ARTICLE

Neurogenic Dysphagia

Systematic Review and Proposal of a Classification System

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Abstract

Objective

Introduction and validation of a phenotypic classification of neurogenic dysphagia based on flexible endoscopic evaluation of swallowing (FEES).

Methods

A systematic literature review was conducted, searching MEDLINE from inception to May 2020 for FEES findings in neurologic diseases of interest. Based on a retrospective analysis of FEES videos in neurologic diseases and considering the results from the review, a classification of neurogenic dysphagia was developed distinguishing different phenotypes. The classification was validated using 1,012 randomly selected FEES videos of patients with various neurologic disorders. Chi-square tests were used to compare the distribution of dysphagia phenotypes between the underlying neurologic disorders.

Results

A total of 159 articles were identified, of which 59 were included in the qualitative synthesis. Seven dysphagia phenotypes were identified: (1) "premature bolus spillage" and (2) "delayed swallowing reflex" occurred mainly in stroke, (3) "predominance of residue in the valleculae" was most common in Parkinson disease, (4) "predominance of residue in the piriform sinus" occurred only in myositis, motoneuron disease, and brainstem stroke, (5) "pharyngolaryngeal movement disorder" was found in atypical Parkinsonian syndromes and stroke, (6) "fatigable swallowing weakness" was common in myasthenia gravis, and (7) "complex disorder" with a heterogeneous dysphagia pattern was the leading mechanism in amyotrophic lateral sclerosis. The interrater reliability showed a strong agreement (kappa = 0.84).

Conclusion

Neurogenic dysphagia is not a symptom, but a multietiologic syndrome with different phenotypic patterns depending on the underlying disease. Dysphagia phenotypes can facilitate differential diagnosis in patients with dysphagia of unclear etiology.

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Glossary

ALS = amyotrophic lateral sclerosis; **ESSD** = European Society for Swallowing Disorders; **FEES** = flexible endoscopic evaluation of swallowing; **PD** = Parkinson disease; **UES** = upper esophageal sphincter.

Neurogenic dysphagia represents an enormous burden for patients, health care professionals, and society. It is highly prevalent in most neurologic diseases such as stroke,[1,2] Parkinson disease (PD),[3] dementia,[4,5] amyotrophic lateral sclerosis (ALS),[6] and neuromuscular disorders, for example, myositis[7] and myasthenia gravis.[8] Dysphagia can lead to severe complications and cause malnutrition, dehydration, and aspiration pneumonia.[1,9,10]

Swallowing is a highly complex neuromuscular process that requires the precise coordination of more than 25 muscle pairs, intact pharyngeal sensation, and central control in the brainstem and cortex.[11–14] The large variety of structures involved suggests that different pathophysiologic mechanisms can result in dysphagia depending on the underlying disease and the associated structural and functional impairment. The phenotypic pattern of dysphagia caused by extrapyramidal motor dysfunction as in PD[15,16] may substantially differ from the pattern caused by pharyngeal hypesthesia as in stroke.[14] However, the established classification systems focus on severity—that is, penetration and aspiration—whereas phenomenological aspects are barely taken into account.

In recent years, besides videofluoroscopy, flexible endoscopic evaluation of swallowing (FEES) has proven to be a safe and feasible method commonly used for the objective evaluation of dysphagia in neurologic patients.[17] The aim of this study was to introduce and validate a FEES-based phenotypic classification of neurogenic dysphagia. In a first step, a systematic literature review on disease-typical FEES findings was carried out. In a second step, a classification system was defined and validated using a retrospective cohort.

Methods

Standard Protocol Approvals, Registrations, and Patient Consents

The study design was approved by the local ethics committee. Because the design was completely retrospective, the ethics committee waived the need for informed consent.

The study design is illustrated in a flowchart in figure 1.

Literature Review

A systematic literature review was performed focusing on disease-specific FEES findings besides penetration and aspiration in neurogenic dysphagia. To identify all relevant studies in MEDLINE from inception to May 2020, the following PubMed search terms were used (latest update for this article in May 2020): "([stroke] or [brainstem stroke] or [Parkinson's disease] or [myasthenia gravis] or [amyotrophic lateral sclerosis] or [dementia] or [myositis]) and ([flexible endoscopic evaluation of swallowing] or [fiberoptic endoscopic evaluation of swallowing] or [flexible endoscopic examination of swallowing] or [flexible endoscopic assessment of swallowing] or [fiberoptic endoscopic examination of swallowing] or [fiberoptic endoscopic assessment of swallowing])."

The results were reviewed by one of the authors (B.L.). All original contribution articles in English or German that reported disease-specific FEES findings in at least one patient with stroke, parkinsonian syndromes, dementia, ALS, myasthenia gravis, or myositis were included in the review. Articles were excluded if:

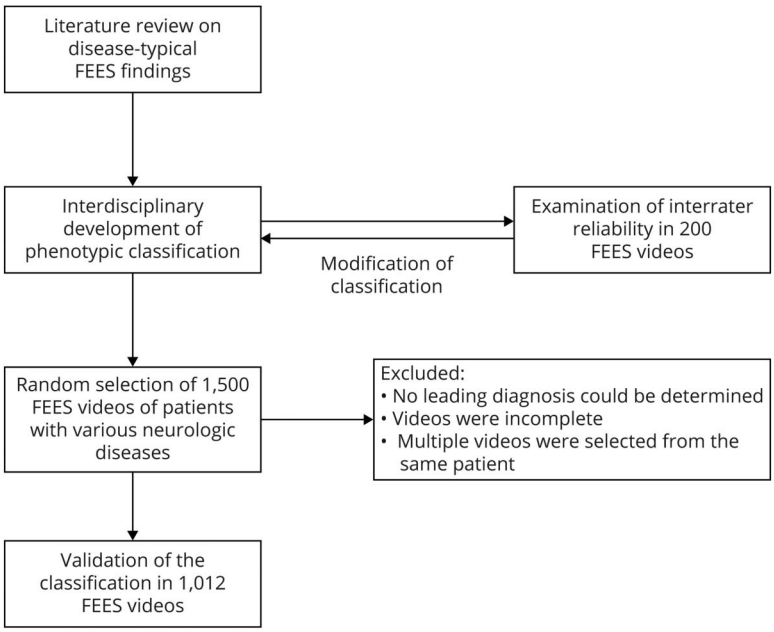
- They did not report phenomenologic FEES findings besides penetration/aspiration
- Dysphagia could not be attributed to one of the disease groups listed above (e.g., exclusion of tracheotomized patients, heterogeneous disease groups, patients with multiple diseases)
- The FEES results of swallowing examination with a normal bolus were not reported separately (e.g., exclusion if only pill swallowing was investigated or if FEES and videofluoroscopy findings were reported together)
- They reported results on overlapping cohorts with a less detailed description of the dysphagia phenomenology than another included study

The following data items were extracted from the studies by one of the authors (B.L.) and summarized in a table: study design, patient cohort (disease type and sample size), information about the FEES paradigm used, and the described FEES findings.

