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Central cholinergic dysfunction could be associated with oropharyngeal dysphagia in early Parkinson's disease

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Abstract Dysphagia is an important issue in the prognosis of Parkinson's disease (PD). Although several studies have reported that oropharyngeal dysphagia may be associated with cognitive dysfunction, the exact relationship between cortical function and swallowing function in PD patients is unclear. Therefore, we investigated the association between an electrophysiological marker of central cholinergic function, which reflected cognitive function, and swallowing function, as measured by videofluoroscopic studies (VFSS). We enrolled 29 early PD patients. Using the Swallowing Disturbance Questionnaire (SDQ), we divided the enrolled patients into two groups: PD with dysphagia and PD without dysphagia. The videofluoroscopic dysphagia scale (VDS) was applied to explore the nature of the dysphagia. To assess central cholinergic dysfunction, short latency afferent inhibition (SAI) was evaluated. We analyzed the relationship between central cholinergic dysfunction and oropharyngeal dysphagia and investigated the characteristics of the dysphagia. The SAI values were significantly different between the two groups. The comparison of each VFSS component between the PD with dysphagia group and the PD without dysphagia group showed statistical significance for most of the oral phase components and for a single pharyngeal phase component. The total score on the VDS was higher in the PD with dysphagia group than in the PD without dysphagia group. The Mini-Mental State Examination and SAI values showed significant correlations with the total score of the oral phase components. According to binary logistic regression analysis, SAI value independently contributed to the presence of dysphagia in PD patients. Our findings suggest that cholinergic dysfunction is associated with dysphagia in early PD and that an abnormal SAI value is a good biomarker for predicting the risk of dysphagia in PD patients.

Keywords Parkinson's disease · Dysphagia · Electrophysiology · VFSS · Short latency afferent inhibition

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Introduction

Dysphagia is a common consequence of Parkinson's disease (PD), occurring in approximately 40–80 % of PD patients (Fuh et al. 1997; Johnston et al. 1995; Potulska et al. 2003; Tjaden 2008). It is known to be a relatively late clinical symptom in the course of the disease (Monte et al. 2005; Robbins et al. 1986). This is because PD patients typically have a low level of awareness of the presence of dysphagia and the use of compensatory techniques (Manor et al. 2007). However, dysphagia has been found in some patients with PD early in the course of the disease, and it does not always correlate with disease severity (Han et al. 2011).

In PD patients, the pathophysiology of dysphagia is not well established, and swallowing itself is a complex process, which consists of oral, pharyngeal, and esophageal phases. The pathophysiologies of the abnormalities in each phase are thought to be related to the different patterns of neurodegeneration that occur in PD (Cersosimo and Benarroch 2012; Rofes et al. 2013). With regard to dysfunction of the oral and pharyngeal phases, dysphagia in PD results in abnormal bolus formation, multiple tongue elevations, delayed swallowing reflex, and prolongation of pharyngeal transit time with repetitive swallows to clear the throat (Nagaya et al. 1998; Luchesi et al. 2015). Recently, Cereda et al. 2014 reported that gender, age, disease duration, and dementia could independently contribute to the occurrence of dysphagia in PD patients, and Suntrup et al. 2013 reported that reduced cortical activation is prominent in temporal areas in PD patients with dysphagia. Furthermore, several studies revealed that severe cognitive dysfunction is inversely related to swallowing ability and that dysphagia is observed more frequently in patients with low Mini-Mental State Examination (MMSE) scores (Tjaden 2008; Walshe 2014). Therefore, cortical function, as well as brainstem and basal ganglia integrity, could also affect the modulation of swallowing function.

Short latency afferent inhibition (SAI) of the motor cortex is a non-invasive technique that provides information about the integrity of cholinergic circuits in the human brain (Tokimura et al. 2000). SAI is known to be significantly reduced in cholinergic forms of dementia, including in Alzheimer's dementia, dementia with Lewy bodies, and even multiple-domain amnestic mild cognitive impairment (MCI) (Nardone et al. 2006, 2008, 2012). In patients with PD, PD-MCI, PD dementia, and PD-related hallucination, there are reduced SAI responses, which indicates a central cholinergic deficit (Celebi et al. 2012; Manganelli et al. 2009; Yarnall et al. 2013). Therefore, if cognitive dysfunction is potentially associated with dysphagia in PD, we hypothesized that central cholinergic dysfunction may be related to dysphagia in PD, and there have not been any studies that have investigated SAI in PD patients with dysphagia.

