Progression of Dysarthria and Dysphagia in Postmortem-Confirmed Parkinsonian Disorders

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Background: Dysarthria and dysphagia are known to occur in parkinsonian syndromes such as Parkinson disease (PD), dementia with Lewy bodies (DLB), corticobasal degeneration (CBD), multiple system atrophy (MSA), and progressive supranuclear palsy (PSP). Differences in the evolution of these symptoms have not been studied systematically in postmortem-confirmed cases.

Objective: To study differences in the evolution of dysarthria and dysphagia in postmortem-confirmed parkinsonian disorders.

Patients and Methods: Eighty-three pathologically confirmed cases (PD, n=17; MSA, n=15; DLB, n=14; PSP, n=24; and CBD, n=13) formed the basis for a multicenter clinicopathological study organized by the National Institute of Neurological Disorders and Stroke, Bethesda, Md. Cases with enough clinicopathological documentation for the purpose of the study were selected from research and neuropathological files of 7 medical centers in 4 countries (Austria, France, England, and the United States).

Results: Median dysarthria latencies were short in PSP and MSA (24 months each), intermediate in CBD and DLB (40 and 42 months), and long in PD (84 months). Median dysphagia latencies were intermediate in PSP (42 months), DLB (43 months), CBD (64 months), and MSA (67 months), and long in PD (130 months). Dysarthria or dysphagia within 1 year of disease onset was a distinguishing feature for atypical parkinsonian disorders (APDs) (specificity, 100%) but failed to further distinguish among the APDs. Survival time after onset of a complaint of dysphagia was similar in PD, MSA, and PSP (15 to 24 months, P=.7) and latency to a complaint of dysphagia was highly correlated with total survival time (p=0.88; P<.001) in all disorders.

Conclusions: Latency to onset of dysarthria and dysphagia clearly differentiated PD from the APDs, but did not help distinguish different APDs. Survival after onset of dysphagia was similarly poor among all parkinsonian disorders. Evaluation and adequate treatment of patients with PD who complain of dysphagia might prevent or delay complications such as aspiration pneumonia, which in turn may improve quality of life and increase survival time.

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Dysarthria and dysphagia are well-recognized complications of parkinsonian disorders such as Parkinson disease (PD),1 multiple system atrophy (MSA),2 dementia with Lewy bodies (DLB),3 corticobasal degeneration (CBD),3 and progressive supranuclear palsy (PSP).3 However, to our knowledge, the temporal evolution of dysarthria and dysphagia has never been explored systematically in these disorders. Therefore, we retrospectively analyzed the temporal evolution of dysarthria and dysphagia, as well as the median survival time of these symptoms after symptom onset, and the correlation between latency to dysphagia and total survival time in patients with postmortem-confirmed PD, MSA, DLB, CBD, and PSP. Furthermore, we investigated whether the early appearance of dysarthria or dysphagia (within 1 year of disease onset) could improve the accuracy of diagnosis of these disorders as measured by sensitivity and specificity.

The main demographic characteristics are shown in Table 1. The proportion of dysarthria was similar in all patient groups (P=.50), ranging from 72% to 100% (DLB,
METHODS

SAMPLE AND DATA COLLECTION

Eighty-three pathologically confirmed parkinsonian disorders (PD, n=17; MSA, n=15; DLB, n=14; PSP, n=24; and CBD, n=13) formed the basis for a multicenter clinicopathological study organized by the National Institute of Neurological Disorders and Stroke, Bethesda, Md, to improve the differential diagnosis of parkinsonian disorders. Eighty-three of 144 clinicopathological cases selected from research and neuropathological files of 7 medical centers in 4 countries (Austria, France, England, and the United States) were included in the study because they had sufficient documentation of the studied clinical features. The information considered was abstracted from medical records by neurologists who were blinded to the pathological diagnosis and who used predefined criteria recorded the information in standardized forms. The cases met the neuropathological criteria of the National Institute of Neurological Disorders and Stroke for the diagnosis of PSP and related disorders8 and the guidelines of McKeith et al9 for the diagnosis of DLB. Eighty percent of the DLB cases were referred from a dementia clinic. Time to onset of a speech disorder diagnosed by the treating neurologist and latencies to subjective swallowing difficulties reported by the patients were recorded. Duration until death was determined by retrospective chart review.