Development of Classification

Taking into account the results of the literature review and the clinical experience of the authors, the phenotypes of the classification were further defined by an interdisciplinary team of neurologists (n = 4) and speech–language pathologists (n = 2). For this purpose, selected FEES videos of patients with PD, supratentorial stroke, brainstem stroke, ALS, myositis, or myasthenia gravis were evaluated (approximately 10–20 videos in each disease group). The focus was placed on typical dysphagia entities and their similarities as well as their differences within and throughout the disease groups. For each disease group, attention was paid to the findings described in the literature review as typical for the respective disease (table

Figure 1 Flowchart Illustrating the Study Design



FEES = flexible endoscopic evaluation of swallowing.

1). For each of these findings, it was evaluated whether it occurred in the respective FEES video and if so, whether or not it represented the decisive pathomechanism of dysphagia. A phenotypic entity was only considered if a characteristic pattern of FEES findings could be identified as the main mechanism of dysphagia in different subjects and varying degrees of severity. After determining the interrater reliability, the interdisciplinary team met again to discuss further modifications of the classification, based on the first experience with this approach. In this meeting, the 2 raters showed selected video sequences in which further discussion was needed. In both team meetings, decisions were made by mutual consensus.

Interrater Reliability

To determine the interrater reliability of the previously defined classification (see Definition of Dysphagia Phenotypes), 200 randomly selected FEES videos of patients with different neurologic disorders (PD, stroke other than brainstem, brainstem stroke, ALS, myositis, and myasthenia gravis) were evaluated by 2 independent raters (J.S. and T.W.) who were blinded to the diagnosis of the patients. Both raters had several years of experience in the field of neurogenic dysphagia and held the FEES certificate of the European Society for Swallowing Disorders (ESSD).[18] Both raters were part of the interdisciplinary team defining the phenotypes.

The agreement of the 2 raters with respect to the 5 phenotypes (see Definition of Dysphagia Phenotypes) was evaluated both for the overall mixed diagnostic cohort (the above mentioned disorders combined) and for each single diagnostic group individually using Cohen kappa. The results were interpreted as follows: 0–0.2: no agreement; 0.21–0.39: minimal agreement; 0.4–0.59: weak agreement; 0.6–0.79: moderate agreement; 0.8–0.9 strong agreement; above 0.9: almost perfect agreement.[19]

Validation of Classification

Patient Cohort

A total of 1,500 FEES videos were randomly selected from all available FEES videos in our clinic of patients with various neurologic diseases. All FEES investigations were conducted between 2007 and 2017 on inpatients or outpatients at the University Hospital of Münster. FEES was regularly performed by a speech–language pathologist together with a trained neurologist using semisolid, liquid, and solid consistencies. The diagnostic group of the patient was noted. If no leading neurologic diagnosis could be determined, FEES videos were incomplete so no assessment of swallowing was possible, or multiple videos were selected from the same patient, the respective videos were excluded from the analysis.

Assessment of FEES

The dysphagia phenotype according to the introduced classification system (Definition of Dysphagia Phenotypes) was determined in all FEES examinations by an experienced physician in the field of neurogenic dysphagia (J.S. or T.W.) who held the FEES certificate of the ESSD.[18] Both physicians were part of the interdisciplinary team defining the phenotypes. The examiner was blinded to the underlying disease. The phenotypes were only assigned if they represented the typical swallowing pattern during the examination and if impaired swallowing safety and efficacy were mainly caused by

Table 1 Typical Flexible Endoscopic Evaluation of Swallowing (FEES) Findings in Various Neurologic Diseases

Neurologic disorder	Typical FEES findings
Stroke	Premature bolus spillage,[25–28,e14,e15] often reported as main finding[25–28]
	Pharyngeal residue[25–28,e14,e16–e19] with reduced response to residue[e20]
	Impaired secretion management[25,27,28,e14,e15,e18,e21–e24]
	Impaired swallowing reflex[25,28,e14,e16]
	Rarely reported: piecemeal deglutition[e25]
	Rarely reported in association with specific lesions: pharyngolaryngeal movement disorders[e4]
Brainstem stroke	Cricopharyngeal spasm[47,e22]
	Pharyngolaryngeal movement disorders[e4]
Parkinson disease	Pharyngeal residue,[15,36–41,e19,e26–e30] sometimes reported in nearly all patients,[37,39] often reported as leading finding,[36–41] with predominance in the valleculae[37,38,e19,e30]
	Premature bolus spillage[15,38,e27–e30]
	Impaired swallowing reflex[47,e29,e30]
	Pharyngolaryngeal movement disorders[15,47,e29,e31]
	Rarely reported: impaired secretion management[e27,e28]
Amyotrophic lateral sclerosis	Pharyngeal residue[e9,e19,e32–e38] in the valleculae[e19,e37] as well as in the piriform sinus[e19,e32,e37]
	Premature bolus spillage[e32–e35,e38]
	Reduced pharyngeal contractility and reduced bolus clearance[e32,e39]
	Pharyngeal impairment always in combination with oral impairment[e8,e9]
Myasthenia gravis	Residue,[e6,e11,e40] reported as main finding,[e11,e40] with predominance in the valleculae[e40]
	Premature bolus spillage[e6,e11]
	Impairment of swallowing reflex[e6,e40]
	Prolonged oral or pharyngeal transit time[47]
	Piecemeal deglutition[47]
	Impaired secretion management[e6]
	Fatigable swallowing weakness[e6]
Myositis	Pharyngeal residue as leading finding[42,e41,e42]
	Premature bolus spillage[e41]
Dementia	Increased leakage time during mastication[4]
	Increased swallow onset time[4]
	Premature bolus spillage[4]
	Reduced bolus clearance[4]

the respective phenotypic pattern (e.g., predeglutitive aspiration due to premature spillage).