For the diagnosis of dysphagia in PD, only a few validated, PD-specific screening methods in the form of a patient questionnaire are available (Evatt et al. 2009; Han et al. 2011; Manor et al. 2007). Of these, the Swallowing Disturbance Questionnaire (SDQ) is a self-reported questionnaire consisting of 15 items and has high sensitivity and specificity (Manor et al. 2007). A commonly used objective method for the diagnosis of PD is the use of videofluoroscopic swallowing studies (VFSS), which can detect higher rates of swallowing dysfunction than assessment of subjective awareness of dysphagia in PD patients (Nagaya et al. 1998, 2004). Furthermore, few studies have evaluated swallowing dysfunction in early PD patients. Therefore, we used these two tools to investigate the characteristics of dysphagia in early PD patients.

In this study, we aimed to determine the relationship between central cholinergic dysfunction and oropharyngeal dysphagia, defined by the SDQ, in early PD and to investigate the characteristics of dysphagia in relatively early PD using VFSS.

Patients and methods

Patients and clinical assessment

This study was designed as an observational study and evaluated 29 PD patients who were diagnosed according to the criteria defined by the United Kingdom Parkinson's Disease Society Brain Bank. We prospectively enrolled 12 early PD patients with dysphagia as diagnosed by the Swallowing Disturbance Questionnaire. The SDQ is a self-reported questionnaire consisting of 15 items. Fourteen items are rated from 0 (no disability) to 3 (severe disability), and the final item is a "yes/no" question in which yes is scored 2.5 points and no is scored 0.5 points. PD with dysphagia was defined as an SDQ score of greater than or equal to 11, in accordance with a previous study (Manor et al. 2007). Seventeen age-matched early PD patients without dysphagia who possessed SDQ scores of less than 11 were also recruited. All of the PD patients attended the Neurology Clinic of Gangneung Asan Hospital from July 2014 to December 2014. A total of 9 PD patients were excluded based on the exclusion criteria defined below.

The exclusion criteria included the following: (1) history of a medical disorder affecting swallowing function, including stroke, dementia, traumatic brain or spinal injury, autoimmune disease, demyelinating disorder, or inflammatory myopathy; (2) cognitive decline, defined as a Mini-Mental State Examination (MMSE) score <24, or severe depression, defined as a Beck Depression Inventory (BDI) score >16; (3) a modified Hoehn and Yahr (H&Y) stage ≥ 2.5 (to recruit early stage PD patients); (4) ongoing use of medications that could affect cortical excitability and SAI, including anticholinergics, cholinesterase inhibitors, benzodiazepines, and antiepileptic drugs; (5) dementia, as defined by the DSM-IV criteria or PD psychosis; and (6) age <60 or >80.

Basic demographic data, including gender, age, body mass index, disease duration, and levodopa equivalent daily dose (LEDD), were recorded. Disease severity was assessed by the "on" state Unified Parkinson's Disease Rating Scale-III (UPDRS-III) and the modified H&Y stage. MMSE and BDI were also evaluated in all of the PD patients.

Ethics statement

The study protocol was approved by the ethics committee of Gangneung Asan Hospital. Detailed information regarding the present study was provided to all of the participants, and written informed consent was obtained from each, in accordance with the Declaration of Helsinki.

Measurement of swallowing impairment and VFSS

To identify oral and pharyngeal function, each patient underwent a VFSS study with the use of medication during the 'on' state. The VFSS were performed as follows: each subject was placed upright and instructed to hold contrast food and/or liquid that was placed into the mouth until instructions to swallow were given. After the instructions were given, rice gruel, ground fruit, or egg custard containing contrast medium were placed in the mouth with a spoon, and 3, 5, or 8 ml of the contrast medium was placed in each subject's mouth using a syringe. Fluorographic images were recorded on a videotape running at 15 frames/s, using a videocassette recorder (Sonialvision, KF-7) coupled to a counter-timer that provided timing information on each video field (Nagaya et al. 1998). The fluoroscope was activated just before the instructions to swallow were given. The instructions to swallow were then given immediately, and the subjects swallowed the contrast food and/or liquid. Each of the patients underwent swallowing evaluation while ingesting 3, 5, and 8 ml of thick liquid and 3, 5, and 8 ml of thin liquid. Each subject performed 1 swallow of both food and fluid containing the contrast medium. The videotapes were analyzed frame-by-frame in slow motion to detect abnormalities in swallowing (Nagaya et al. 2004).

