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Review article

Dysphagia in multiple system atrophy consensus statement on diagnosis, prognosis and treatment

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ABSTRACT

Multiple system atrophy (MSA) is a neurodegenerative disorder characterized by a combination of autonomic failure plus cerebellar syndrome and/or parkinsonism. Dysphagia is a frequent and disabling symptom in MSA and its occurrence within 5 years of motor onset is an additional diagnostic feature. Dysphagia can lead to aspiration pneumonia, a recognized cause of death in MSA. Guidelines for diagnosis and management of dysphagia in MSA are lacking. An International Consensus Conference among experts with methodological support was convened in Bologna to reach consensus statements for the diagnosis, prognosis, and treatment of dysphagia in MSA. Abnormalities of the oral and pharyngeal phases of swallowing, esophageal dysfunction and aspiration occur in MSA and worsen as the disease progresses. According to the consensus, dysphagia should be investigated through available screening questionnaires and clinical and instrumental assessment (videofluoroscopic study or fiberoptic endoscopic evaluation of swallowing and manometry) at the time of MSA diagnosis and periodically thereafter. There is evidence that dysphagia is associated with poor survival in MSA, however effective treatments for dysphagia are lacking. Compensatory strategies like diet modification, swallowing maneuvers and head postures should be applied and botulinum toxin injection may be effective in specific conditions. Percutaneous endoscopic gastrostomy may be performed when there is a severe risk of malnutrition and pulmonary complications, but its impact on survival is undetermined. Several research gaps and unmet needs for research involving diagnosis, prognosis, and treatment were identified.

1. Introduction

Multiple system atrophy (MSA) is a neurodegenerative disorder characterized by a combination of autonomic failure plus cerebellar syndrome and/or parkinsonism. The current criteria define three degrees of certainty for diagnosis, possible, probable and definite, the latter requiring pathological confirmation, and two phenotypes, parkinsonian (MSA-P) or cerebellar (MSA-C), according to the predominant features at the time of evaluation [1].

Dysphagia is a frequent and disabling symptom in MSA, with a prevalence ranging from 31% to 78% and its occurrence within 5 years of motor onset is one of the additional features for the diagnosis of possible MSA-P [1–10].

The clinical consequences of dysphagia are linked to the patient's overall prognosis, and may include aspiration pneumonia, sudden death due to aspiration, malnutrition, and dehydration [11]. Also, elevated rates of infectious complications have been reported [8–12]. Furthermore, severe dysphagia or the need for percutaneous endoscopic gastrostomy (PEG) for feeding are considered milestones of disease progression in MSA [2]. However, only a few studies have analyzed the impact of dysphagia and of PEG placement on survival in MSA [2,6,8,13] and there are no specific guidelines for early diagnosis nor for management.

The "Istituto di Ricovero e Cura a Carattere Scientifico delle Scienze Neurologiche di Bologna" (IRCCS-ISNB) organized an International Consensus Conference of experts in the field with methodological support. This meeting took place in Bologna, Italy, on October 6th-7th 2017.

A subsequent review process with update of literature search was performed between August 2019 and May 2020.

The aims of the consensus were: (1) to establish how dysphagia in MSA should be diagnosed and assessed, (2) to define the prognostic significance of dysphagia with regard to survival, (3) to suggest how to manage dysphagia in MSA, and (4) to provide indications for future research after systematically reviewing the evidence and identifying unmet needs for clinical practice and research.

2. Methods

The Bologna Consensus Conference project on dysphagia was conducted, together with the parallel topic on stridor, between February and October 2017. The detailed method, adapted from the Methodological Handbook of the Italian National Guidelines System, is described elsewhere [14,15]. The following four phases were carried out:

1) Assignment phase. Four bodies were appointed: the Scientific Committee; the Technical Committee; a Workgroup of experts on dysphagia; the Consensus Development Panel.
2) Scoping phase. The scope with clinical questions and the protocol for the systematic review were devised (PROSPERO 2018 CRD42018079084) [16] by the Scientific Committee and the Technical Committee.
3) Assessment phase. The Technical Committee drafted a systematic review with evidence mapping [16–18]. The studies eligible for inclusion were those published of any design reporting original data on subjects with MSA suffering from dysphagia. The National Library of Medicine's MEDLINE, Elsevier's EMBASE, and The Cochrane Central Register of Controlled Trials were searched (PROSPERO CRD42018079084). Each study was graded from Class I (highest quality) to Class IV (lowest quality) on the basis of the "Classification of Evidence Schemes of the Clinical Practice Guideline Process Manual of the American Academy of Neurology". These schemes are specific for each kind of question (diagnosis, prognosis, therapy) and consider as principal study quality determinants the design, the spectrum of persons included and the blinding of the crucial study phases [19]. On the basis of the systematic review, the Workgroup drafted answers to clinical questions, to be discussed at the Consensus Conference. In cases where evidence in MSA was lacking, knowledge from other settings was integrated by applying the analogy principle.
4) Consensus Conference meeting. The Consensus Development Panel, after an open discussion with experts, drafted the statements.

For any remaining unsolved issues, a subsequent phase was performed to provide additional literature. The final text was achieved after an internal review process by all the authors.

3. Results

3.1. Systematic review with evidence mapping

The literature search was performed in July 2017 and updated between August 2019 and May 2020, and retrieved a total of 279 articles after removal of duplicates (Fig. 1). Each of these articles was screened for relevance, and the full texts of 70 articles were assessed for eligibility. Of these, a total of 27 studies met the prespecified inclusion criteria and formed the basis for the statements generated by experts. The majority of studies regarding diagnosis were categorized as Class III or IV, those on prognosis as Class II, III, or IV, and those on treatment as Class IV quality (Tables 1–3). Due to the limited evidence available, a further group of non-MSA primary or secondary studies (narrative

reviews, clinical practice guidelines) were adopted on the basis of the analogy principle (i.e., adapting knowledge from the literature on dysphagia).

3.2. Diagnosis of dysphagia in MSA

Dysphagia in MSA becomes clinically evident within 5 years from onset of motor abnormalities [3,5]. The clinical presentation of dysphagia usually refers to penetration/aspiration events, like aspiration pneumonia. Aspiration (bolus below the true vocal folds) or penetration (when the bolus enters the airway but not below the true vocal folds) events were found by means of videofluoroscopic swallow study (VFSS) and fiberoptic endoscopic evaluation of swallowing (FEES) in 21%–68% of MSA patients in different series [20–22]. History of aspiration pneumonia was not correlated with instrumental finding of aspiration events, patient's age and disease duration, but only with disease severity. However dysphagic symptoms are usually already present when instrumentally assessed before becoming clinically evident [20]. Therefore diagnosis of dysphagia early in the disease course in MSA patients remains complex and often underestimated because silent forms of penetration and aspiration of liquids and solid boluses in the airway may occur [12,20,21,23].

The act of swallowing is commonly divided into four stages (oral preparation, oral, pharyngeal, and esophageal phase) and studies assessing swallowing function with VFSS, FEES and high-resolution manometry, showed that all phases can be affected in MSA patients.

Instrumental findings of oral phase dysfunction included delayed bolus transport from the oral cavity to the pharynx, insufficient movement of the tongue base, and disturbance of bolus holding in the oral cavity. Pharyngeal phase impairment included slowed upward relocation of the larynx, vallecular residue, constriction of the pharynx and pyriform sinus residue [20–22,24].

Few studies have assessed differences between MSA-P and MSA-C in dysphagia features, severity, and evolution. The pattern of dysphagia in the early disease stages differs according to the MSA phenotype. Swallowing dysfunctions in the oral phase, particularly delayed bolus transport from the oral cavity to the pharynx, were observed in MSA-C early in the disease course, caused by disturbed coordination of the tongue due to cerebellar dysfunction [12], while pharyngeal phase was not affected at onset. On the contrary the pharyngeal phase is more frequently impaired in MSA-P early in the disease course [21].

Further in the early stage of the disease, the swallowing dysfunction induced by parkinsonism in MSA-P patients appears worse than the dysfunction induced by cerebellar impairment in MSA-C patients, and progressive worsening of dysphagia in MSA-C seems related to overlapping parkinsonism [12,21,24]. A recent cross-sectional and longitudinal study retrospectively comparing the progression of oropharyngeal dysphagia in MSA subtypes found that patients with MSA-P required diet modification earlier than those with MSA-C, but no significant difference between the two groups was found in the latency of tube feeding onset [25].

