RESEARCH ARTICLE

# Endoscopic Characteristics of Dysphagia in Multiple System Atrophy Compared to Parkinson's Disease


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**ABSTRACT: Background:** Dysphagia is a major clinical concern in multiple system atrophy (MSA). A detailed evaluation of its major endoscopic features compared with Parkinson's disease (PD) is lacking.
**Objective:** This study systematically assessed dysphagia in MSA compared with PD and correlated subjective dysphagia to objective endoscopic findings.
**Methods:** Fifty-seven patients with MSA (median, 64 [interquartile range (IQR): 59–71] years; 35 women) underwent flexible endoscopic evaluation of swallowing using a specific MSA–flexible endoscopic evaluation of swallowing task protocol. Findings were compared with an age-matched cohort of 57 patients with PD (median, 67 [interquartile range: 60–73] years; 28 women). In a subcohort, subjective dysphagia was assessed using the Swallowing Disturbance Questionnaire and correlated to endoscopy findings.
**Results:** Patients with MSA predominantly showed symptoms suggestive of oral-phase disturbance (premature spillage, 75.4%, piecemeal deglutition, 75.4%). Pharyngeal-phase symptoms occurred less often (pharyngeal residues, 50.9%; penetration/aspiration, 28.1%). In contrast, pharyngeal symptoms were the most common finding in PD (pharyngeal residues, 47.4%). Oral symptoms occurred less frequently in PD (premature spillage, 15.8%, $P < 0.001$; piecemeal deglutition, 1.8%, $P < 0.01$). Patients with MSA had a greater risk for oral-phase disturbances with increased disease severity ($P < 0.05$; odds ratio, 3.15). Patients with MSA showed a significantly higher intraindividual interswallow variability compared with PD. When correlating Swallowing Disturbance Questionnaire scores with endoscopy results, its cutoff, validated for PD, was not sensitive enough to identify patients with MSA with dysphagia. We developed a subscore for identifying dysphagia in MSA and calculated a new cutoff (sensitivity 85%, specificity 100%).
**Conclusions:** In contrast with patients with PD, patients with dysphagic MSA more frequently present with oral-phase symptoms and a significantly higher intraindividual interswallow variability. A novel Swallowing Disturbance Questionnaire MSA subscore may be a valuable tool to identify patients with MSA with early oropharyngeal dysphagia. © 2021 The Authors. *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society

**Key Words:** multiple system atrophy; dysphagia; FEES; Swallowing Disturbance Questionnaire; SDQ

Multiple system atrophy (MSA) is a rapidly progressing sporadic neurodegenerative disorder, clinically characterized by autonomic dysfunction combined with motor impairment of either predominant parkinsonian (MSA-P) or cerebellar symptoms (MSA-C).[1] Early in the course of the disease, delineation of its parkinsonian phenotype from idiopathic Parkinson's disease (PD) is challenging.[2]



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**Relevant conflicts of interest/financial disclosures:** Nothing to report.

Full financial disclosures and author roles may be found in the online version of this article.

**Received:** 20 April 2021; **Revised:** 17 September 2021; **Accepted:** 2 October 2021

**Published online 13 November 2021 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.28854**

Dysphagia is a major clinical concern in MSA, occurring in up to 73% of patients.[3-6] It may lead to malnutrition and dehydration, facilitates aspiration pneumonia, whereby determining the disease prognosis,[6-8] and is considered a factor for sudden death.[9,10] Compared with PD, the onset of dysphagia is earlier in the course of MSA.[3,11] Therefore, timely identification of dysphagia and intervention is essential to avoid complications. Nevertheless, studies objectively evaluating dysphagia in MSA are rare, and symptoms so far were assessed only by videofluoroscopic swallowing studies (VFSSs), manometric methods, or electrophysiological methods in small cohorts.[4,11-16]

Recently, flexible endoscopic evaluation of swallowing (FEES) has emerged as a standard tool for objective swallowing assessment in neurogenic dysphagia[17-19] and is key for the evaluation of oropharyngeal dysphagia following previously published guidelines.[20] Endoscopic characteristics of MSA-related dysphagia have so far not been systematically examined and compared with PD. In this regard, we previously suggested a standardized, easy-to-implement MSA-FEES task protocol to systematically assess laryngeal motion abnormalities and dysphagia symptoms in patients with MSA. A pilot study showed that the task protocol was feasible and well tolerated.[21] Furthermore, we recently showed that patients with MSA present with MSA-specific laryngeal motion abnormalities when using this task protocol, allowing for a highly sensitive and specific delineation from patients with PD.[22]

The Swallowing Disturbance Questionnaire (SDQ), a self-reporting 15-item questionnaire, has emerged as a validated screening method for early detection of dysphagia in PD[23] and other disease etiologies.[23] Although dysphagia is an important symptom when assessing the medical history of patients with MSA,[5,24] studies evaluating subjective dysphagia symptoms assessed by the SDQ and related to an objective swallowing assessment such as FEES have so far not been done in MSA.

In this study, we assessed dysphagia in an MSA cohort using FEES and the aforementioned MSA-FEES task protocol. Our goal was to investigate endoscopic characteristics of dysphagia and dysphagia severity in patients with MSA compared with patients with PD. We furthermore intended to assess whether endoscopic characteristics of dysphagia differed between MSA phenotypes. Moreover, we assessed subjective dysphagia symptoms using the SDQ and examined whether this questionnaire was suitable for detecting dysphagia in patients with MSA.

## Patients and Methods

This observational study was approved by the Ethics Committee of the Brandenburg Medical Board (S21 (a)/2017) and the University of Münster (2017-585-b-S) and was registered in the Fox Trial Finder (https://www.michaeljfox.org/trial-finder; trial number: 005066).

### Participants

Participants were recruited at two German hospitals specialized in the diagnosis and treatment of movement disorders. Between September 2017 and January 2020, 57 consecutive patients with MSA and 57 consecutive patients with PD were included. Participants were diagnosed with either possible or probable MSA-P or MSA-C according to the second consensus criteria,[24] or they met the diagnosis of PD according to the Movement Disorders Society diagnostic criteria.[25] All participants provided written informed consent.