A videofluoroscopic dysphagia scale (VDS) was used to score abnormalities in the VFSS. The VDS is composed of 14 items that represent the oral (lip closure, bolus formation, mastication, apraxia, premature bolus loss, and oral transit time) and pharyngeal functions (pharyngeal triggering, vallecular and pyriform sinus residue, laryngeal elevation and epiglottic closure, pharyngeal coating, pharyngeal transit time, and aspiration) that can be observed in VFSS (Chun et al. 2011; Kim et al. 2012).

Conventional transcranial magnetic stimulation (TMS) study

Conventional TMS parameters were applied to a Magstim magnetic stimulator (Magstim Company, Dyfed, UK) using a circular coil. Each subject was comfortably seated in a chair and had the surface of an Ag/AgCl electrode placed over their abductor pollicis brevis (APB). First, the compound motor action potential (CMAP) was obtained from the APB muscle on the ipsilateral side following a supramaximal stimulus to the median nerve at the wrist. The resting motor threshold (RMT) was defined as the lowest stimulation intensity that elicited a motor-evoked potential (MEP) with a 50 μV peak-to-peak amplitude from the APB in more than 5 out of 10 trials. Next, the MEP amplitude ratio (MEPAR) was calculated as the ratio of the baseline-to-peak CMAP amplitude to the peak-to-peak amplitude of the MEP. Afterward, the central motor conduction time (CMCT) was calculated as the difference in latency between the cortical- and cervical root-evoked potentials. To obtain the cortical motor-evoked potential, a circular coil was located over the frontoparietal area to stimulate the APB. When the stimulus intensity (maximum intensity: 130 % of RMT) was greater than the threshold, the onset latency of the MEP was obtained. The onset latency was determined as the shortest latency of the MEP. Next, the cervical nerve root was stimulated by placing a magnetic coil over C7, and the onset latency of the cervical root-evoked potential was obtained.

Short latency afferent inhibition

To evaluate central cholinergic function, SAI was evaluated, and the SAI examiner was blind to each patient's' group assignment. The protocol that was used to obtain the SAI value was based on a previously presented report by Tokimura et al. (Tokimura et al. 2000). First, an MEP without peripheral nerve stimulation was obtained as the control MEP. Next, conditioned MEPs were assessed by delivering conditioned stimuli to the median nerve that preceded the cortical TMS by various interstimulus intervals (ISIs). The ISIs were determined relative to the N20 latency that was obtained by the somatosensory-evoked potential (SEP). Five-hundred sweep signals were averaged to determine the latency of the N20. Five interstimulus intervals were used to evaluate SAI (from N20 to N20 + 4 ms in steps of 1 ms), and ten cortical stimuli with a median nerve stimulation at the wrist were performed at each ISI. The peak-to-peak conditioned MEPs were averaged at each interval and regarded as the test MEP. The test MEP was expressed as a percentage of the control MEP, and conditioned responses at five ISIs were also averaged to obtain a grand mean. The mean percentage of inhibition of the test MEP amplitude relative to the control MEP amplitude was regarded as the SAI (%). Each of the subjects was given audio-visual feedback based on EMG monitoring to maintain maximal relaxation, and optimal dopaminergic medication was maintained to obtain complete relaxation.

Statistical analysis

All of the data were analyzed using a commercial statistical software program (SPSS 12.0, Chicago, IL, USA), and all are presented as the mean ± standard deviation, with categorical data being presented as frequency. For data with non-Gaussian distributions, the Mann–Whitney test was applied to compare clinical parameters, conventional TMS parameters, and SAI between the PD with dysphagia and PD without dysphagia groups. To compare categorical data, Fisher's exact test was applied. The correlation analyses between the total score in each stage and the variables reflecting cognitive markers, including MMSE-K and SAI (%), were also explored. A binary logistic regression test was performed using the enter method to evaluate the odds ratio (OR) of each variable. The dependent variable was the presence of dysphagia in PD patients according to the SDQ questionnaire, and the independent variables included age, modified H&Y stage, MMSE-K score, LEDD, disease duration and SAI (%). In a multivariate logistic model, the dependent variable was also the presence of dysphagia in PD patients, and the independent variable was SAI (%). Other variables were considered covariates. The Hosmer–Lemeshow goodness-of-fit statistic was used to assess model fit. $p < 0.05$ was regarded as significant.