Statistical Analysis

The distribution of the different dysphagia phenotypes in the validation study was illustrated in a bar chart for the following diagnostic groups: total cohort, supratentorial stroke, infratentorial stroke excluding medulla oblongata stroke, medulla oblongata stroke, PD, atypical parkinsonian syndromes combined, ALS, myasthenia gravis, inflammatory myopathy combined, and noninflammatory myopathy combined. The distribution of the dysphagia phenotypes depending on the underlying disorder was evaluated in a cross table (observed counts) and matched with the expected counts according to the χ^2 statistics. For each disorder with n ≥5, a χ^2 test of independence was performed to examine the relation between each dysphagia phenotype and each disorder. In cases of expected counts <5, the Fisher exact test was used. As 112

tests were performed, according to the Bonferroni correction, results were considered to be statistically significant when $p < 0.05/112 = 4.5E\text{-}4$. Sensitivity and specificity were calculated for each phenotype to predict the underlying disease.

Data Availability

Systematic Review

A detailed table illustrating the included articles with disease group, cohort, FEES paradigm, and FEES findings can be found online in table e-1 (available from Dryad: doi.org/10.5061/dryad.tb2rbnzz5).

Validation Study

The raw data on which the statistical analyses of the validation study are based are published in full in this article.

Results

Literature Review

The flow chart according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)[20] is illustrated in figure 2. Fifty-one articles were included in the review. A detailed table illustrating the included articles with disease group, cohort, FEES paradigm, and FEES findings can be found online in table e-1 (available from Dryad: doi.org/10.5061/dryad.tb2rbnzz5). Table 1 summarizes disease-typical FEES findings.

Definition of Dysphagia Phenotypes

The basis for consideration as a phenotypic entity was that a characteristic, leading mechanism in the impairment of swallowing safety or efficiency could be determined, so that further dysphagia symptoms such as penetration and aspiration could be attributed mainly to the phenotypic constellation of findings. In the first meeting, 5 different phenotypes were defined (1, 2, 3, 4, and 7 of the listed phenotypes below). In a further meeting after determination of the interrater reliability, both raters agreed that there were 2 additional, albeit rare, patterns of dysphagia that met the definition of a phenotype. The classification was therefore modified and these further phenotypes (5 and 6) were included:

1. Premature bolus spillage: Premature spillage before triggering of the swallowing reflex regularly occurs
2. Delayed swallowing reflex: No swallowing reflex is regularly triggered for at least 3 seconds after the bolus has reached the valleculae
3. Predominance of residue in the valleculae: Pharyngeal residues regularly accumulate in the valleculae (residue in the valleculae > residue in the piriform sinus)
4. Predominance of residue in the piriform sinus: Pharyngeal residue regularly accumulate in the piriform sinus (residue in piriform sinus ≥ residue in the valleculae)
5. Pharyngolaryngeal movement disorders: Pharyngolaryngeal movement disorders for example, oropharyngeal freezing, pharyngeal bradykinesia or pharyngolaryngeal tremor regularly occur and interfere with the physiologic bolus transportation
6. Fatigable swallowing weakness: Repeated swallowing trials (>5 trials) lead to pharyngeal residue or an increase in the volume of residue compared to the initial swallowing
7. Complex swallowing disorder: At least 2 of the above-mentioned mechanisms occur equivalently, a different mechanism occurs, or it is not possible to assign a mechanism

Interrater Reliability

The interrater agreement within the mixed diagnostic group and using 5 of the 7 phenotypes was n = 173 (86.5%), $\kappa = 0.84$, which can be considered as strong agreement. The interrater agreement in the individual diagnostic groups can be seen in table 2.

Validation of the Classification

Distribution of Phenotypes in Different Neurologic Diseases

Of the 1,500 FEES videos selected, 223 were excluded as no leading neurologic disease could be determined, 143 were excluded as the patient was tracheotomized while the FEES was performed, 68 were excluded because multiple videos of the same patient were selected, and 54 were excluded due to insufficient video quality. Therefore, 1,012 videos were included in the analysis.

The distribution of the dysphagia phenotypes depending on the diagnostic groups is illustrated in figure 3. The exact counts of phenotypes as well as the expected counts according to the χ^2 statistics throughout the different diagnostic groups are shown in table 3.

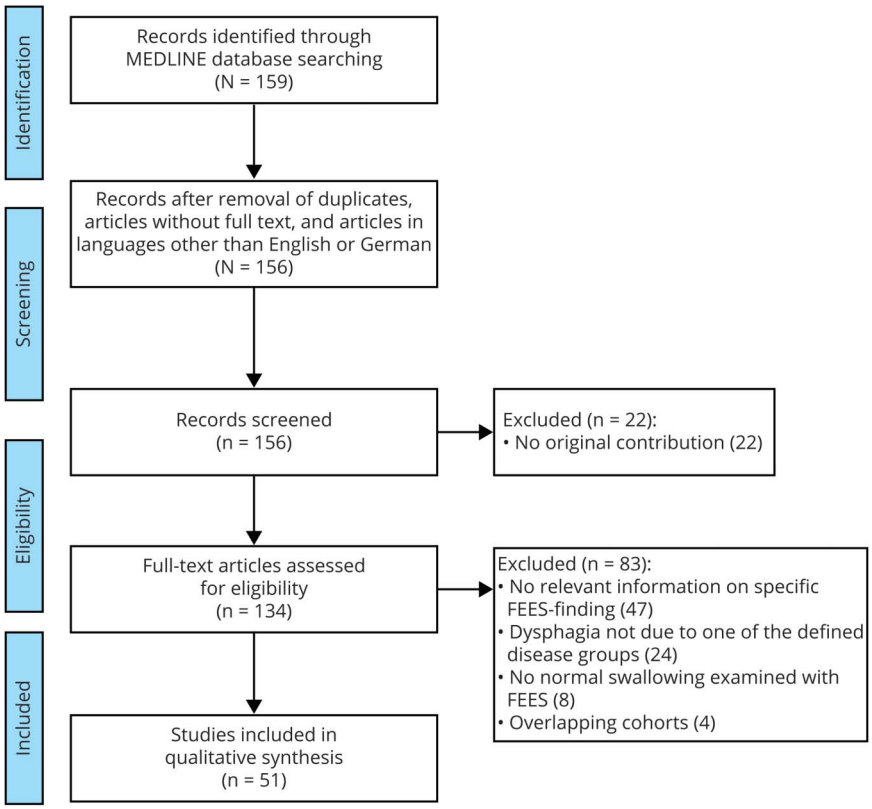
Association of the Individual Dysphagia Phenotypes With Diagnostic Groups

All 7 phenotypes were significantly associated with specific diagnostic groups. The results of the χ^2 or Fisher exact tests for the relation between each dysphagia phenotype and each disorder with n ≥5 as well as sensitivity and specificity to predict the underlying disease for each phenotype are shown in table 4.