When the dysarthria was first noted, all patients with PD were benefiting from levodopa replacement therapy (median daily dose, 600 mg [range, 200-1000 mg/d]), whereas only 33% of the 49% patients with atypical parkinsonian disorders (APDs) who were receiving levodopa benefited.

STATISTICS

Data are expressed as median values throughout the text. Pearson χ², nonparametric 1-way analysis of variance (Kruskal-Wallis test), Mann-Whitney U tests, and the Spearman ρ test were used for statistical analysis, as appropriate. Box-plots were applied to determine the distribution of latency data across the groups. Analyses of covariance (general linear model) were performed to investigate the possible effects of (1) diagnosis, (2) age at onset, (3) severity of parkinsonism according to Hoehn and Yahr stages at the last clinic visit (median, 5 months before death), (4) presence of dementia according to Diagnostic and Statistical Manual of Mental Disorders, Third Edition,9 criteria, (5) latency to onset of dysarthria, and (6) latency to onset of dysphagia on total survival time after symptom onset. The diagnostic accuracy of a predefined latency (clinical onset of dysarthria and dysphagia within 12 months from symptom onset) was evaluated by analyzing sensitivity and specificity.

However, the proportion of subjective dysphagia differed significantly (P=.01) among the 5 disorders (DLB, 21%; CBD, 31%; PD, 41%; MSA, 73%; and PSP, 83%); between-group differences were significant for DLB vs MSA (P=.005); DLB vs PSP (P=.001); CBD vs PSP (P=.01); and PD vs PSP (P=.005). Comparison of median latencies to onset of dysarthria revealed significant differences among patient groups (P=.02). Dysarthria latencies were short in PSP and MSA (24 months each), intermediate in CBD and DLB (40 and 42 months), and long in PD (84 months). Direct group analysis showed significantly longer latencies to dysarthria in patients with PD than in those with PSP (P=.009) or MSA (P=.01) (Figure 1). Dysarthria profiles differed among the disorders as follows: hypophonic/monotonous speech predominated in DLB (70%) and PD (73%), whereas imprecise or slurred articulation predominated in MSA (71%), CBD (75%), and PSP (88%). At the last clinical visit (median, 5.0 months before death), severe speech impairment, defined as unintelligible speech (score, 4) according to the Unified Parkinson’s Disease Rating Scale,10 was variably present in PD (18%), DLB (29%), CBD (31%), PSP (46%), and MSA (60%).

Median latencies to subjective dysphagia differed significantly among patient groups (P=.04), with intermediate latencies in PSP (42 months), DLB (43 months), CBD (64 months), and MSA (67 months) and long latencies in PD (130 months, Figure 2). Post hoc analysis revealed significantly longer latencies to dysphagia in patients with PD than in those with PSP (P=.006) or MSA (P=.02).

With the exception of 1 patient with CBD, dysphagia occurred only in parkinsonian patients with concomitant dysarthria. Latencies to dysphagia after onset of dysarthria were significantly longer in PD than in APDs (P=.05, Table 2). The median survival time between onset of dysphagia and death was similarly short in PD, MSA, and PSP, ranging from 15 to 24 months (P=.70, Table 2). Accordingly, latency to dysphagia was significantly correlated with total survival time (Spearman ρ=0.88; P<.001) in all parkinsonian disorders (Figure 3), and analyses of covariance revealed that total survival was associated only with latency to dysphagia (P<.001). However, after dysphagia latency as a covariate was eliminated, age at onset (P=.002), latency to dysarthria (P=.005), and diagnosis (P=.04) all showed a significant effect on survival, while no significant effect of Hoehn and Yahr stage and survival was observed (P=.80).