Results

The demographic data and baseline characteristics of each of the patients are shown in Table 1. As presented in Table 1, age, gender, and disease duration were similar in both groups. BMI and MMSE scores were higher in the PD without dysphagia group than in the PD with dysphagia group (26.34 ± 3.33 versus 23.19 ± 2.00, $p < 0.05$; 26.82 ± 1.55 versus 25.25 ± 1.60, $p < 0.05$). The modified H&Y staging and SDQ scores were significantly higher in the PD with dysphagia group than in the PD without dysphagia group (1.92 ± 0.56 versus 1.50 ± 0.47, $p < 0.05$; 14.17 ± 2.92 versus 4.71 ± 3.10, $p < 0.01$). Neither age, gender, disease duration, UPDRS-III and Beck depression scale score, nor LEDD showed significant differences between the two groups.

The electrophysiological parameters of the PD with dysphagia and PD without dysphagia groups are described in Table 2 and Fig. 1. The SAI values were significantly different between the two groups (74.35 ± 15.09 versus 49.36 ± 8.34, $p < 0.01$). Other TMS parameters, including RMT, CMCT, MEPAR, and the N20, did not show significant differences between the two groups. The SAI value also revealed no significant correlation with disease duration, modified H&Y stage, or UPDRS-III score.

In comparing each VFSS component between the PD with dysphagia and PD without dysphagia groups, statistical significance was found for most of the oral phase components and for a single component of the pharyngeal phase (Table 3). During the oral phase, scores for mastication, apraxia, premature bolus loss, oral transit time, and overall oral stage were higher in the PD with dysphagia group than in the PD without dysphagia group (mastication, $p < 0.01$; apraxia, $p < 0.05$; premature bolus loss, $p < 0.05$; oral transit time, $p < 0.01$; and overall oral stage, $p < 0.01$). During the pharyngeal phase, only the triggering of pharyngeal swallow score was statistically higher in the PD with dysphagia group than in the PD without dysphagia

Table 1 The demographic parameters of the enrolled PD subjects

	PD with dysphagia ($n = 12$)	PD without dysphagia ($n = 17$)	p value
Age	73.33 ± 6.48	71.06 ± 6.98	0.29
Gender (male/female)	6/6	6/11	0.34*
Disease duration (month)	17.92 ± 9.16	11.94 ± 4.98	0.07
BMI (kg/m^2)	23.19 ± 2.00	26.34 ± 3.33	**<0.05**
UPDRS-III	24.17 ± 6.53	20.06 ± 4.07	0.11
Modified H&Y	1.92 ± 0.56	1.50 ± 0.47	**<0.05**
Beck depression scale	4.50 ± 3.71	3.88 ± 3.02	0.72
MMSE-K	25.25 ± 1.60	26.82 ± 1.55	**<0.05**
SDQ	14.17 ± 2.92	4.71 ± 3.10	**<0.01**
LEDD	589.58 ± 254.50	488.82 ± 181.86	0.35

Bold values are statistically significant

These values represent the means, with the standard deviation in parentheses, or the number of patients, with percentages in parentheses

PD Parkinson's disease, *BMI* body mass index, *UPDRS-III* Unified Parkinson's disease Rating Scale Part 3, *H&Y* Hoehn and Yahr stage, *MMSE-K* Korean version of the Mini-Mental State Examination Scale, *SDQ* Swallowing Disturbance Questionnaire, *LEDD* levodopa equivalent daily dose

* Chi-squared test

Table 2 Comparison of electrophysiological parameters between the PD with dysphagia and PD without dysphagia groups

	PD with dysphagia ($n = 12$)	PD without dysphagia ($n = 17$)	p value
RMT (%)	63.08 ± 8.01	62.65 ± 7.30	0.93
CMCT (ms)	8.15 ± 1.33	7.70 ± 0.95	0.31
MEPAR (%)	49.44 ± 25.97	41.21 ± 18.57	0.43
N20 (ms)	19.61 ± 1.19	18.78 ± 1.22	0.12
SAI (%)	74.35 ± 15.09	49.36 ± 8.34	**<0.01**