Discussion

The main finding of our study is that the proposed phenomenologic classification of dysphagia using FEES provides valid results with a different distribution of phenotypes in the various neurologic disorders. In fact, all of the 7 phenotypes are associated with specific disease groups, although there is some overlap. This shows that the syndrome-based approach that is typically used to classify neurologic symptoms, such as dysarthria[21,22] or vertigo,[23] may also be appropriate for neurogenic dysphagia. The individual phenotypes and their relation to specific disease groups are discussed in the following.

Figure 2 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flow Chart of the Systematic Literature Review



FEES = flexible endoscopic evaluation of swallowing.

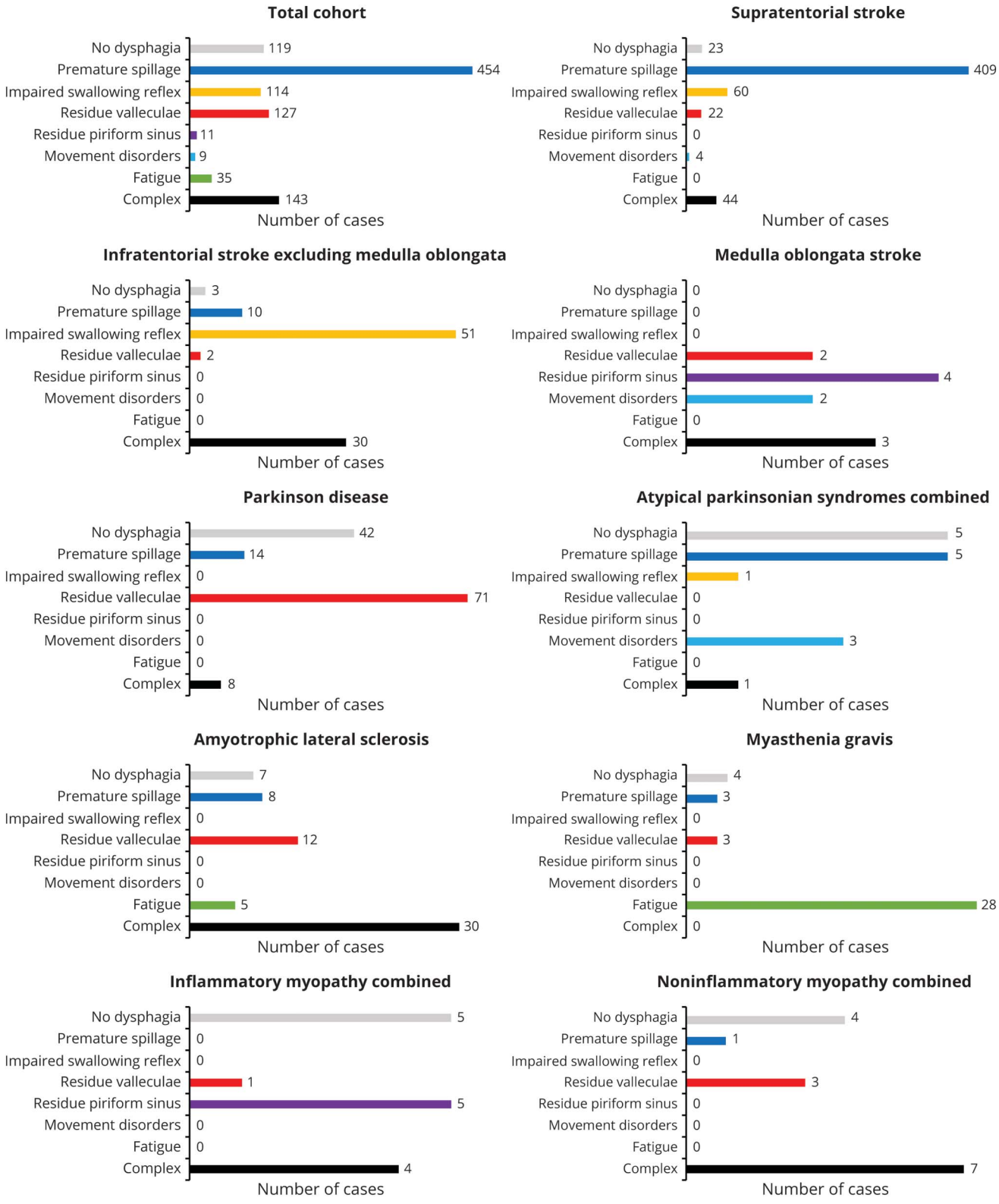
The phenotype of premature bolus spillage most frequently occurred in patients with supratentorial stroke. This is in line with the results of other FEES studies, which also report premature bolus spillage as the leading finding in patients with acute stroke.[24–28] However, the phenotype also occurred in almost all other disease groups, albeit in much smaller numbers. Premature bolus spillage can lead to predeglutitive aspiration, as the airway is not protected before the initiation of swallowing. Poor oral bolus containment is the main cause,[29] suggesting that impairment of the oral phase may play a role in different disease groups but is dominant in patients with stroke. As pathophysiologic mechanisms, both pseudobulbar paresis due to lesions of the projection neurons to the nuclei of the cranial nerves as well as higher cortical dysfunction such as oropharyngeal apraxia or attention deficits, may be contributing factors.[30] Oral hypesthesia and associated reduced oral bolus control due to lack of sensory feedback could also be a plausible pathomechanism.

The phenotype of delayed swallowing reflex occurred mainly in patients with stroke and here mostly in patients with infratentorial stroke. In other diseases, this phenotype seems to be of minor importance. Pathophysiologically, a sensory

Table 2 Interrater Agreement in the Different Diagnostic Groups

Diagnostic group	Videos, n	Agreement, n	Agreement, %	Cohen kappa	Interpretation of agreement
Stroke, other than brainstem	86	75	87	0.84	Strong
Brainstem stroke	11	9	82	0.73	Moderate
Parkinson disease	50	43	86	0.81	Strong
Amyotrophic lateral sclerosis	25	20	80	0.72	Moderate
Myasthenia gravis	20	18	90	0.83	Strong
Myositis	8	8	100	1.0	Perfect

Figure 3 Distribution of Dysphagia Phenotypes in the Total Cohort as Well as in Major Diagnostic Groups



deficit may be of key relevance here, so that despite reaching the trigger points in the pharynx the swallowing reflex is not elicited. This is consistent with the observation that pharyngeal hypesthesia contributes to poststroke dysphagia and affects swallowing initiation.[14,31] In line with the results of our study, Williams et al.[32] reported that absent swallowing response as dysphagia mechanism only occurred in patients with CNS pathology and not in patients with myositis.