None of the patients with PD developed dysarthria within the first year of disease onset. Therefore, early dysarthria (≤12 months after disease onset) was a characteristic feature in APDs (specificity, 100%). In contrast, diagnostic sensitivity was low in APDs (19%), and highest in MSA (27%), followed by PSP (25%), CBD (8%), and DLB (7%). Dysphagia was reported by only 2 patients with PSP and 1 patient with MSA during the first year of disease onset (specificity, 100% for APDs), representing a poor diagnostic sensitivity of 8% and 7%, respectively.
This study has several limitations. First, the different parkinsonian disorders were diagnosed pathologically; therefore, data were obtained retrospectively and the neurologists evaluating these patients did not follow a protocol that had been agreed on. Second, because of the rarity of the APDs, the sample was not population based, and may not be representative of patients with APDs in the population. Despite these limitations, these data permitted the identification of important differences in the frequency and time course of dysarthria and dysphagia among parkinsonian disorders. In fact, to our knowledge, this study is the first to investigate and compare the progression of dysarthria and dysphagia in postmortem-confirmed parkinsonian disorders, including PD, CBD, DLB, MSA, and PSP. Except in PSP,\textsuperscript{11,12} the association between dysarthria and dysphagia and their correlation with survival have not yet been investigated in parkinsonian disorders, and we could find no published data on the frequency and progression of dysphagia in DLB and CBD.

Our analysis in cases of postmortem-confirmed parkinsonian disorders corroborates the theory that early dysarthria and perceived swallowing dysfunction are not features of PD. However, when one or both features were present, the sensitivity and specificity of their early occurrence within the first year failed to further distinguish among the various APDs. In agreement with the findings of previous studies, dysarthria was frequently observed in all patient groups,\textsuperscript{2,4,13-15} with significantly longer latencies in PD than in MSA and PSP. Similar to our findings, dysarthria as a presenting symptom has been described in clinical series of CBD,\textsuperscript{4} MSA,\textsuperscript{14} and PSP.\textsuperscript{16} In PD and DLB, hypophonic/monotonous speech represented the most frequent type of dysarthria, whereas imprecise or slurred articulation predominated in CBD, MSA, and PSP, in accordance with the literature.\textsuperscript{4,17,18}

In a clinical study of CBD, Rinne et al\textsuperscript{4} described dysarthria as one of the initial symptoms in 11% of the patients, which is close to our findings. At follow-up, on average 5.2 years, dysarthria was diagnosed in 70% of the patients.\textsuperscript{4} In a recent study of 147 CBD cases,
including 7 autopsy-confirmed cases, dysarthria was noted only in 29% of patients, but there was no information on disease duration.\textsuperscript{19} According to our findings, dysarthria occurred in almost every patient with CBD.

Golbe et al\textsuperscript{11} reported comparable intervals to dysarthria in a clinical series of 50 cases of PSP, including 4 pathologically confirmed cases. In agreement with our results, Quinn\textsuperscript{12} described the speech of patients with MSA as more severely affected than that of patients with PD, with slurring dysarthria, as well as the low volume and monotone of parkinsonism. In both PSP and MSA, progressive dysarthria is believed to represent a manifestation of brainstem and cerebellar involvement.\textsuperscript{18,20} In fact, positron emission tomography studies revealed marked hypometabolism in the cerebellum and brainstem of patients with MSA, which correlated with dysarthria.\textsuperscript{21}

In our study, dysphagia was associated with concomitant dysarthria in all parkinsonian patients except one. This sequence of dysphagia following dysarthria has also been reported in clinical series of PD, MSA, and PSP.\textsuperscript{11,14} In a clinical study of swallowing abnormalities in PSP, objective assessments of swallowing dysfunction were also associated with overall speech impairment, and voice and articulation were among other features identified as predictors of abnormal swallowing; however, dysarthria was not always paired with dysphagia in the same patient.\textsuperscript{12} Comparable to our results, Golbe et al\textsuperscript{11} reported dysphagia after a median of 1 year after the onset of dysarthria in PSP.