Bold value is statistically significant

These values represent the mean with the standard deviation

PD Parkinson's disease, *RMT* resting motor threshold, *CMCT* central motor conduction time, *MEPAR* motor-evoked potential amplitude ratio, *SAI* short latency afferent inhibition

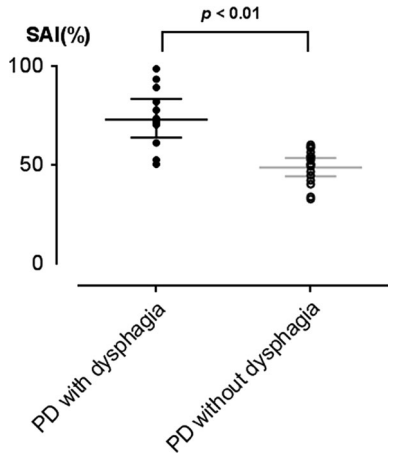

Fig. 1 Box plot of a comparison of short latency afferent inhibition between the PD with dysphagia and PD without dysphagia groups. The SAI value showed a statistically significant difference between the PD with dysphagia and PD without dysphagia groups ($p < 0.01$)

group ($p < 0.05$). Other components also trended toward being higher in the PD with dysphagia group, but there were no statistically significant differences. The total score on the videofluoroscopic dysphagia scale (VDS) was higher in the PD with dysphagia group than in the PD without dysphagia group ($p < 0.01$).

The sum of each score in the oral stage showed a significant correlation with MMSE-K score and SAI (%) value ($r = -0.41$, $p < 0.05$, $r = 0.48$, $p < 0.01$, Fig. 2). However, the total pharyngeal stage score and all sub-item scores in the pharyngeal stage of VDS revealed no significant correlations with either the MMSE-K score or SAI (%).

In univariate logistic regression, MMSE-K score, modified H&Y stage, and SAI (%) all had significant influence on the presence of dysphagia in PD patients [OR 0.54; confidence interval (CI) 0.31–0.91; $p < 0.05$, OR 5.20; confidence interval (CI) 1.01–26.65; $p < 0.05$, OR 1.25; CI 1.05–1.48; $p < 0.05$]. After adjusting for covariates, SAI (%) was found to have an independent significant influence on the presence of dysphagia in PD patients (OR 1.59; CI 1.03–2.44; $p < 0.05$, Table 4).

Discussion

In this study, we found that there was a difference in central cholinergic activity, as measured electrophysiologically by SAI, between PD patients with dysphagia and PD patients without dysphagia. Furthermore, in relatively early stage PD, dysphagia mainly presented as oral phase dysfunction. MMSE-K score and SAI (%) were also significantly correlated with oral phase dysfunction, but not with pharyngeal phase dysfunction. After adjusting for variables that could affect swallowing function in PD, SAI (%) was independently related with the presence of dysphagia in PD patients. The main strength of our study is that we provided the first demonstration that cholinergic dysfunction reflecting cognitive impairment or the risk of progressive dementia might also contribute to dysphagia in early PD patients. Furthermore, we found that oral phase abnormalities in dysphagia components predominantly constitute the pathophysiology of dysphagia in early stage PD.

Swallowing difficulties in PD may be apparent in any of the oral, pharyngeal, or esophageal phases (Tjaden 2008; Nagaya et al. 1998; Luchesi et al. 2015). The oral phase of swallowing is under voluntary control. Considering that bradykinesia and rigidity are representative symptoms in PD patients, hypokinetic dysphagia could be considered initially responsible for oral dysphagia, which suggests that oral phase dysphagia may be more responsive to dopaminergic stimulation than dysphagia due to other mechanisms (Bushmann et al. 1989; Johnston et al. 1995; Mancopes et al. 2013; Potulska et al. 2003). Leopold et al. suggested that the limited excursion of the mandible may contribute to the extension of the prepharyngeal swallowing process (Leopold and Kagel 1996). In this study, decreased motility in the oral phase of swallowing, causing prolongation of oral–pharyngeal transit time, was observed, and this finding is consistent with previous reports (Nilsson et al. 1996; Nagaya et al. 1998; Luchesi et al. 2013).