Table 3 Dysphagia Phenotype Depending on the Diagnostic Groups (Counts) and Expected Counts According to the χ^2 Statistics as Well as Percentage of the Counts in Relation to the Total Cohort of the Diagnostic Group

	No dysphagia	Spillage[a]	Reflex[b]	Residue V[c]	Residue SP[d]	Movement[e]	Fatigue[f]	Complex[g]
Alzheimer dementia, n = 16								
Count (%)	12 (75)	1 (6)	0 (0)	3 (19)	0 (0)	0 (0)	0 (0)	0 (0)
Expected count	1.9	7.2	1.8	2.0	0.2	0.1	0.6	2.3
Amyotrophic lateral sclerosis, n = 62								
Count (%)	7 (11)	8 (13)	0 (0)	12 (19)	0 (0)	0 (0)	5 (8)	30 (48)
Expected count	7.3	27.8	7.0	7.8	0.7	0.6	2.1	8.8
Anti-NMDA encephalitis, n = 1								
Count (%)	0 (0)	0 (0)	0 (0)	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)
Expected count	0.1	0.4	0.1	0.1	0.0	0.0	0.0	0.1
Frontotemporal lobar degeneration, n = 10								
Count (%)	7 (70)	1 (10)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (20)
Expected count	1.2	4.5	1.1	1.3	0.1	0.1	0.3	1.4
Guillain-Barré syndrome, n = 11								
Count (%)	3 (27)	1 (9)	1 (9)	1 (9)	0 (0)	0 (0)	2 (18)	3 (27)
Expected count	1.3	4.9	1.2	1.4	0.1	0.1	0.4	1.6
Hereditary motor sensory neuropathy, n = 1								
Count (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (100)
Expected count	0.1	0.4	0.1	0.1	0.0	0.0	0.0	0.1
Huntington disease, n = 3								
Count (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (100)
Expected count	0.4	1.3	0.3	0.4	0.0	0.0	0.1	0.4
Inclusion body myositis, n = 12								
Count (%)	3 (25)	0 (0)	0 (0)	1 (8)	5 (42)	0 (0)	0 (0)	3 (25)
Expected count	1.4	5.4	1.4	1.5	0.1	0.1	0.4	1.7
Infratentorial stroke, n = 96								
Count (%)	3 (3)	10 (10)	51 (53)	2 (2)	0 (0)	0 (0)	0 (0)	30 (31)
Expected count	11.3	43.1	10.8	12.0	1.0	0.9	3.3	13.6
Lewy body dementia, n = 3								
Count (%)	2 (67)	1 (33)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Expected count	0.4	1.3	0.3	0.4	0.0	0.0	0.1	0.4
Medullary stroke, n = 11								
Count (%)	0 (0)	0 (0)	0 (0)	2 (18)	4 (36%)	2 (18)	0 (0)	3 (27)
Expected count	1.3	4.9	1.2	1.4	0.1	0.1	0.4	1.6
Mitochondrial myopathy, n = 2								
Count (%)	1 (50)	0 (0)	0 (0)	1 (50)	0 (0)	0 (0)	0 (0)	0 (0)
Expected count	0.2	0.9	0.2	0.3	0.0	0.0	0.1	0.3

Continued

Table 3 Dysphagia Phenotype Depending on the Diagnostic Groups (Counts) and Expected Counts According to the χ^2 Statistics as Well as Percentage of the Counts in Relation to the Total Cohort of the Diagnostic Group *(continued)*

	No dysphagia	Spillage[a]	Reflex[b]	Residue V[c]	Residue SP[d]	Movement[e]	Fatigue[f]	Complex[g]
Multiple system atrophy, n = 9								
Count (%)	2 (22)	2 (22)	1 (11)	0 (0)	0 (0)	3 (33)	0 (0)	1 (11)
Expected count	1.1	4.0	1.0	1.1	0.1	0.1	0.3	1.3
Myasthenia gravis, n = 38								
Count (%)	4 (11)	3 (8)	0 (0)	3 (8)	0 (0)	0 (0)	28 (74)	0 (0)
Expected count	4.5	17.0	4.3	4.8	0.4	0.3	1.3	5.4
Myotonic dystrophy type 1, n = 7								
Count (%)	0 (0)	0 (0)	0 (0)	2 (29)	0 (0)	0 (0)	0 (0)	5 (71)
Expected count	0.8	3.1	0.8	0.9	0.1	0.1	0.2	1.0
Myotonic dystrophy type 2, n = 2								
Count (%)	0 (0)	0 (0)	0 (0)	1 (50)	0 (0)	0 (0)	0 (0)	1 (50)
Expected count	0.2	0.9	0.2	0.3	0.0	0.0	0.1	0.3
Oculopharyngeal dystrophy, n = 2								
Count (%)	0 (0)	1 (50)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (50)
Expected count	0.2	0.9	0.2	0.3	0.0	0.0	0.1	0.3
Parkinson disease, n = 135								
Count (%)	42 (31)	14 (10)	0 (0)	71 (53)	0 (0)	0 (0)	0 (0)	8 (6)
Expected count	15.9	60.6	15.2	16.9	1.5	1.2	4.7	19.1
Polymyositis, n = 3								
Count (%)	2 (67)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (33)
Expected count	0.4	1.3	0.3	0.4	0.0	0.0	0.1	0.4
Pompe disease, n = 2								
Count (%)	2 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Expected count	0.2	0.9	0.2	0.3	0.0	0.0	0.1	0.3
Progressive supranuclear palsy, n = 6								
Count (%)	3 (50)	3 (50)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Expected count	0.7	2.7	0.7	0.8	0.1	0.1	0.2	0.8
Spinal and bulbar muscular atrophy, n = 7								
Count (%)	2 (29)	0 (0)	0 (0)	4 (57)	0 (0)	0 (0)	0 (0)	1 (14)
Expected count	0.8	3.1	0.8	0.9	0.1	0.1	0.2	1.0
Spinal muscular atrophy, n = 11								
Count (%)	1 (9)	0 (0)	1 (9)	1 (9)	2 (18)	0 (0)	0 (0)	6 (55)
Expected count	1.3	4.9	1.2	1.4	0.1	0.1	0.4	1.6
Supratentorial hemorrhage, n = 57								
Count (%)	0 (0)	39 (68)	8 (14)	2 (4)	0 (0)	0 (0)	0 (0)	8 (14)
Expected count	6.7	25.6	6.4	7.2	0.6	0.5	2.0	8.1