Median latencies to dysarthria and subjective dysphagia were at least twice as long in PD than in APDs, including DLB (Table 1). Total survival time, as well as survival time after onset of dysarthria, was significantly longer in PD; however, the onset of dysphagia predicted a similarly short remaining median survival time in MSA, PSP, and PD (Table 2). Furthermore, latencies to dysphagia were highly correlated with overall survival time in all parkinsonian disorders (Figure 3). These important findings suggest that the perceived swallowing dysfunction in PD and APDs indicates functionally relevant dysphagia. Indeed, in PD,\textsuperscript{22} DLB,\textsuperscript{3} CBD,\textsuperscript{23} MSA,\textsuperscript{24} and PSP,\textsuperscript{12} bronchopneumonia has been reported as a leading cause of death, which may be subsequent to silent aspiration resulting from dysphagia.\textsuperscript{12} Evaluation and adequate treatment of parkinsonian patients who complain of dysphagia might thus prevent or delay complications such as aspiration pneumonia and increase survival time in these patients. Also, an appropriate and timely swallowing evaluation may provide patients and caregivers with techniques and resources that may in turn improve their quality of life (eg, straws, food thickeners, and percutaneous endoscopic gastrostomy).\textsuperscript{12}

Most of our patients with MSA and PSP complained of a swallowing dysfunction, in contrast to patients with PD, CBD, and DLB. In PD, the reported prevalence of dysphagia varies from 18.5% to 100%,\textsuperscript{24-26} depending on the measurement method. Investigators who carried out assessment with barium swallow found abnormalities in all study patients with PD,\textsuperscript{1} and complaints of dysphagia in patients with PD were found to correlate poorly with radiologic and videofluoroscopic findings.\textsuperscript{1,27,28} Impaired lingual proprioception is hypothesized to contribute to the unawareness of swallowing difficulties in PD and might in part explain significantly longer latencies to dysphagia in our PD cases. In contrast, patients with PSP were reported to be keenly aware of swallowing problems,\textsuperscript{18} including those with cognitive impairment.\textsuperscript{12} In a clinical study on swallowing abnormalities in PSP, Litvan et al\textsuperscript{12} reported abnormal results on modified barium swallow or ultrasound studies in 96% of patients, which exceeds the 83% dysphagia in our PSP cases, a finding that is probably related to the higher sensitivity of objective measurements. However, the similarly short remaining survival time in PD and PSP after the onset of perceived dysphagia suggests that this symptom represents a reliable marker for the onset of functionally relevant swallowing abnormalities in both disorders. Similar to PSP, dysphagia within the first year of disease onset was observed in MSA, and dysphagia represented a frequent complaint in MSA. Comparable to our results, dysphagia was among the first clinical symptoms in 1 of 18 cases of probable MSA.\textsuperscript{13}

Table 2. Median Latencies to Dysphagia After Onset of Dysarthria and Duration Until Death in Postmortem-Confirmed Parkinsonian Disorders\textsuperscript{*}

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Latencies From Dysarthria Until Dysphagia, mo</th>
<th>Survival Time After Onset of Dysarthria, mo</th>
<th>Survival Time After Onset of Dysphagia, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD</td>
<td>64 (0-124)</td>
<td>85† (8-124)</td>
<td>24 (2-61)</td>
</tr>
<tr>
<td>CBD</td>
<td>22 (0-53)</td>
<td>41 (8-78)</td>
<td>49 (23-89)‡</td>
</tr>
<tr>
<td>DLB</td>
<td>23 (0-45)</td>
<td>48 (8-276)</td>
<td>10 (3-17)‡</td>
</tr>
<tr>
<td>MSA</td>
<td>12 (0-73)</td>
<td>36 (12-100)</td>
<td>15 (6-68)</td>
</tr>
<tr>
<td>PSP</td>
<td>6 (0-50)</td>
<td>44 (6-150)</td>
<td>18 (6-96)</td>
</tr>
</tbody>
</table>