In PD, the pharyngeal phase of swallowing can be disrupted due to delayed oral delivery, incoordination of striated muscles, reduced somatosensory stimuli, and

Table 3 Comparison of each sub-item in the oral and pharyngeal stages obtained by a videofluoroscopic swallowing study (VFSS) between the PD with dysphagia and PD without dysphagia groups

	PD with dysphagia	PD without dysphagia	*p* value
Oral stage			
Lip closure	0.83 ± 1.03	0.32 ± 0.34	0.18
Bolus formation	1.00 ± 1.48	0.18 ± 0.73	0.23
Mastication	4.00 ± 1.71	0.71 ± 1.47	**<0.01**
Apraxia	0.88 ± 0.77	0.27 ± 0.59	**<0.05**
Tongue to palate contact	0.42 ± 1.44	0.00 ± 0.00	0.71
Premature bolus loss	1.75 ± 1.67	0.35 ± 1.00	**<0.05**
Oral transit time	2.75 ± 0.87	0.35 ± 1.00	**<0.01**
Overall oral stage	11.63 ± 2.18	2.18 ± 2.90	**<0.01**
Pharyngeal stage			
Triggering of pharyngeal swallowing	1.13 ± 2.04	0.00 ± 0.00	**<0.05**
Vallecular residue	2.33 ± 1.67	1.88 ± 1.65	0.54
Laryngeal elevation	0.75 ± 2.60	0.00 ± 0.00	0.23
Pyriform sinus residue	4.50 ± 3.32	3.18 ± 3.47	0.29
Coating on the pharyngeal wall	3.75 ± 4.63	1.06 ± 2.99	0.07
Pharyngeal transit time	0.50 ± 1.73	0.00 ± 0.00	0.23
Aspiration	1.50 ± 3.73	0.71 ± 1.99	0.66
Overall pharyngeal stage	14.46 ± 15.91	6.82 ± 7.16	0.12
Total score	26.08 ± 19.80	9.00 ± 7.23	**<0.01**

Bold values are statistically significant

Mann–Whitney test for comparison of each variable

These values represent the means, with the standard deviation in parentheses, or the number of patients, with percentages in parentheses

PD Parkinson's disease

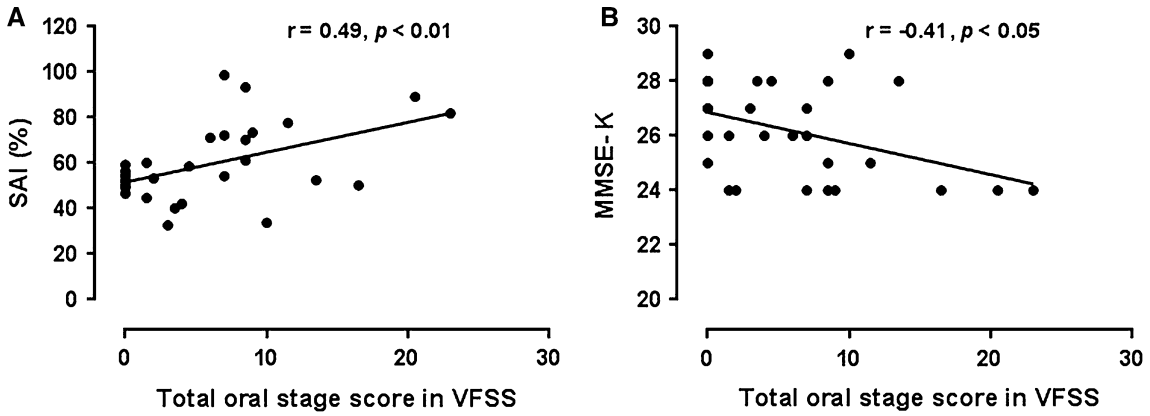

Fig. 2 Scatter plot of the MMSE-K scores, SAI (%) values and the sums of all of the oral phase components. The sum of each score in the oral stage showed a significant correlation with MMSE-K score and SAI (%) value ($r = -0.41$, $p < 0.05$, $r = 0.48$, $p < 0.01$)

abnormal autonomic function (Mu et al. 2013; Steele and Miller 2010). Degeneration of the dorsal vagal nucleus has been found to be additionally responsible for pharyngeal dysfunction (Grinberg et al. 2010; Monte et al. 2005). However, in our study, the involvement of the oral phase was predominant over that of the pharyngeal phase, and we only found a delay in the triggering of the pharyngeal swallowing reflex. Therefore, we suppose that as PD progresses swallowing dysfunction might progress towards the pharyngeal phase, which is preceded by the oral phase. This finding indicates that the mechanisms underlying the abnormalities in each phase could be different and attributable to patterns of neurodegeneration.