Disease severity was measured using the motor score of the Unified Parkinson's Disease Rating Scale-motor, Part III and the Hoehn & Yahr (H&Y) stage. Cerebral magnetic resonance imaging (MRI) scans of patients with MSA were assessed for MSA-related imaging findings such as atrophy either in the putamen, cerebellum, pons, or middle cerebellar peduncle, according to the diagnostic criteria.[24]

### Procedures

All participants underwent FEES, and the procedure was video recorded. Three raters (A.V., F.G., and I.C.), all blinded to the patients' diagnosis, performed post hoc video analyses. FEES equipment consisted of a 3.9-mm-diameter (ENF-VH; Olympus, Shinjuku, Japan) or 3.5-mm-diameter (Storz 11,101 RP2; Karl Storz, Tuttlingen, Germany) flexible fiberoptic rhinolaryngoscope with a video processor (Olympus CV-170; Olympus, Shinjuku, Japan) and processing software (rpSzene 10.7 g on Panel-PC-226/227; Rehder/Partner, Hamburg, Germany), or a 2.9 mm-diameter flexible fiberoptic rhinolaryngoscope with a portable video processor linked to a 19-inch flat-screen monitor (CMOS, CMAC and 9519NB; Karl Storz, Tuttlingen, Germany).

### FEES Protocol

To investigate dysphagia, we performed a standardized MSA-FEES task protocol as previously described.[21,22] In brief, this protocol is divided into an examination of laryngeal function at rest and during specific task performances followed by a detailed evaluation of swallowing. For the laryngeal assessment, please refer to the previous publications.[21,22] Swallowing was assessed as follows: during FEES, participants received 11 consecutive standardized test boluses in the following order: (1) 3 teaspoons of applesauce (approximately 3 mL each), (2) 1 teaspoon of blue-dyed liquid (approximately 3 mL) to test oral

control of a liquid bolus (task to hold a liquid bolus in the oral cavity until told to swallow), (3) 2 teaspoons of blue-dyed water (approximately 3 mL), (4) one sip of blue-dyed water from a glass or straw, (5) three pieces of buttered soft white bread (about 3-cm square), and (6) one swallow of a placebo tablet (10-mm diameter) ingested with either blue-dyed water or applesauce.

### Outcome Measures

To objectify endoscopic characteristics of dysphagia, we rated three endoscopic swallowing parameters, each on a five-point scale (0–4), for each of the 11 swallowing tasks, as previously described[26]: (1) premature spillage was assessed by describing the bolus position at the moment of initiation of swallowing, where 0 = the bolus is behind the tongue, 1 = the bolus is at the base of the tongue or the valleculae, 2 = the bolus moves to the lateral channels or to the tip of the epiglottis, 3 = the bolus is located in the piriform sinus or touches the laryngeal rim, and 4 = the bolus falls into the laryngeal vestibule; (2) pharyngeal residues were assessed after completion of swallowing, where 0 = no residues, 1 = coating, no pooling, 2 = mild pooling, less than half of the cavities, 3 = moderate pooling, fills the cavities, and 4 = severe pooling, overflows the cavities; and (3) penetration/aspiration events were rated at any time, where 0 = no penetration/aspiration, 1 = penetration with protective reflex, 2 = penetration without protective reflex, 3 = aspiration with protective reflex, and 4 = aspiration without protective reflex. Premature spillage and pharyngeal residues scores ≥ 2 and a penetration/aspiration score ≥ 1 were defined as clinically relevant abnormalities. In addition to these parameters, piecemeal deglutition (more than one swallow needed to clear a bolus from the oral cavity) and premature spillage during the test of oral control of a liquid bolus (spillage of a liquid bolus from the oral cavity before told to swallow) were noted dichotomously (0 = no, 1 = yes).

Dysphagia severity, assessed by FEES, was classified according to a four-point scale (0–3) developed for patients with PD and atypical parkinsonism[27]: 0 = no relevant dysphagia, 1 = mild dysphagia (premature spillage and/or residues without penetration/aspiration events), 2 = moderate dysphagia (penetration/aspiration events of one consistency), and 3 = severe dysphagia (penetration/aspiration events of two or more consistencies). A score ≥ 1 indicates the presence of an endoscopically detected dysphagia.

A subgroup of 29 randomly selected patients with MSA completed the Swallowing Disturbance Questionnaire (SDQ) to examine subjective dysphagia.[40] We scored the 15 items as previously described: 0 = symptom never appears, 1 = appears seldom (≤1/month), 2 = appears often (1–7/week), 3 = appears very often (>7/week); item 15 was scored dichotomously: yes = 0.5, no = 2.5. To be able to additionally calculate relations to positive responses to items, we dichotomized the answers to "yes/no," related to the occurrence of a symptom: 0 = no and a score ≥ 1 = yes. The optimal SDQ cutoff score for detecting dysphagia was previously defined as ≥11 for patients with PD.[23]

### Statistical Analysis

Data were statistically analyzed using R (Release 4.0.3) and Real Statistics Resource Pack software (Release 7.1). For all calculations, the level of significance was set to $P = 0.05$.

Frequencies of endoscopically assessed swallowing parameters were summed up for all swallows in each consistency condition for each group. Swallows from the test of oral control of a liquid bolus and placebo tablet were not included in the overall frequency calculation and were summed up separately. Logistic regression models were calculated with R function glm with binomial family taking "disease duration, disease severity, and group" as predictors. The exponentiated regression coefficients are presented with $P$ values and can be interpreted as odds ratios (ORs) when changing the corresponding variable by one unit and holding the other predictors constant. In case of the statistical special case "complete separation" (if the frequency of a dysphagic symptom equaled zero), the logistic regression model fails to calculate a correct result. We then applied $\chi^2$ tests. For target variables that had more than two ordered categories, ordinal logistic regression was performed with R package MASS. Multiple groups were compared applying the Kruskal–Wallis H test, when the sum of all swallows was analyzed.

For analysis of the correlation between the endoscopic dysphagia severity score and disease duration, disease severity, age, and subjective dysphagia score in the MSA cohort, Spearman's correlation coefficient was calculated. For intraindividual interswallow variability analysis, the variance of swallowing scores of swallows for each food consistency was calculated. For cohort comparison, means were calculated and compared applying an unpaired $t$ test. To calculate the relationship between positive responses to SDQ items and endoscopically detected dysphagia, we performed a $\chi^2$ test and calculated Cramer's phi. In addition, SDQ items showing a positive correlation with dysphagia on FEES were extracted into an MSA-SDQ subscore, and Cronbach's alpha was calculated to evaluate test reliability. A receiver operating characteristic (ROC) analysis was performed to define the optimal cutoff score for the MSA-SDQ subscore.