\textsuperscript{*}PD indicates Parkinson disease; CBD, corticobasal degeneration; DLB, dementia with Lewy bodies; MSA, multiple system atrophy; and PSP, progressive supranuclear palsy. Numbers in parentheses are ranges. 
†Significant difference between PD and atypical parkinsonian disorders, P<.05. 
‡Includes a single patient with dysphagia but without dysarthria.

Figure 3. Correlation between latency to dysphagia and total survival time in postmortem-confirmed parkinsonian disorders (Spearman \( p=0.88; \) P<.001).
In DLB, dysphagia was noticed by only 21% of patients, but after a median latency of 43 months since disease onset, which was similar to the latency in PSP and only one third of the median latency to dysphagia in PD (Table 1). In a study of 9 postmortem-confirmed DLB cases, Hely et al.\(^\text{11}\) reported dysphagia in only 1 patient (11%); similarly, Burkhart et al.,\(^\text{29}\) in a review of 34 postmortem cases, including 4 previously unpublished DLB cases, reported dysphagia in 12% of the cases, without information on symptom latency. However, in most clinicopathological studies, dysphagia was not mentioned.\(^\text{8,30-33}\) The short latency to dysphagia in our DLB cases might be explained by the fact that there are more widespread Lewy body lesions in DLB than in PD; however, a higher prevalence of swallowing disturbances should be expected. The discrepancy between the low proportion and short latency to subjective dysphagia might in part be attributable to dementia interfering with the perception or reporting of swallowing dysfunction in DLB. Notably, the median survival time after the onset of subjective dysphagia in DLB was only 10 months and was thus shorter than in all other parkinsonian disorders. These findings indicate that some patients with DLB develop early and severe dysphagia with reduced survival time. However, these latency data should be interpreted cautiously due to the limited number of cases and deserve further investigation.

In CBD, dysphagia was noticed in 31% of our cases after a median disease duration of 64 months. Dysphagia in CBD is believed to result from bulbar dysfunction, which is uncommon initially, but often appears after several years of disease.\(^\text{34}\) Accordingly, none of our patients with CBD noticed early dysphagia (Table 1). To our knowledge, dysphagia has not yet been investigated systematically in CBD, and the 2 largest studies of CBD, by Kompoliti et al.\(^\text{19}\) (147 cases) and Rinne et al.\(^\text{4}\) (36 cases), provided no data on frequency or latency of dysphagia.

Our findings of increased latency to dysarthria and dysphagia and similar time interval from onset of dysphagia to death in patients with PD compared with patients with APDs suggest that extrastriatal and nondopaminergic lesions represent an important factor for the development of dysarthria and dysphagia. Indeed, Bonnet et al.\(^\text{35}\) reported that dysarthria, gait, and postural stability had a decreased levodopa response in patients with long-standing PD who still benefited from the levodopa effects on tremor, rigidity, and akinesia. Whereas the APDs are characterized by multiple system neuronal degenerations, in PD disease progression is determined by a progressive dopaminergic deficit arising from the selective neuronal degeneration of the substantia nigra pars compacta. It may be the overall degenerative lesion load in excess of the dopaminergic projection that shortens the onset of axial features, such as dysarthria and dysphagia, and therefore predicts poor survival in patients with PD. However, the presence of distinct neuropathological lesion patterns in these disorders suggests that disease-specific factors may contribute to the pathophysiological processes underlying dysarthria and dysphagia.

In conclusion, our study demonstrates that the latency to the onset of dysarthria and dysphagia, as well as the duration of dysarthria, differentiates patients with PD from those with APDs, but not among those with APDs, while survival after onset of a complaint of dysphagia was similarly poor in those with PD and APDs.

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REFERENCES