Continued

Table 3 Dysphagia Phenotype Depending on the Diagnostic Groups (Counts) and Expected Counts According to the χ^2 Statistics as Well as Percentage of the Counts in Relation to the Total Cohort of the Diagnostic Group *(continued)*

	No dysphagia	Spillage[a]	Reflex[b]	Residue V[c]	Residue SP[d]	Movement[e]	Fatigue[f]	Complex[g]
Supratentorial ischemic stroke, n = 505								
Count (%)	23 (5)	370 (73)	52 (10)	20 (4)	0 (0)	4 (1)	0 (0)	36 (7)
Expected count	59.4	226.6	56.9	63.4	5.5	4.5	17.5	71.4
Total								
Count (%)	119 (12)	454 (45)	114 (11)	127 (13)	11 (1)	9 (1)	35 (4)	143 (14)

[a] Premature bolus spillage.
[b] Impaired swallowing reflex.
[c] Residue with predominance in the valleculae.
[d] Residue with predominance in the piriform sinus.
[e] Pharyngolaryngeal movement disorders.
[f] Fatigable swallowing weakness.
[g] Complex swallowing disorder.

Consistent with the results of our review, the phenotype of residue with predominance in the valleculae occurred in all disease groups. Pathophysiologically, reduced pharyngeal contractility or insufficient contact between the base of the tongue and the posterior pharyngeal wall could be the underlying mechanisms.[33,34] This would explain the high frequency in various diseases, as these mechanisms, particularly reduced contraction, can result from impairment of various anatomical structures (e.g., direct involvement of the swallowing muscles, bulbar paresis, pseudobulbar paresis, impaired central motor coordination). However, residue in the valleculae was the major dysphagia manifestation in PD, which is in line with the results of previous studies.[35–41] Possibly, oropharyngeal bradykinesia contributes to reduced bolus clearance with accumulation in the valleculae in PD.[15]

The phenotype of residue with predominance in the sinus piriformis was seen only rarely in the present study and occurred mainly in medulla oblongata stroke and inclusion body myositis. An insufficient opening of the upper esophageal sphincter (UES) may be the cause of residue accumulation in the piriform sinus and can result in postdeglutitive aspiration.[7,42,43] UES impairment can be caused by cricopharyngeal dysfunction, which is a common finding of myositis.[32,44–46] In line with this, Williams et al.[32] reported that restrictive pharyngo-esophageal segment abnormalities occurred significantly more frequently in patients with myositis compared to patients with dysphagia due to CNS pathology. In our study, residue with predominance in the piriform sinus in the group of patients with inflammatory myopathies occurred only in inclusion body myositis. Given the disease's distinct pathophysiology, this phenotype may therefore be limited to inclusion body myositis, although the small number of cases in this patient group does not allow a definitive conclusion. Also, in brainstem strokes, an impaired UES opening with residue in the piriform sinus or postdeglutitive aspiration is reported as a characteristic dysphagia mechanism[43,47] and is specifically associated with stroke lesions in the medulla oblongata.[48] Pathophysiologically, this can be explained by a disrupted connection of the central pattern generator, located in the brainstem, to the cranial nerve nuclei responsible for UES relaxation.[49]

Pharyngolaryngeal movement disorders, in particular oropharyngeal freezing,[16,50] oropharyngeal bradykinesia,[15,e1,e2] and pharyngolaryngeal tremor,[e3,e4] have also been suggested to cause dysphagia (e-References available on Dryad: doi.org/10.5061/dryad.tb2rbnzz5). According to the results of our study, this rare phenotype seems to occur mainly in atypical parkinsonian disorders. It was sporadically also seen in patients with stroke, possibly due to lesions to the extrapyramidal motor system such as the basal ganglia or the mesencephalon. Previously, pharyngolaryngeal movement disorders have been described in patients with multiple system atrophy,[e3,e5] progressive supranuclear palsy,[50] and stroke with hypertrophic olivary degeneration.[e4]

Fatigable swallowing weakness was the main phenotype in myasthenia gravis and occasionally also occurred in ALS but was not seen in other disorders as the main mechanism. Thus, myasthenia gravis manifests in the oropharynx similarly to other systemic symptoms and is characterized by exertion-related muscle weakness[e6] with an increase of residue with repetitive swallowing trials.

The complex phenotype was present in almost all diagnostic groups (except myasthenia gravis), but with varying frequencies. Possibly, this phenotype represents the final stage of dysphagia in which several mechanisms occur in addition to the initial predominant dysphagia pattern. Examples for this include (1) myositis with initial cricopharyngeal dysfunction leading to residue primarily in the piriform sinus, but in the further course of the disease also the pharyngeal constrictor and oral muscles are affected, resulting in additional widespread hypopharyngeal residue and premature bolus spillage[7]; (2) PD with initial premature bolus spillage but in the further

Table 4 *p* Value of the χ^2 Test of Independence or in Cases of Expected Counts <5 of the Fisher Exact Test and Sensitivity and Specificity for the Relation Between Each Dysphagia Phenotype and Each Disorder With n ≥ 5