## Results

The cohort was previously described in detail.[22] In brief, we compared a cohort of patients with MSA

(median, 64 [interquartile range (IQR): 59–71] years) with an age-matched cohort of patients with PD (median, 67 [IQR: 60–73] years; $P = 0.06$). Patients with MSA had a shorter disease duration (median, 4 [IQR: 3–5] vs. 7 [5–10] years; $P < 0.0001$), a higher disease severity (H&Y stage 4 [IQR: 3–4] vs. 3 [2–4]; $P < 0.0001$), and were physically more impaired (Unified Parkinson's Disease Rating Scale-motor, Part III: 35.5 [IQR: 29.8–41.8] vs. 28 [19–36]; $P < 0.01$; Table 1). Cerebral MRI scans of 49 patients with MSA were available for analysis to support the clinical diagnosis. Seventeen of 49 patients did not show any MSA-related imaging findings; 18 of 49 patients presented with one MSA-specific finding, 3 patients showed 2 abnormalities on MRI, 10 patients presented with 3 abnormalities, and 1 patient showed 4 MSA-characteristic MRI changes.

## Endoscopic Characteristics and Severity of Dysphagia

The MSA-FEES task protocol was successfully performed in all participants without any adverse events.

In the MSA cohort, the most frequent dysphagic finding for all food consistencies was premature spillage, observed in 75.4% of patients with MSA, and occurred significantly more often than in PD (15.8%; $P < 0.001$; OR, 24.97). The second most frequent symptom was relevant piecemeal deglutition, which also occurred significantly more often in patients with MSA than in the PD cohort (75.4% vs. 1.8%; $P < 0.01$; OR, 8.63). Also, penetration and aspiration (28.1% vs. 3.5%; $P < 0.01$; OR, 41.93) were observed more frequently in patients with MSA than in the PD cohort. In more detail, 12 patients with MSA (21%; thereof 8 with efficient protective reflex) and 2 patients with PD (3.5%) exhibited penetration events. Aspiration events were observed in four (7%) patients with MSA and two (3.5%) patients with PD. Relevant pharyngeal residues occurred third most in the MSA cohort and in nearly half of the patients in both groups (50.9% vs. 47.37%; $P = 0.16$; OR, 2.27) (Table 2). The linear logistic regression showed overall no influence of disease duration or severity on the dysphagia severity. The calculation solely showed in both the MSA and PD cohorts an influence of disease duration on the occurrence of pharyngeal residues ($P < 0.05$; OR, 0.42) and penetration/aspiration events ($P < 0.05$; OR, 0.42) with semisolid food consistencies. Furthermore, patients with MSA had a greater risk for piecemeal deglutition for all food consistencies with increased disease severity ($P < 0.5$; OR, 3.15). All other dysphagic symptoms were not influenced by disease duration ($P = 0.06$–$0.99$; OR, 0.13–1.34) or disease severity ($P = 0.13$–$0.99$; OR, 0.09–1.98). In 10 cases, $\chi^2$ tests were calculated because of complete separation. Beforehand, the logistic regression model showed no significant effects of disease duration or disease severity. Overall, in the MSA cohort, oral-phase symptoms were significantly more frequent than pharyngeal-phase symptoms. In contrast, patients with PD showed more pharyngeal-phase symptoms, such as pharyngeal residue. Interestingly, we observed no significant differences in the frequency of dysphagic symptoms when comparing the two MSA phenotypes (Table 2). Supporting Information Video S1 shows the most common endoscopic characteristics in patients with MSA.

Each cohort performed 513 swallows in total, with 171 swallows for each consistency. An additional 57 swallows per cohort were evaluated for the test of oral control of a liquid bolus, and another 57 swallows per cohort for swallowing a placebo tablet (Supporting Information Table S1). Similar to the earlier findings, significantly more symptoms suggestive of oral-phase disturbance were found in the MSA cohort, while patients with PD showed pharyngeal-phase symptoms to be more frequent, when all swallows in each group were included in the analysis. Comparisons of the different consistencies tested showed that in both groups, relevant premature spillage was most severe with liquids. The highest degree of relevant pharyngeal residues occurred with solids. Penetration and aspiration events occurred most frequently with liquid bolus consistency. Patients with MSA presented with more disturbances when swallowing placebo tablets compared with the PD cohort. Patients with MSA showed a significantly higher proportion of relevant premature spillage

**TABLE 1.** *Demographic data of cohorts*

| Clinical Characteristics | MSA (n = 57) | PD (n = 57) | *P* |
|---|---|---|---|
| Age, y | 64 (59–71) | 67 (60–73) | 0.06 |
| Women/Men | 35/22 | 28/29 | 0.19 |
| Disease duration, y | 4 (3–5) | 7 (5–10) | <0.0001 |
| Disease severity, Hoehn & Yahr stage | 4 (3–4) | 3 (2–4) | <0.0001 |
| UPDRS III score | 35.5 (29.8–41.8) | 28 (19–36) | <0.01 |

Data are presented as median (interquartile range).
MSA, multiple system atrophy; PD, Parkinson's disease; UPDRS-III, Unified Parkinson's Disease Rating Scale-motor, Part III.

**TABLE 2.** *Dysphagic symptoms as measured by flexible endoscopic evaluation of swallowing in patients with MSA and PD*