Dopaminergic stimulation is known to improve swallowing dysfunction in PD patients. Recently, Hirano et al. 2015 reported that dopamine agonists improved swallowing in VFSS in dysphagic PD patients. However, there was also a report that swallowing dysfunction in PD patients is

Table 4 Univariate and multivariate logistic regression analysis for the presence of dysphagia in PD patients, with the odds ratios, 95 % confidence intervals and *p* values displayed for various variables, including SAI (%) values (adjusted for all variables)

	Univariate regression analysis			Multivariate regression analysis		
	Odds ratio	95 % CI	*p* value	Odds ratio	95 % CI	*p* value
Age	1.04	0.94–1.16	0.42			
Disease duration	1.14	1.00–1.29	0.05	1.01	0.79–1.42	0.72
Modified H&Y stage	5.20	1.01–26.65	**<0.05**	149.73	0.24–93,175.11	0.13
LEDD	1.01	0.99–1.01	0.22			
MMSE-K	0.54	0.32–0.92	**<0.05**	1.84	0.46–7.39	0.39
SAI (%)	1.25	1.05–1.48	**<0.05**	1.59	1.03–2.44	**<0.05**

Bold values are statistically significant

CI confidence interval, *MMSE-K* Mini-Mental State Examination for Korean, *Modified H&Y stage* modified Hoehn and Yahr stage, *LEDD* levodopa equivalent daily dose, *SAI* short latency afferent inhibition

predominantly resistant to dopaminergic stimulation and may not only be related to nigrostriatal dopaminergic deficits but also to an additional non-dopaminergic disturbance (Hunter et al. 1997). Furthermore, various reports have indicated that dysphagia in PD does not reveal a clear correlation with motor severity or disease duration (Leopold and Kagel 1997). Therefore, the pathologic mechanism of dysphagia in PD remains unclear and controversial. In this study, the modified H&Y stage showed significant differences between those with PD with dysphagia and those without, while UPDRS-III and disease duration did not. The SAI value also showed no correlation with disease severity. However, recruiting early stage PD patients could have potentially biased our results, and further investigations, including of advanced stage PD, are necessary to clarify whether disease severity and duration, which mainly reflect dopaminergic degeneration, could be associated with dysphagia and cholinergic dysfunction in PD. Considering that swallowing is controlled by a hierarchical system that extends from the frontal and limbic cortex to the basal ganglia and brainstem, swallowing dysfunction in PD patients could be mediated by cortical function via a non-dopaminergic mechanism (especially the central cholinergic system), as well as by the dopaminergic system.

Screening for oropharyngeal dysphagia is important for identifying individuals who are at risk of impairment and to provide appropriate onward referral for a more thorough assessment (Walshe 2014). SDQ scores were used to screen dysphagia in this study. The sensitivity of the SDQ has been reported to be as high as 80.5 %, and its specificity has been reported to be as high as 81.3 % (Manor et al. 2007).

However, Kalf et al. (2011, 2012) showed that patients in the early stages of PD with no subjective symptoms of dysphagia also had a high percentage of objective swallowing abnormalities, including abnormal VFSS findings. That is, the frequency of subjective complaints may be poorly correlated with the severity of oropharyngeal swallowing abnormalities that were found using an objective method.