	Spillage[a]	Reflex[b]	Residue V[c]	Residue SP[d]	Movement[e]	Fatigue[f]	Complex[g]
Alzheimer dementia, n = 16							
***p* Value**	0.002	0.241	0.440	1.000	1.000	1.000	0.148
Sensitivity; specificity	6%; 55%	0%; 89%	19%; 88%	0%; 99%	0%; 99%	0%; 97%	0%; 86%
Amyotrophic lateral sclerosis, n = 62							
***p* Value**	1.8E-7[h]	0.004	0.095	1.000	1.000	0.057	1.3E-15[h]
Sensitivity; specificity	13%; 53%	0%; 88%	19%; 88%	0%; 99%	0%; 99%	8%; 97%	48%; 88%
Frontotemporal lobar degeneration, n = 10							
***p* Value**	0.027	0.614	0.623	1.000	1.000	1.000	0.640
Sensitivity; specificity	10%; 55%	0%; 89%	0%; 87%	0%; 99%	0%; 99%	0%; 97%	20%; 86%
Guillain-Barré syndrome, n = 11							
***p* Value**	0.028	1.000	1.000	1.000	1.000	0.053	0.194
Sensitivity; specificity	9%; 55%	9%; 89%	9%; 87%	0%; 99%	0%; 99%	18%; 97%	27%; 86%
Inclusion body myositis, n = 12							
***p* Value**	0.002	0.380	1.000	4.0E-8[h]	1.000	1.000	0.234
Sensitivity; specificity	0%; 55%	0%; 89%	8%; 87%	42%; 99%	0%; 99%	0%; 97%	25%; 86%
Infratentorial stroke, n = 96							
***p* Value**	9.9E-13[h]	2.5E-42[h]	0.001	0.613	1.000	0.069	4.2E-7[h]
Sensitivity; specificity	10%; 52%	53%; 93%	2%; 86%	0%; 99%	0%; 99%	0%; 96%	31%; 88%
Medullary stroke, n = 11							
***p* Value**	0.002	0.623	0.638	2.0E-6[h]	0.004	1.000	0.194
Sensitivity; specificity	0%; 55%	0%; 89%	18%; 88%	36%; 99%	18%; 99%	0%; 97%	27%; 86%
Multiple system atrophy, n = 9							
***p* Value**	0.199	1.000	0.612	1.000	4.0E-5[h]	1.000	1.000
Sensitivity; specificity	22%; 55%	11%; 89%	0%; 87%	0%; 99%	33%; 99%	0%; 97%	11%; 86%
Myasthenia gravis, n = 38							
***p* Value**	3.0E-6[h]	0.017	0.615	1.000	1.000	9.4E-40[h]	0.011
Sensitivity; specificity	8%; 54%	0%; 88%	8%; 87%	0%; 99%	0%; 99%	74%; 99%	0%; 85%
Myotonic dystrophy type 1, n = 7							
***p* Value**	0.019	1.000	0.216	1.000	1.000	1.000	0.001
Sensitivity; specificity	0%; 55%	0%; 89%	29%; 88%	0%; 99%	0%; 99%	0%; 97%	71%; 86%
Parkinson disease, n = 135							
***p* Value**	4.9E-18[h]	9.0E-6[h]	2.0E-51[h]	0.377	0.617	0.010	0.003
Sensitivity; specificity	10%; 50%	0%; 87%	53%; 94%	0%; 99%	0%; 99%	0%; 96%	6%; 85%
Progressive supranuclear palsy, n = 6							
***p* Value**	1.000	1.000	1.000	1.000	1.000	1.000	1.000
Sensitivity; specificity	50%; 55%	0%; 89%	0%; 87%	0%; 99%	0%; 99%	0%; 97%	0%; 86%

Continued

Table 4 *p* Value of the χ^2 Test of Independence or in Cases of Expected Counts <5 of the Fisher Exact Test and Sensitivity and Specificity for the Relation Between Each Dysphagia Phenotype and Each Disorder With n ≥ 5 *(continued)*

	Spillage[a]	Reflex[b]	Residue V[c]	Residue SP[d]	Movement[e]	Fatigue[f]	Complex[g]
Spinal and bulbar muscular atrophy, n = 7							
***p* Value**	0.019	1.000	0.006	1.000	1.000	1.000	1.000
Sensitivity; specificity	0%; 55%	0%; 89%	57%; 88%	0%; 99%	0%; 99%	0%; 97%	14%; 86%
Spinal muscular atrophy, n = 11							
***p* Value**	0.002	1.000	1.000	0.006	1.000	1.000	0.002
Sensitivity; specificity	0%; 55%	9%; 89%	9%; 87%	18%; 99%	0%; 99%	0%; 97%	55%; 86%
Supratentorial hemorrhage, n = 57							
***p* Value**	2.3E-4[h]	0.496	0.034	1.000	1.000	0.256	0.983
Sensitivity; specificity	68%; 57%	14%; 89%	4%; 87%	0%; 99%	0%; 99%	0%; 96%	14%; 86%
Supratentorial ischemic stroke, n = 505							
***p* Value**	1.7E-73[h]	0.331	1.8E-16[h]	0.001	1.000	1.9E-9[h]	1.8E-10[h]
Sensitivity; specificity	73%; 83%	10%; 88%	4%; 79%	0%; 98%	1%; 99%	0%; 93%	7%; 79%

[a] Premature bolus spillage.
[b] Impaired swallowing reflex.
[c] Residue with predominance in the valleculae.
[d] Residue with predominance in the piriform sinus.
[e] Pharyngolaryngeal movement disorders.
[f] Fatigable swallowing weakness.
[g] Complex swallowing disorder.
[h] Significant.

course additional pharyngeal hypesthesia[e7] leads to residue that are not cleared due to lack of perception; (3) ALS where with disease progression oral and pharyngeal phase abnormalities may occur leading to a combination of premature spillage and hypopharyngeal residue in different locations. The different distribution of the complex phenotype in the various diagnostic groups could indicate that this final stage is reached earlier for some diseases than others. Especially diseases affecting various anatomical swallowing structures, such as ALS (e.g., bulbar and pseudobulbar paresis), may predispose for a heterogeneous impairment pattern. In line with this, it has been shown that pharyngeal dysphagia in ALS is always associated with oral impairment and does not occur in isolation.[e8,e9] In addition to these disease-specific factors, age-related changes in swallowing, such as presbyphagia,[e10] may also contribute to a complex dysphagia phenotype. Also, different FEES findings in different bolus consistencies can lead to a complex phenotype, such as premature bolus spillage in liquid and residue in solid consistencies.

The interrater reliability in the overall cohort can be considered as strong and ranges between moderate and excellent agreement in the individual diagnostic groups. As a limiting factor, it must be mentioned that interrater reliability was only determined for 5 of the 7 phenotypes. The phenotypes "pharyngolaryngeal movement disorder" and "fatigable swallowing weakness" were included after the determination of interrater reliability. However, these are rare phenotypes that accounted for only 4.4% of cases in our study. In addition, recent studies have shown that pharyngolaryngeal movement disorders in patients with PD and an improvement in fatigable swallowing weakness in patients with myasthenia gravis can be reliably determined in FEES with moderate and strong agreement.[16,e11]

Some phenotypes, such as premature spillage, residue in the valleculae, or the complex disorder occurred in many neurologic diseases and can therefore be considered as transdiagnostic patterns in neurogenic dysphagia. Other phenotypes such as residue with predominance in the piriform sinus, impaired swallowing reflex, pharyngolaryngeal movement disorders, and fatigable swallowing weakness appear to be pathognomonic for specific diseases. Thus, these phenotypes might be particularly useful in the differential diagnosis in case of unclear dysphagia: in patients with fatigable swallowing weakness, the FEES edrophonium test, in which dysphagia improves after application of edrophonium chloride, may allow the diagnosis of myasthenia gravis.[e6,e11] Also, the phenotype of residue with predominance in the piriform sinus may give rise to further investigations looking for hallmarks of general or focal myositis syndromes.[7,42] In patients with multiple system atrophy, laryngeal movement disorders may have differential diagnostic relevance in differentiating the disease from idiopathic Parkinson disease. In a recent study, laryngeal movement disorders such as irregular arytenoid cartilage movements, vocal fold motion

impairment, paradoxical vocal fold motion, and vocal fold fixation were detected in 93% of patients with multiple system atrophy using FEES, but only occurred in 1.8% of patients with idiopathic PD.[e5] However, future studies are necessary to clarify the diagnostic accuracy, for example, by determining the positive predictive value of the respective phenotypes for specific diseases in relevant patient groups; for example, patients with dysphagia of unclear etiology.