| | MSA (n = 57) | | | | |
|---|---|---|---|---|---|
| **Endoscopic Swallowing Parameter** | **MSA-C (n = 12)** | **MSA-P (n = 45)** | **PD (n = 57)** | ***P*** | **OR or $\chi^2$** |
| I. Over all consistencies | | | | | |
| Relevant premature spillage (scores 2–4) | 43/57 (75.44) | | 9/57 (15.79) | <0.001 | 24.97 |
| | 9/12 (75) | 34/45 (75.56) | | 0.48 | 0.54 |
| Relevant pharyngeal residue (scores 2–4) | 29/57 (50.88) | | 27/57 (47.37) | 0.16 | 2.27 |
| | 6/12 (50.0) | 23/45 (51.11) | | 0.77 | 1.21 |
| Penetration/aspiration (scores 1–4) | 16/57 (28.1) | | 2/57 (3.5) | <0.01 | 41.93 |
| | 5/12 (41.7) | 11/45 (24.4) | | 0.13 | 0.34 |
| Piecemeal deglutition | 43/57 (75.4) | | 11/57 (1.8) | <0.01 | 8.63 |
| | 8/12 (66.7) | 35/45 (77.8) | | 0.21 | 2.69 |
| II. Semisolid consistency | | | | | |
| Relevant premature spillage (scores 2–4) | 24/57 (42.1) | | 2/57 (3.5) | <0.001 | 23.1 |
| | 6/12 (50.0) | 16/45 (35.5) | | 0.38 | 0.55 |
| Relevant pharyngeal residue (scores 2–4) | 10/57 (17.54) | | 0/57 (0) | <0.001 | $\chi^2 = 10.96$ |
| | 4/12 (33.33) | 6/45 (13.3) | | 0.1 | 0.23 |
| Penetration/aspiration (scores 1–4) | 3/57 (5.26) | | 1/57 (1.75) | 0.09 | 3.93 |
| | 1/12 (8.33) | 2/45 (4.4) | | 0.1 | 0.24 |
| Piecemeal deglutition | 29/57 (50.88) | | 0/57 (0) | <0.001 | $\chi^2 = 38.89$ |
| | 6/12 (13.33) | 23/45 (51.0) | | 0.92 | 1.07 |
| III. Liquids | | | | | |
| Relevant premature spillage (scores 2–4) | 34/57 (59.65) | | 10/57 (17.54) | <0.001 | 13.5 |
| | 7/12 (58.33) | 27/45 (60.0) | | 0.58 | 1.47 |
| Relevant pharyngeal residue (scores 2–4) | 2/57 (3.5) | | 1/57 (1.75) | 0.9 | 9.83 |
| | 0/12 (0) | 2/45 (4.4) | | 0.9 | $\chi^2 = 8.73$ |
| Penetration/aspiration (scores 1–4) | 12/57 (21.05) | | 2/57 (3.51) | <0.01 | 21.35 |
| | 4/12 (33.33) | 8/45 (17.78) | | 0.3 | 0.46 |
| Piecemeal deglutition | 20/57 (35.09) | | 0/57 (0) | <0.001 | $\chi^2 = 24.26$ |
| | 4/12 (33.33) | 16/45 (35.56) | | 0.69 | 1.31 |
| Disturbed oral control of liquid bolus | 16/57 (28.07) | | 8/57 (14.04) | 0.2 | 2.56 |
| | 4/12 (22.33) | 12/45 (26.67) | | 0.76 | 0.8 |
| IV. Solids | | | | | |
| Relevant premature spillage (scores 2–4) | 12/57 (21.05) | | 0/57 (0) | <0.001 | $\chi^2 = 13.41$ |
| | 2/12 (16.67) | 10/45 (22.22) | | 0.3 | 1.05 |
| Relevant pharyngeal residue (scores 2–4) | 28/57 (49.12) | | 27/57 (47.37) | 0.19 | 2.11 |
| | 6/12 (50.0) | 22/45 (48.89) | | 0.99 | 0.99 |
| Penetration/aspiration (scores 1–4) | 4/57 (7.02) | | 0/57 (0) | 0.13 | $\chi^2 = 2.64$ |
| | 0/12 (0) | 4/45 (8.89) | | 0.53 | $\chi^2 = 2.42$ |
| Piecemeal deglutition | 38/57 (66.67) | | 11/57 (19.3) | <0.01 | 5.59 |
| | 6/12 (50.0) | 32/45 (71.11) | | 0.1 | 3.14 |

*(Continues)*

**TABLE 2.** *Continued*

| Endoscopic Swallowing Parameter | MSA (n = 57) | | PD (n = 57) | *P* | OR or $\chi^2$ |
|---|---|---|---|---|---|
| | MSA-C (n = 12) | MSA-P (n = 45) | | | |
| IV. Tablet swallow | | | | | |
| Relevant premature spillage (scores 2–4) | 11/57 (19.3) | | 0/57 (0) | <0.001 | $\chi^2 = 12.17$ |
| | 3/12 (25.0) | 8/45 (17.78) | | 0.62 | 0.68 |
| Relevant pharyngeal residue (scores 2–4) | 15/57 (26.4) | | 1/57 (1.75) | <0.05 | 1.29 |
| | 4/12 (33.33) | 11/45 (24.44) | | 0.34 | 2.7 |
| Penetration/aspiration (scores 1–4) | 3/57 (5.26) | | 2/57 (3.51) | 0.82 | 1.5 |
| | 3/12 (25.0) | 0/45 (0) | | 0.71 | $\chi^2 = 1.37$ |
| Piecemeal deglutition | 18/57 (31.58) | | 0/57 (0) | <0.001 | $\chi^2 = 21.38$ |
| | 4/12 (33.33) | 14/45 (31.11) | | 0.98 | 1.01 |

*P* values and odds ratio (OR) are results of the logistic regression or $\chi^2$ test in cases of complete separation.
MSA, multiple system atrophy; MSA-C, MSA with cerebellar symptoms; MSA-P, MSA with predominant parkinsonian; PD, Parkinson's disease; OR, odds ratio.

(19.3% vs. 0%; $P < 0.001$) and presented with significantly more relevant pharyngeal residues (24.6%) compared with patients with PD (3.5%; $P < 0.05$) when swallowing the placebo tablet (Supporting Information Table S1).

Not only did the dysphagia pattern differ between the MSA and PD cohorts, patients with MSA showed more pronounced oral-phase disturbances and patients with PD more pronounced pharyngeal-phase disturbances. Patients with MSA also presented with a significantly higher intraindividual interswallow variability, especially for premature spillage and piecemeal deglutition, with both symptoms suggestive of oral swallowing phase disturbance (Supporting Information Table S2). The difference was found for those two symptoms with all food consistencies, while pharyngeal residue differed only with semisolid and liquid boluses. Penetration/aspiration events showed no difference (Supporting Information Table S2).

