Characterization of Corticobulbar Pharyngeal Neurophysiology in Dysphagic Patients With Parkinson's Disease

Emilia Michou,[*] Shaheen Hamdy,[*] Mary Harris,[*] Adil Vania,[*] Jeremy Dick,[‡] Mark Kellett,[‡] and John Rothwell[§]

*Centre for Gastrointestinal Sciences, Institute of Inflammation and Repair, University of Manchester, Manchester Academic Health Sciences Centre, Salford Royal Hospital, Salford; [‡]Department of Neurology, Salford Royal Hospital National Health System (NHS) Trust, Salford; and [§]Institute of Neurology, University College London, London, United Kingdom

BACKGROUND & AIMS: **Dysphagia in patients with Parkinson's disease, persisting despite dopaminergic treatment, affects intake of nutrients and medication, and reduces quality of life (QOL). We investigated the neurophysiologic mechanisms that contribute to dysphagia in these patients, on and off L-3,4-dihydroxyphenylalanine (levodopa), using transcranial magnetic stimulation.**

METHODS: **We studied 26 patients with Parkinson's disease (age, 65 ± 9 y; 10 men). Dysphagia and QOL were first assessed with qualitative questionnaires. Twelve hours after patients were taken off levodopa, they underwent cortical transcranial magnetic stimulation mapping of the pharyngeal musculature and trigeminal (bulbar) transcranial magnetic stimulation, as well as videofluoroscopy to examine swallowing. The analyses were repeated after administration of levodopa.**

RESULTS: **Eleven patients initially reported dysphagia and reduced QOL scores. Videofluoroscopy identified 10 patients with swallowing impairments on and off levodopa, and 6 patients with swallowing impairments only on levodopa; the remaining 10 subjects showed no swallowing impairments, on or off the drug. While patients were on levodopa, those with swallowing impairments had bilateral increases in pharyngeal cortical excitability compared with those with no swallowing impairment ($P < .05$). By contrast, with medication, amplitudes of brainstem reflexes were altered only in patients with swallowing impairments on levodopa; these were decreased compared with when the patients were off levodopa.**

CONCLUSIONS: **In patients with Parkinson's disease, dopaminergic medications such as levodopa can negatively affect swallowing. The increased cortical excitability observed in dysphagic patients after they begin taking levodopa likely results from compensatory mechanisms, perhaps secondary to subcortical disease, because we observed associated inhibition of brainstem reflexes in patients with affected swallowing on medication. UK clinical trials registration no., 9882.**

Keywords: Neurodegeneration; Compensation; Brain; Nervous System.

At least a third of patients diagnosed with Parkinson's disease (PD) experience swallowing impairment,[1] with consequent difficulties in oral consumption of medications and nutrient intake. Swallowing difficulties in PD may increase the risk of aspiration pneumonia,[2,3] which inevitably reduces quality of life.[4,5]

Although several mechanisms are proposed to explain the pathophysiology of PD,[6] its neuropathology has been attributed mainly to disorganization of basal ganglia circuits via dopaminergic neuronal connections in the substantia nigra.[7] However, an explanation of the mechanisms of dysphagia in PD still largely is undefined.

Recently, evidence from studies in rodents has shown that unilateral lesioning of nigrostriatal pathways resulted in deficits of cranial-oromotor function, which is important for swallowing and voice production.[8] Equally, histologic and histochemical studies showed the presence of denervated and atrophied pharyngeal fibers in

Abbreviations used in this paper: ANOVA, analysis of variance; CoG, center of gravity; ED, Euclidian distance; EMG, electromyography; HADS, Hospital Anxiety and Depression Scale; levodopa, L-3,4-dihydroxyphenylalanine; M1, motor cortex; MT, motor threshold; NSI, no swallowing impairment; PA, penetration-aspiration; PD, Parkinson's disease; PMEP, pharyngeal motor evoked potential; QOL, quality of life; SDQ, Swallowing Disturbance Questionnaire; SI, swallowing impairments both on and off medication; SIon, swallowing impairment only on medication; SWAL-QOL, Swallowing Quality of Life Questionnaire; TMS, transcranial magnetic stimulation; VFS, videofluoroscopy.

