory pressure, Fontana and colleagues showed that the reduced motor component of cough efficacy started in the early stages of PD. This result is consistent with our observation that was assessed by cough peak flow. The abnormal flow-volume curve in patients with PD is well-established. The decreased or less coordinated respiratory muscle force and/or upper airway obstruction are thought to be causes for the

**Table 1** Characteristics of Control Subjects and Patients With PD

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Control Subjects</th>
<th>Early PD (n = 15)</th>
<th>Advanced PD (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H-Y stage</td>
<td>0 ± 0</td>
<td>2.6 ± 0.7</td>
<td>4 ± 0</td>
</tr>
<tr>
<td>Age, yr</td>
<td>60 ± 10.3</td>
<td>67.1 ± 8.4</td>
<td>70.9 ± 8.8</td>
</tr>
<tr>
<td>Duration, yr</td>
<td>0 ± 0.0</td>
<td>5.8 ± 5.2</td>
<td>9.7 ± 6.3</td>
</tr>
<tr>
<td>Height, cm</td>
<td>145 ± 6</td>
<td>146 ± 5</td>
<td>145 ± 5</td>
</tr>
<tr>
<td>FVC, % predicted</td>
<td>87.1 ± 12.1</td>
<td>82.1 ± 9.0</td>
<td>75.6 ± 20.0</td>
</tr>
<tr>
<td>FEV1, % predicted</td>
<td>85.8 ± 9.4</td>
<td>84.1 ± 7.2</td>
<td>77.4 ± 16.6</td>
</tr>
</tbody>
</table>

*Values given as mean ± SD. There was no significant difference in age, height, FVC, and FEV1 among the three groups. H-Y = Hoehn-Yahr.
change in flow-volume curves in patients with PD. Reduced expiratory muscle strength is thought to be an important factor in decreased cough peak flow.\textsuperscript{16} Since the effective cough could require more delicate coordination of pharyngeal, laryngeal, and respiratory muscles than forced expiratory flow,\textsuperscript{32} the cough might be more susceptible to the disease than the maximal expiratory flow-volume curve. FVC values tended to decrease in the advanced stages of PD (Table 1). Therefore, a failure to inspire to total lung capacity levels also may have contributed to a lowered cough peak flow. However, judging from the relatively large decrease in cough peak flow with increasing severity of disease, compared with the smaller decrease in FVC, we speculate that a significant influence of this mechanism is unlikely.

Our finding about the sensory component of cough in patients with PD differs from those of previous reports. Fontana and colleagues\textsuperscript{16} showed that cough reflex sensitivity was not significantly different between healthy control subjects and patients with PD. Smith and Wiles\textsuperscript{17} reported that patients with neurogenic dysphagia, including patients with PD, did not have a reduced cough reflex sensitivity. The apparent contradiction between their studies and ours seems to be based on differences in the severity of the disease rather than on differences in methodology. Since patients with early PD are less likely to have aspiration pneumonia, it is important to classify the stages of the disease to correlate the clinical significance of mortality from PD with impaired cough efficacy. Moreover, gender differences in cough reflex sensitivity have been reported using various stimuli.\textsuperscript{18–20} Women have a more sensitive cough reflex than men, whether in premenopausal or postmenopausal states.\textsuperscript{18} In the present study, we focused on the cough reflex sensitivity of female patients with different stages of PD and found that cough reflex sensitivity was significantly impaired in female patients with advanced stages of PD.

It is well-known that cough reflex sensitivity is seriously impaired in elderly patients with aspiration pneumonia.\textsuperscript{33} SP, which may play an important role in the cough reflex,\textsuperscript{21} was found to be decreased in

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Figure 1. Comparison of cough peak flow among control subjects and patients with early PD (ie, Hoehn-Yahr stage II-III) and advanced stages of PD (ie, Hoehn-Yahr stage IV). Each symbol represents a single subject. Mean values are indicated by a horizontal bar. N.S. = no significant difference.
the sputum of elderly patients with aspiration pneumonia. Since the major cause of death in patients with PD is aspiration pneumonia, we hypothesized that sputum SP concentrations in patients with PD also were lower. Indeed, SP concentrations in the saliva of patients with PD were found to be lower than those of age-matched control subjects. Moreover, the loss of SP-containing neurons in the brainstem and striatum from autopsy samples of PD patients have been reported, suggesting the systemic depletion of SP in patients with advanced stages of PD. Therefore, we measured the sputum SP concentration in patients in various stages of PD and showed a significantly decreased concentration of sputum SP only in patients with advanced PD. The result suggests that the sputum SP concentration may be related to the sensory component of cough rather than to the motor component in patients with PD. In guinea pigs, SP released from the sensory nerves in the airway has been shown as a possible endogenous substance causing cough.

Since aspiration pneumonia usually occurs in the advanced stages of PD, the combined impairment of cough intensity and reflex sensitivity may play important roles in the development of aspiration pneumonia in PD patients. A strong relationship between impaired cough reflex sensitivity and the risk of aspiration pneumonia has been shown in stroke patients. Smith Hammond and colleagues have shown that an impaired cough intensity, as assessed by the flow of voluntary cough, was a risk factor for aspiration in stroke patients. Thus, the combined impairment of both the motor and sensory components of cough might be a common mechanism of aspiration pneumonia for patients with both stroke and PD.

Because aspiration pneumonia is the most common cause of death in PD patients, the related conditions should be treated more extensively in order to improve their survival. This study and observations of the elderly with cerebral vascular diseases suggest that reduced SP concentration is related to aspiration pneumonia in patients with advanced PD. The effort to increase the concentration of SP by angiotensin-converting enzyme inhibitors could be useful to reduce the risk of pneumonia.

![Figure 2](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21998/)

**Figure 2.** Comparison of cough reflex sensitivity among control subjects and patients with mild PD (ie, Hoehn-Yahr stage II-III) and severe PD (ie, Hoehn-Yahr stage IV). Each symbol represents a single subject. Mean values are indicated by a horizontal bar. See the legend of Figure 1 for abbreviation not used in the text.
nia in patients with PD, just as it is useful in older patients with cerebral vascular diseases. Further studies are needed to clarify whether interventions that are useful for treating aspiration pneumonia in the elderly are also beneficial for patients with PD.

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