Dysphagia was observed in 48 of 57 (84.2%) patients with MSA and was observed significantly more frequently than in the PD cohort (45.6%; $P < 0.05$). Moreover, dysphagia scores were higher in patients with MSA than in the PD cohort (1.2 ± 0.7

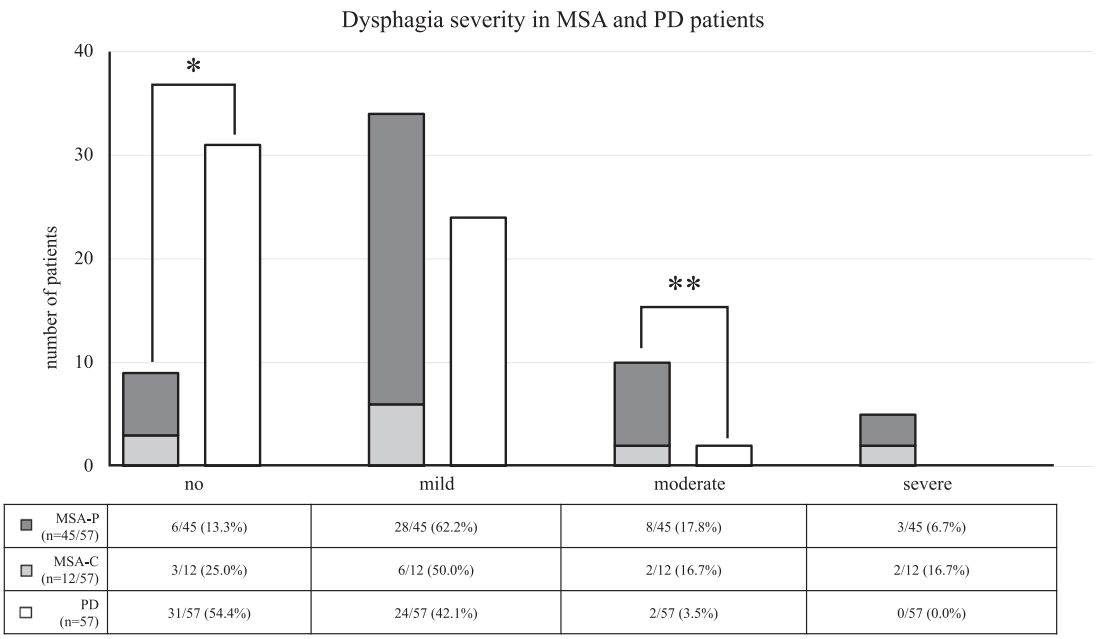


**FIG. 1.** Dysphagia severity as measured by flexible endoscopic evaluation of swallowing in patients with multiple system atrophy (MSA) and Parkinson's disease (PD). Values in n (% of cohort). *$P < 0.05$; **$P < 0.01$. MSA-C, MSA with cerebellar symptoms; MSA-P, MSA with predominant parkinsonian.

**TABLE 3** . *The MSA-SDQ subscore and the correlation of each item with dysphagia detected on flexible endoscopic evaluation of swallowing*

| SDQ Item | Question | *P* |
|---|---|---|
| 1 | Do you experience difficulties chewing solid food like an apple, cookie or cracker? | 0.02 |
| 2 | Are there any food residues in your mouth, cheeks, under your tongue or stuck to your palate after swallowing? | <0.0001 |
| 6 | Do you swallow chewed up food several times before it goes down your throat? | 0.02 |
| 10 | Do you cough while swallowing liquids? | 0.02 |
| 13 | Other than during meals, do you experience coughing or difficulty breathing as a result of saliva entering your windpipe? | 0.04 |

MSA-SDQ, multiple system atrophy Swallowing Disturbance Questionnaire.

vs. 0.5 ± 0.3; $P < 0.01$; OR, 10.77; Fig. 1). Disease duration ($P = 0.33$; OR, 1.07) and disease severity ($P = 0.52$; OR, 0.82) showed no significant influence on dysphagia severity. Dysphagia severity in the MSA cohort was not correlated with disease duration ($\rho = -0.06$, $P = 0.70$), disease severity ($\rho = -0.02$, $P = 0.89$), or age ($\rho = -0.07$, $P = 0.59$).

### Subjective Dysphagia Expressed by SDQ Scores and Relationship to Dysphagia Detected by FEES

Of the 29 patients with MSA who completed the SDQ (age: median, 64 [IQR: 59–69] years; disease duration: 4 years [3–5]; H&Y stage: 4 [3–5]), 26 presented with dysphagia on FEES (mild: n = 21; moderate: n = 4; severe: n = 1). Applying the SDQ cutoff of 11 points to this MSA cohort, we found a sensitivity of only 54% for identifying patients who presented with dysphagia on FEES, despite a specificity of 100%. We therefore analyzed which SDQ items were strongly associated with dysphagia detected on FEES in this MSA cohort (Supporting Information Table S3) and found five items that strongly correlated with endoscopically detected dysphagia (Table 3). Extracting those five SDQ items into an MSA-SDQ subscore with a possible total score of 15 points, we found a good test reliability with Cronbach's alpha of 0.81. Using a ROC analysis, we defined a score ≥ 4 to be a valuable cutoff with a sensitivity of 85% and a specificity of 100% (Fig. 2).

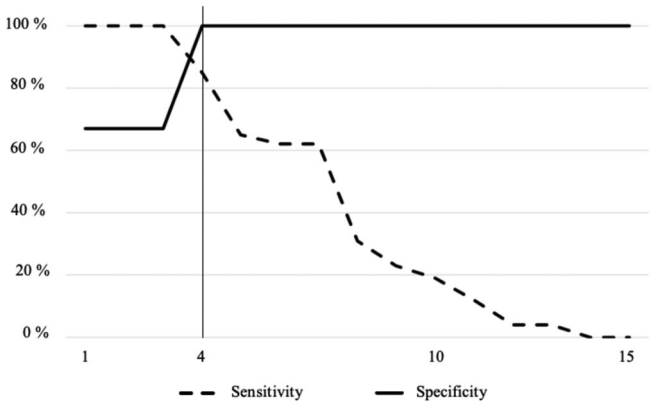


**FIG. 2.** Receiver operating characteristic (ROC) curve for multiple system atrophy Swallowing Disturbance Questionnaire (MSA-SDQ) subscore. The ROC curve shows the optimum score of crossing sensitivity and specificity curves. At a score of 4 the sensitivity is 85% and the specificity is 100%. Values on the *x* axis are MSA-SDQ sum scores; values on the *y* axis are percentage of sensitivity (dashed line) and specificity (solid line).