The results of our study show that there is not only a different distribution of phenotypes between different diagnostic groups but also that within one disease group there are varying leading dysphagia mechanisms. This again illustrates the heterogeneity and complexity of neurogenic dysphagia with a large number of anatomical structures involved that can be affected to varying degrees even within one disease group.

A phenomenologic classification approach may be helpful to enable targeted therapies or pathophysiologically driven research in the field of dysphagia. Potential examples could include (1) a drug therapy with acetylcholinesterase inhibitors in patients with myasthenia gravis and fatigable swallowing weakness phenotype[e11]; (2) cricopharyngeal myotomy in patients with residue in the piriform sinus phenotype due to myositis-related dysphagia and UES relaxation deficit[7,32]; (3) start of dopaminergic therapy in patients with PD with premature bolus spillage phenotype, as levodopa application can lead to an earlier triggering of the swallowing reflex[e12]; (4) stimulation therapy to trigger sensory remodeling, for example, pharyngeal electrical stimulation, in patients with stroke with impaired swallowing reflex phenotype due to pharyngeal hypesthesia.[e13]

Because the classification was developed and validated on the basis of FEES, it remains unclear to what extent the classification can also be applied using videofluoroscopy. In general, pharyngeal residue, premature bolus spillage, and impaired swallowing reflex can presumably also be evaluated in videofluoroscopy. Due to limited visibility of the anatomical structures of the larynx, it may be more challenging to detect pharyngolaryngeal movement disorders, although some authors have described movement disorder phenomena using videofluoroscopy.[50] When evaluating swallowing fatigue, radiation exposure may also be problematic, due to the need for a prolonged examination recording multiple swallows. Conversely, the proposed classification is limited by the usual constraints of FEES; for example, videofluoroscopy may be superior in case of intradeglutitive dysfunction.

When interpreting the results of this study, various limitations must be taken into account. In the review, no bias risk analysis was performed. Because there was no quantitative data synthesis, small differences between patient collectives, for example, due to a selection bias, are not critical. Nevertheless, it must be mentioned that the disease-specific findings of the review may not be representative of the diseases due a potential bias of the included studies. The retrospective design may have led to a selection bias, so that the videos examined may not be representative of the diagnostic groups: patients were subjected to a FEES examination for clinical reasons, due to subjective swallowing difficulties, suspected dysphagia by the attending physician, or indications based on a previous dysphagia screening. However, the threshold for FEES diagnostics may have been different between individual patients as well as between disease groups, depending on the care setting within the clinic (e.g., patients with dementia were primarily outpatients and patients with stroke inpatients). Age-related swallowing changes were not considered, which may also have led to a bias. The number of cases in certain disease groups is small, so that no final conclusions can be drawn with regard to the underlying diseases. This particularly applies for inflammatory myopathy, non-inflammatory myopathy, atypical parkinsonian syndromes, and medullary stroke. The calculated values of sensitivity and specificity may be different in a cohort of patients with dysphagia of unclear etiology, because the prevalence of the underlying diseases is presumably different in this patient group. As mentioned before, the classification was developed only on the basis of FEES and it is therefore unclear if it can also be applied using videofluoroscopy. The classification was used only by very experienced raters, so it is unclear whether less experienced raters can handle this classification equally reliably. Because the severity of dysphagia is not assessed, this classification cannot be used alone to guide therapeutic decisions.

Overall, our study shows that neurogenic dysphagia is a multietiologic syndrome with different phenotypic dysphagia patterns that are associated with specific disease groups. The classification introduced complements the existing classifications, which focus primarily on the severity of dysphagia. Dysphagia phenotypes not only facilitate pathophysiologically driven therapy and research but can also help in the differential diagnosis of unclear dysphagia.

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Appendix Authors

Name	Location	Contribution
Tobias Warnecke, MD	Department of Neurology with Institute for Translational Neurology, University of Muenster	Study concept and design, acquisition of data, rating of FEES videos, definition of phenotypes, critical revision of the manuscript for important intellectual content
Bendix Labeit, MD	Department of Neurology with Institute for Translational Neurology, University of Muenster	Statistical analysis (excluding interrater reliability), systematic review, drafting of the manuscript, definition of phenotypes

Appendix *(continued)*

Name	Location	Contribution
Jens Schroeder, MD	Department of Neurology with Institute for Translational Neurology, University of Muenster	Acquisition of data, rating of FEES videos, definition of phenotypes, critical revision of the manuscript for important intellectual content
Alexander Reckels, MD	Department of Neurology with Institute for Translational Neurology, University of Muenster	Acquisition of data, rating of FEES videos, statistical analysis on interrater reliability, definition of phenotypes, critical revision of the manuscript for important intellectual content
Sigrid Ahring	Department of Neurology with Institute for Translational Neurology, University of Muenster	Definition of phenotypes, critical revision of the manuscript for important intellectual content
Sriramya Lapa	Department of Neurology with Institute for Translational Neurology, University of Muenster	Definition of phenotypes, critical revision of the manuscript for important intellectual content
Inga Claus, MD	Department of Neurology with Institute for Translational Neurology, University of Muenster	Definition of phenotypes, critical revision of the manuscript for important intellectual content
Paul Muhle, MD	Department of Neurology with Institute for Translational Neurology, University of Muenster	Definition of phenotypes, critical revision of the manuscript for important intellectual content
Sonja Suntrup-Krueger, MD	Department of Neurology with Institute for Translational Neurology, University of Muenster	Definition of phenotypes, critical revision of the manuscript for important intellectual content
Rainer Dziewas, MD	Department of Neurology with Institute for Translational Neurology, University of Muenster	Critical revision of the manuscript for important intellectual content

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Neurogenic Dysphagia: Systematic Review and Proposal of a Classification System

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