Several studies have reported that oropharyngeal dysphagia may be associated with cognitive impairment (Tjaden 2008; Walshe 2014). Cereda et al. (2014) reported that dementia could be a contributing factor to swallowing disturbances in PD, and Miller et al. (2006) suggested that there was a moderate correlation between swallowing speed and cognition. Considering that mild cognitive impairment (MCI) is a common non-motor problem in PD and is indicative of central cholinergic dysfunction, which has been recognized as a high risk factor for dementia (Yarnall et al. 2013), there is a possibility that cholinergic dysfunction might be associated with oropharyngeal dysphagia. It could even be a possible marker for predicting oral phase dysfunction. In this study, we demonstrated that the SAI value, which provides a relatively simple neurophysiological method of evaluating cholinergic dysfunction, showed a significant difference between the PD with dysphagia and the PD without dysphagia groups. The MMSE value also showed a difference between the two groups. Therefore, we propose that both cholinergic dysfunction and cognitive dysfunction could contribute to dysphagia in early PD patients and could serve as useful biomarkers to identify dysphagia in the early stages of PD, providing an opportunity for early clinical intervention. Furthermore, for the treatment of cortical dysfunction, cholinesterase inhibitors have been widely used in various degenerative diseases, including in Alzheimer's disease and PD (Rolinski et al. 2012). Di Lazzaro et al. (2002) reported that the use of an acetylcholinesterase inhibitor normalized the SAI value in addition to improving cognitive dysfunction. Therefore, an acetylcholinesterase inhibitor might be a potent therapeutic candidate for the treatment of dysphagia in patients with PD. Further studies are necessary to investigate its pros and cons.

Overall, we suggest that early detection of dysphagia using VFSS and intervention for dysphagia-related complications are required in PD patients with low SAI values

and that SAI value could be a useful tool for identifying subclinical dysphagia in PD patients. Dysphagia in PD is associated with increased mortality and morbidity, and it may place a considerable psychological and social burden on patients and their families (Miller et al. 2006). The complications of dysphagia include a negative impact on quality of life, malnutrition due to low caloric intake, and even dehydration due to difficulty drinking (Fuh et al. 1997; Johnston et al. 1995; Luchesi et al. 2015). The most serious complication of dysphagia is aspiration pneumonia, which is the leading cause of death in Parkinson's disease (Tjaden 2008; Manor et al. 2007; Kalf et al. 2012). Evidently, the early diagnosis and treatment of swallowing difficulties will improve the clinical course of PD.

We are aware that there were several limitations in this study. First, the small number of subjects was the main limitation of our study. Second, we did not administer an extensive battery of cognitive function tests, such as the Montreal Cognitive Assessment (MOCA), a visuospatial function test (e.g., the clock drawing test), an attention-estimating battery (e.g., the trail making test), a frontal function test (e.g., the Go-no-Go test or the Stroop test), or a language-related test (e.g., the Boston naming test). Considering the low sensitivity of the MMSE in discriminating subtle cognitive dysfunction, further studies on a larger number of subjects using various cognitive batteries are necessary to confirm these findings. Third, the TMS parameters that were used in this study were rater-limited. Di Lazzaro et al. (2005a, b) reported that SAI could be influenced by GABAergic and dopaminergic dysfunction, as well as by cholinergic dysfunction. Therefore, a further exploration of TMS parameters, including of short latency intracortical inhibition using paired-pulse TMS, is necessary. Fourth, the lack of a control group was an important limitation of this study, and a further study including normal controls is needed to confirm that an association between reduced SAI and dysphagia is indeed characteristic of PD patients. Fifth, there are several reports of dissociation between subjective awareness of dysphagia and objective measurement using VFSS (Kalf et al. 2012; Ertekin 2014). Therefore, it is possible that the classification of the subjective dysphagia group using the questionnaire in our study did not fully reflect a PD dysphagia group. Finally, in this study, all of the patients received dopaminergic medication; dopamine is well known to modulate cholinergic excitability, specifically SAI. Martorana et al. (2009, 2013) reported that dopamine agonists and L-DOPA affect cortical excitability and central cholinergic function in Alzheimer's disease patients. Dopaminergic medication has also been shown to improve swallowing dysfunction in PD patients, as previously described. Therefore, although we intended to control some variables that could influence SAI (%) and swallowing dysfunction in PD, the data in our study should be interpreted cautiously.

In conclusion, our electrophysiological and VFSS findings in PD patients support the hypothesis that cholinergic dysfunction is associated with dysphagia in early PD and that an abnormal SAI value might be a good marker to determine the risk of dysphagia and to detect subclinical dysphagia in PD patients. Furthermore, cholinergic dysfunction may be a therapeutic target for dysphagia in PD patients.

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Compliance with ethical standards

Conflict of interest The authors have reported no potential conflicts of interest concerning this article and have equally contributed to this study in a meaningful manner. None of the authors have anything to disclose.

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