## Discussion

To the best of our knowledge, this is the first study that systematically assessed dysphagia in patients with MSA and directly compared results with an age-matched cohort of patients with PD using a standardized MSA-FEES task protocol. Even though previous studies demonstrated that laryngeal pathology causing inspiratory stridor is highly prevalent in patients with MSA,[21,22] FEES could be easily and successfully performed in all participants without any episode of laryngospasm or other negative side effects.

The pattern of swallowing impairment differed significantly between MSA and PD, with patients with MSA showing oral symptoms more frequently and patients with PD presenting pharyngeal symptoms more frequently. This was detected with all food consistencies, as well as with tablet swallowing. With increased disease severity, patients with MSA had a greater risk for the oral symptoms. Moreover, there was a significantly higher interswallow variability in patients with MSA for symptoms suggesting oral-phase disturbance when compared with patients with PD. Our findings contrast previous results from VFSSs in patients with MSA. Umemoto et al[15] showed an unspecific prolonged oropharyngeal transit time in 61 patients with MSA. Higo et al[28] concluded in a study on 29 patients with MSA that the swallowing dysfunction detected with VFSSs was similar to disturbances found in PD. One longitudinal Korean VFSS on 59 patients with MSA found a higher frequency of pharyngeal symptoms (in up to 90% of patients with MSA) than oral-phase symptoms (in up to 20% of patients with MSA) on initial investigation early in the course of the disease.[11] The follow-up investigations demonstrated that oral-phase symptoms of dysphagia had worsened more severely

than pharyngeal-phase symptoms.[14] However, we replicated previous results from endoscopic examinations in PD, which showed that pharyngeal residues were the most characteristic finding, while symptoms of oral-phase disturbances such as premature spillage or piecemeal deglutition appeared less frequently and later in the course of dysphagia in PD.[27,29,30]

The predominance of oral-phase disturbance in patients with MSA was observed in both MSA subtypes but showed no phenotypical differences, regardless of bolus consistencies. Furthermore, the frequency of oral-phase symptoms in patients with MSA increased with higher disease severity. At first glance, this contrasts previous findings. A previous VFSS on 26 patients with MSA-C showed predominantly oral symptoms to be affected.[4] A longitudinal analysis of 59 patients with MSA showed pharyngeal residue as a symptom of disturbed pharyngeal phase to be more frequent in MSA-P than in MSA-C early in the disease,[11] while its follow-up study demonstrated oral symptoms to progress more rapidly.[14] Another VFSS showed a shorter oropharyngeal transit time in patients with MSA-C compared with MSA-P.[15]

Moreover, we detected relevant penetration in 14% and aspiration in only 7% of patients with MSA, contrasting previous VFSSs that demonstrated aspiration events in up to 73% of patients with MSA.[11,28] The main driver for the contrasting results to previous studies cannot be explained by the different methods of intervention, because FEES has previously been shown to be more accurate than VFSS in detecting penetration/aspiration and pharyngeal residue.[31] We postulate that the previously described high prevalence of aspiration detected by VFSSs may be explained by a selection bias generated by solely referring patients with MSA with obvious dysphagia symptoms to VFSS, whereas in our study, patients were recruited consecutively and independent of subjective dysphagia complaints. Despite the predominance of oral-phase symptoms in patients with MSA, we observed a similar amount of pharyngeal residue in both cohorts, showing an equally disturbed pharyngeal phase in both patients with MSA and patients with PD. Both MSA and PD patients had an increasing chance of experiencing pharyngeal residue and a higher rate of penetration/aspiration events with longer disease duration. Penetration and aspiration events, however, were altogether recorded more frequently in the MSA cohort. Their higher prevalence in the MSA cohort can therefore be attributed to the more frequently occurring oral-phase disturbances in MSA, and although the frequency of penetration and aspiration events was low in our MSA cohort in comparison with other studies, these symptoms still remain a highly relevant finding eventually resulting in secondary complications, such as aspiration pneumonia, contributing to decreased quality of life and shortened life expectancy.[6-10]

In our study, dysphagia severity in patients with MSA was not correlated with disease duration and disease severity, which is in accordance with previous studies.[16,32] Even though pharyngeal dysphagia shows some phenotypical similarities in MSA and PD, dysphagia observed in MSA can be classified as a complex phenotype, whereas dysphagia observed in PD is classified as bradykinetic dysphagia with insufficient pharyngeal bolus cleaning, following a recent suggestion to classify neurogenic dysphagia.[19] The finding that patients with MSA show more disturbances swallowing tablets, which is a complex task for swallowing, may also be caused by the complex dysphagia pattern in MSA compared with PD. The predominant oral-phase symptoms, especially premature spillage, and the higher intraindividual interswallow variability in patients with MSA regardless of MSA phenotype are suggestive for cerebellar involvement as an underlying mechanism of the complex dysphagic phenotype. Although pathophysiological studies on dysphagia in PD are available,[33-37] there are currently no studies on histopathological correlates of MSA-related dysphagia, which is why the pathophysiological mechanisms are still poorly understood.[38] Central nuclei involved in the motor innervation of the pharynx have not been described to show neuronal cell loss in MSA,[39] and it is ultimately more likely that the meticulously coordinated multilevel swallowing reflex is not disturbed at one level, but rather on the level of its central integration, the central pattern generator, as postulated previously.[16] In addition, the fact that oral symptoms are also detected in MSA-P and the dysphagia type in this cohort is not purely bradykinetic as observed in PD might hint toward a cerebellar pathology contributing to oral dysphagia symptoms.

Our study is the first to have assessed subjective dysphagia applying the SDQ in an MSA cohort. When analyzing the SDQ answers of our patients with MSA, it became obvious that items associated with oral-phase disturbances correlated significantly with the endoscopic dysphagia scale. The transfer of the cutoff value used for patients with PD to our MSA cohort yielded low sensitivity despite a high specificity. Extraction of SDQ items associated with dysphagia into a specific MSA-SDQ subscore with a possible total score of 15 points finally showed good reliability with a Cronbach's $\alpha$ of 0.81. The recalculation of a cutoff value using a ROC analysis showed a sensitivity of 85% with a specificity of 100% for an MSA-SDQ score of $\geq$4 points. Based on these results, we propose to use this reliable MSA-SDQ subscore for early screening to detect patients at risk for oropharyngeal dysphagia. Patients with MSA with a total MSA-SDQ subscore of $\geq$4 should be referred to FEES. To confirm this result, the MSA-SDQ subscore should be evaluated in a further, prospective study in a larger patient cohort.