1542-3565/$36.00
http://dx.doi.org/10.1016/j.cgh.2014.03.020

tissue preparations of previously dysphagic deceased PD patients[9] and a higher density of α-synuclein lesions in pharyngeal motor branches compared with nondysphagic PD patients.[10]

However, some physiological studies have shown that dopaminergic medication (L-3,4-dihydroxyphenylalanine [levodopa]), prescribed to enhance synaptic dopamine transmission, does not benefit swallowing.[11,12]

Moreover, an on-medication imaging study with magneto-encephalography in PD patients with and without dysphagia showed that although both groups had reduced cortical activation compared with healthy individuals, there were distinct differences between the 2 PD groups. Nondysphagic patients showed a shift and reduction in activation of the supplementary motor area that was not seen in PD patients with dysphagia; this led to the speculation that PD patients showed adaptive compensatory cerebral changes contributing to the maintenance of preserved swallowing.[13]

Therefore, there is uncertainty about the impairment of swallowing and the underlying neurophysiological mechanisms of swallowing while on and off medication in PD. Such information is important for the timely assessment, application of therapeutic interventions for dysphagia, and any potential adjustment of medicinal prescriptions for patients with PD.[3]

Here, we investigated the effects of levodopa on the neurophysiology (corticobulbar) and trigeminal pathways to pharyngeal musculature, and on swallowing safety in PD patients with and without swallowing impairments. Our hypothesis was that a corticobulbar mechanism would explain behavioral differences in dysphagia severity in PD, and that it would be modulated by levodopa.

Methods

Population

Thirty participants recruited from neurology clinics with the support of the Dementias and Neurodegenerative Diseases Research Network between May 2011 and July 2012 consented to participate in the study. All participants met the inclusion criteria: age 35 to 80 years, diagnosed with idiopathic PD, verified according to UK Parkinson's Disease Society Brain Bank, and disability II to IV on the Hoehn and Yahr scale.[14] The exclusion criteria included the following: a history of epilepsy; cardiac pacemaker; previous brain or ear, nose, and throat surgery; signs of upper motor neuron disease; results in mini-mental state examination of less than 24; pregnancy; and any metal in the head or eyes.

Twenty-six participants completed the study; 4 subjects withdrew consent before assessments. The mean age of the remaining group (17 men, 9 women) (demographics are shown in Supplementary Table 1) was 65 $\pm$ 9 ($\pm$SD) years of age, with a mean duration of levodopa treatment of 5 $\pm$ 1 years.

All patients completed the Swallowing Disturbance Questionnaire (SDQ)[15] and Swallowing Quality of Life Questionnaire (SWAL-QOL),[16] which are validated in PD, before the study day. All patients were unaware of their scores during the study.

All experiments took place in the Centre for Gastrointestinal Sciences laboratories at Salford Royal National Health System Hospital (UK), in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). The research protocol (United Kingdom Clinical Research Network identification number: 9882) was approved by the Greater Manchester South Research Ethics Committee.

All authors had access to the study data and reviewed and approved the final manuscript.

Procedures

Transcranial magnetic stimulation. Focal transcranial magnetic stimulation (TMS) was performed using a flat figure-of-eight–shaped magnetic coil (outer diameter, 70 mm) for corticobulbar stimulation and a smaller-diameter coil (50 mm) for cranial nerve stimulation, connected to a Magstim Bistim^2 magnetic stimulator (Magstim Company, Whitland, UK), which produced a maximal output of 2.2 T.[17]

Pharyngeal electromyography measurements. Pharyngeal motor-evoked potentials (PMEPs) after single TMS pulses were recorded through a 3.2-mm–diameter intraluminal catheter (Gaeltec Ltd, Dunvegan, Isle of Skye, Scotland), with a built-in pair of bipolar platinum ring electrodes, inserted either nasally (15–17 cm from the nasal flare) or orally (13–15 cm) depending on the subject's preference, allowing PMEP recordings at the midpharyngeal level and middle pharyngeal constrictors.[18]

Videofluoroscopy. A research videofluoroscopy (VFS) was performed in the Radiology Department at the Salford Royal National Health System (UK) with 6 swallows of 5-mL boluses of thin liquid barium (60% wt/vol, EZ-HD; E-Z-EM Limited, Bicester Oxfordshire, UK) and images were acquired in the lateral view (Siemens Fluorospot; Sireskop SX Unit, Erlangen, Germany).

Experimental Protocol

PD patients visited the laboratory on a single occasion, after withdrawal from levodopa for at least 12 hours. The Hospital Anxiety and Depression Scale (HADS)[19] was completed, and the pharyngeal catheter was inserted as described earlier. VFS still images were acquired to verify electrode positioning (also serving as a control for subsequent placement). The participants sat comfortably in a reclining chair with the pharyngeal catheter in situ. The cranial vertex was identified[20] and marked on the scalp followed by the application of 2 predetermined 7-cm $\times$ 5-cm scalp grid maps, positioned 2 cm laterally to the vertex