As expected from an age-matched comparison of an MSA and PD cohort, patients with MSA had a shorter disease duration and a higher disease severity. To

exclude an influence of these variables on the group comparison, we included disease duration and disease severity as covariates in the regression model and showed that neither of these variables had an overall effect. We understand that the low proportion of patients with MSA with severe dysphagia in our cohort is a considerable limit, making it difficult to understand our cohort as a representative one that allows for mapping all dysphagia severities. Moreover, there was lack of control for dysphagia latency in our patient cohorts, which potentially limits the homogeneity of dysphagia-characteristic data. Also, the subgroup of patients with MSA available for SDQ analysis was small, and even though patients were selected randomly, the majority presented with mild dysphagia on FEES. It is therefore too early to transfer our findings to the general MSA population just yet.

## Conclusions

In this first study comparing dysphagia symptoms in MSA and PD using a structured MSA-FEES task protocol, we showed that the dysphagia pattern differed significantly between cohorts. Patients with MSA showed a dysphagia pattern with predominantly oral symptom disturbance, while pharyngeal symptoms were primarily affected in the PD cohort. We furthermore showed that the intraindividual interswallow variability differed significantly between groups. The newly developed MSA-SDQ subscore showed to be a valid and reliable screening test that should be regularly applied. When patients with MSA have a score ≥ 4, endoscopic evaluation should be performed using the MSA-FEES task protocol to prove dysphagia endoscopically and prevent related complications. These new clinical findings must result in a different approach to the therapy of dysphagia in patients with MSA compared with patients with PD and focus on oral symptoms of swallowing. In addition, dysphagia in MSA is detectable before its initial clinical manifestation.[28] It is therefore essential to diagnose dysphagia as early as possible.

Further studies with even larger sample sizes collecting dysphagia specific data are warranted. An international multicenter study under the guidance of the Movement Disorders Society MSA study group is underway investigating laryngopharyngeal symptoms in patients with MSA and comparing results with patients with tauopathies and PD using the MSA-FEES task protocol. ●

**Acknowledgments:** We thank Dr. Arno Schroll and Dr. Nadine Külzow for support with statistical data analysis. Open Access funding enabled and organized by Projekt DEAL.

### Data Availability Statement

The study protocol, statistical analysis, informed consent form, and study data, including de-identified participant data, will be made available to others with publication upon formal request and receipt of a signed material transfer agreement. Requests should be directed to the corresponding author. Data will only be shared via individual secured network connections.

## References

1. Fanciulli A, Wenning GK. Multiple-system atrophy. N Engl J Med 2015;372(3):249–263. https://doi.org/10.1056/NEJMra1311488
2. Levin J, Kurz A, Arzberger T, Giese A, Höglinger GU. The differential diagnosis and treatment of atypical parkinsonism. Dtsch Arztebl Int 2016;5(113):61–69. https://doi.org/10.3238/arztebl.2016.0061
3. Müller J, Wenning GK, Verny M, et al. Progression of dysarthria and dysphagia in postmortem-confirmed parkinsonian disorders. Arch Neurol 2001;58(2):259. https://doi.org/10.1001/archneur.58.2.259
4. Higo R, Nito T, Tayama N. Swallowing function in patients with multiple-system atrophy with a clinical predominance of cerebellar symptoms (MSA-C). Eur Arch Otorhinolaryngol 2005;262(8):646–650. https://doi.org/10.1007/s00405-004-0883-0
5. Köllensperger M, Geser F, Seppi K, et al. Red flags for multiple system atrophy. Mov Disord 2008;23(8):1093–1099. https://doi.org/10.1002/mds.21992
6. O'Sullivan SS, Massey LA, Williams DR, et al. Clinical outcomes of progressive supranuclear palsy and multiple system atrophy. Brain 2008;131(5):1362–1372. https://doi.org/10.1093/brain/awn065
7. Rommel N, Hamdy S. Oropharyngeal dysphagia: manifestations and diagnosis. Nat Rev Gastroenterol Hepatol 2016;13(1):49–59. https://doi.org/10.1038/nrgastro.2015.199
8. Krim E, Yekhlef F, Chrysostome V, Ghorayeb I, Tison F. Multiple system atrophy: prognostic factors in the "MSA-Aquitaine" cohort. Rev Neurol (Paris) 2007;163(1):54–65. https://doi.org/10.1016/s0035-3787(07)90355-0
9. Papapetropoulos S, Tuchman A, Laufer D, Papatsoris AG, Papapetropoulos N, Mash DC. Causes of death in multiple system atrophy. J Neurol Neurosurg Psychiatry 2006;78(3):327–329. https://doi.org/10.1136/jnnp.2006.103929
10. Shimohata T, Aizawa N, Nakayama H, et al. Mechanisms and prevention of sudden death in multiple system atrophy. Parkinsonism Relat Disord 2016;30:1–6. https://doi.org/10.1016/j.parkreldis.2016.04.011
11. Lee HH, Seo HG, Kim K, et al. Characteristics of early oropharyngeal dysphagia in patients with multiple system atrophy. Neurodegener Dis 2018;18(2–3):84–90. https://doi.org/10.1159/000487800
12. Taniguchi H, Nakayama H, Hori K, Nishizawa M, Inoue M, Shimohata T. Esophageal involvement in multiple system atrophy. Dysphagia 2015;30(6):669–673. https://doi.org/10.1007/s00455-015-9641-2
13. Ueha R, Goto T, Sato T, et al. High resolution manofluorographic study in patients with multiple system atrophy: possible early detection of upper esophageal sphincter and proximal esophageal abnormality. Front Med 2018;5:286. https://doi.org/10.3389/fmed.2018.00286
14. Do HJ, Seo HG, Lee HH, et al. Progression of oropharyngeal dysphagia in patients with multiple system atrophy. Dysphagia 2020;35(1):24–31. https://doi.org/10.1007/s00455-019-09990-z
15. Umemoto G, Furuya H, Tsuboi Y, et al. Dysphagia in multiple system atrophy of cerebellar and parkinsonian types. J Neurol Neurosci 2017;8(1):1000165. https://doi.org/10.21767/2171-6625.
16. Alfonsi E, Versino M, Merlo IM, et al. Electrophysiologic patterns of oral-pharyngeal swallowing in parkinsonian syndromes. Neurology 2007;68(8):583–589. https://doi.org/10.1212/01.wnl.0000254478.46278.67

17. Langmore SE. History of fiberoptic endoscopic evaluation of swallowing for evaluation and management of pharyngeal dysphagia: changes over the years. Dysphagia 2017;32(1):27–38. https://doi.org/10.1007/s00455-016-9775-x

18. Dziewas R, Auf dem Brinke M, Birkmann U, et al. Safety and clinical impact of FEES - results of the FEES-registry. Neurol Res Pract 2019;1:16. https://doi.org/10.1186/s42466-019-0021-5

19. Warnecke T, Labeit B, Schroeder J, et al. Neurogenic dysphagia: a systematic review and proposal of a classification system. Neurology 2020; 96(6):e876–e889. https://doi.org/10.1212/WNL.0000000000011350

20. Prosiegel M, Weber S. Dysphagie: Diagnostik Und Therapie. Ein Wegweiser Für Kompetentes Handeln. 3rd ed. Berlin, Germany: Springer; 2018. ISBN-10: 366256131X ISBN-13: 978-3662561317

21. Warnecke T, Vogel A, Ahring S, et al. The shaking palsy of the larynx — potential biomarker for multiple system atrophy: a pilot study and literature review. Front Neurol 2019;10(March):1–12. https://doi.org/10.3389/fneur.2019.00241

22. Gandor F, Vogel A, Claus I, et al. Laryngeal movement disorders in multiple system atrophy - a diagnostic biomarker? Mov Disord 2020;35(12):2174–2183. https://doi.org/10.1002/mds.28220

23. Manor Y, Giladi N, Cohen A, Fliss DM, Cohen JT. Validation of a swallowing disturbance questionnaire for detecting dysphagia in patients with Parkinson's disease. Mov Disord 2007;22(13):1917–1921. https://doi.org/10.1002/mds.21625

24. Gilman S, Wenning GK, Low P, et al. Second consensus statement on the diagnosis of multiple system atrophy. Neurology 2008;71(9): 670–676.

25. Postuma RB, Berg D, Stern M, et al. MDS clinical diagnostic criteria for Parkinson's disease. Mov Disord 2015;30(12):1591–1601. https://doi.org/10.1002/mds.26424

26. Warnecke T, Suttrup I, Schröder JB, et al. Levodopa responsiveness of dysphagia in advanced Parkinson's disease and reliability testing of the FEES-levodopa-test. Parkinsonism Relat Disord 2016;28:100–106. https://doi.org/10.1016/j.parkreldis.2016.04.034

27. Warnecke T, Oelenberg S, Teismann I, et al. Endoscopic characteristics and levodopa responsiveness of swallowing function in progressive supranuclear palsy. Mov Disord 2010;25(9):1239–1245. https://doi.org/10.1002/mds.23060

28. Higo R, Tayama N, Watanabe T, Nitou T, Ugawa Y. Videofluoroscopic and manometric evaluation of swallowing function in patients with multiple system atrophy. Ann Otol Rhinol Laryngol 2003;112(7):630–636. https://doi.org/10.1177/000348940311200710

29. Suttrup I, Warnecke T. Dysphagie im verlauf der parkinsonkrankheit: pathophysiologie, diagnostik und therapie TT - dysphagia in Parkinson's disease: pathophysiology, diagnosis and therapy. Fortschr Neurol Psychiatr 2016;84(S01):S18–S23.

30. Ertekin C, Aydoğdu I, Yüceyar N. Piecemeal deglutition and dysphagia limit in normal subjects and in patients with swallowing disorders. J Neurol Neurosurg Psychiatry 1996;61(5):491–496. https://doi.org/10.1136/jnnp.61.5.491

31. Giraldo-Cadavid LF, Leal-Leaño LR, Leon-Basantes GA, et al. Accuracy of endoscopic and videofluoroscopic evaluations of swallowing for oropharyngeal dysphagia. Laryngoscope 2017;127(9):2002–2010. https://doi.org/10.1002/lary.26419

32. Isono C, Hirano M, Sakamoto H, Ueno S, Kusunoki S, Nakamura Y. Differential progression of dysphagia in heredity and sporadic ataxias involving multiple systems. Eur Neurol 2015;74(5–6):237–242. https://doi.org/10.1159/000442252

33. Suzuki M, Saigusa H, Shibasaki K, Kodera K. Multiple system atrophy manifesting as complex sleep-disordered breathing. Auris Nasus Larynx 2010;37(1):110–113. https://doi.org/10.1016/j.anl.2009.02.009

34. Ertekin C. Electrophysiological evaluation of oropharyngeal dysphagia in Parkinson's disease. J Mov Disord 2014;7(2):31–56. https://doi.org/10.14802/jmd.14008/J

35. Leopold NA, Daniels SK. Supranuclear control of swallowing. Dysphagia 2010;25(3):250–257. https://doi.org/10.1007/s00455-009-9249-5

36. Suntrup S, Teismann I, Bejer J, et al. Evidence for adaptive cortical changes in swallowing in Parkinson's disease. Brain 2013;136(Pt 3): 726–738. https://doi.org/10.1093/brain/awt004

37. Mu L, Sobotka S, Chen J, et al. Parkinson disease affects peripheral sensory nerves in the pharynx. J Neuropathol Exp Neurol 2013; 72(7):614–623. https://doi.org/10.1097/NEN.0b013e3182965886

38. Fernagut P-O, Vital A, Canron M-H, Tison F, Meissner WG. Ambiguous mechanisms of dysphagia in multiple system atrophy. Brain 2012;135(Pt 2):e205; author reply e206. https://doi.org/10.1093/brain/awr185

39. Benarroch EE, Schmeichel AM, Sandroni P, Low PA, Parisi JE. Involvement of vagal autonomic nuclei in multiple system atrophy and Lewy body disease. Neurology 2006;66(3):378–383. https://doi.org/10.1212/01.wnl.0000196638.98781.bb

40. Cohen JT, Manor Y. Swallowing disturbance questionnaire for detecting dysphagia. Laryngoscope 2011;121(7):1383–1387. https://doi.org/10.1002/lary.21839

## Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.