The progression of dysphagia, in terms of food consistency involvement has not been investigated in MSA, however studies in PD showed that swallowing is safer with the ingestion of semiliquid than liquid boluses [26].

Although the oropharyngeal phases of swallowing are most impaired in MSA, subtle esophageal dysmotility may also occur. Main dysfunctions observed by means of VFSS and high-resolution manometry, even in patients who were asymptomatic, included food stagnation in the esophagus, reduced esophageal peristalsis, hypomotility of the distal esophagus, abnormally high upper esophageal sphincter (UES) pressure and uncoordinated proximal esophageal contraction pressure during

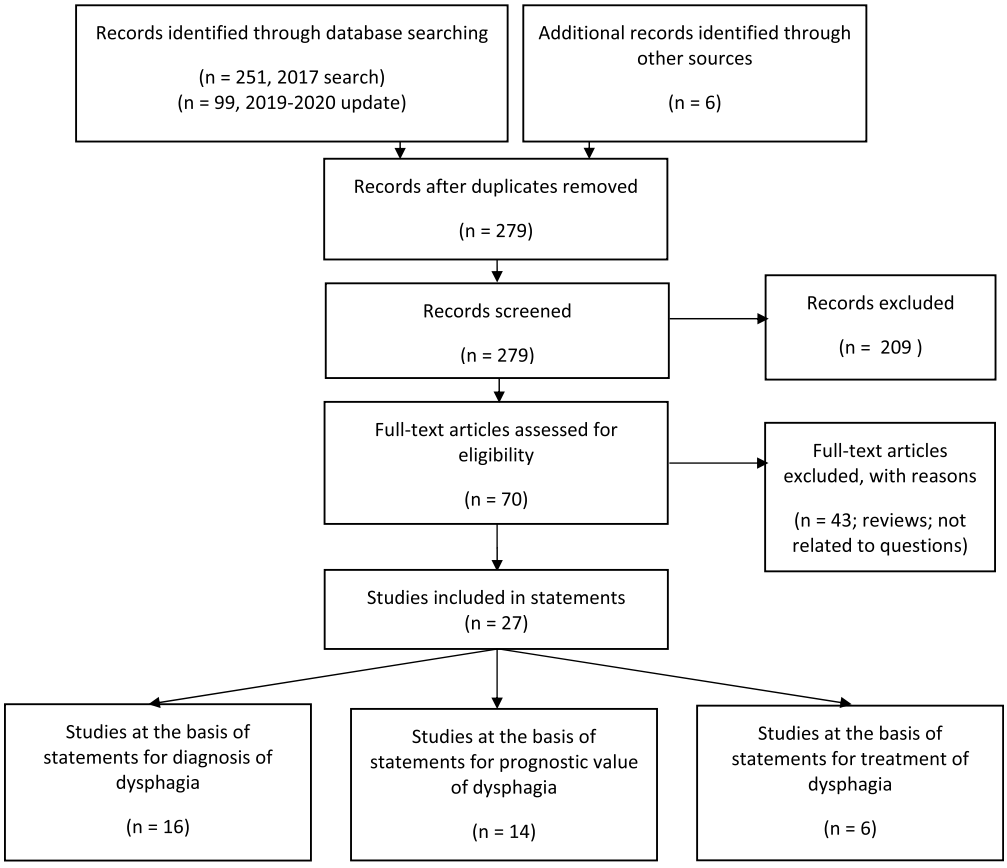

Fig. 1. Preferred reporting items for systematic reviews and meta-analyses flow diagram. Process and result of the systematic search for studies on dysphagia in multiple system atrophy.

Table 1
Primary studies that form the basis of the statements on diagnosis with their level of evidence.

First author, yr	N. of patients	Study design	Topic	Level of evidence class
Higo, 2003 [20]	29 MSA	case series	Dysphagia instrumental features; videofluoroscopy; videomanofluorometry; swallowing function scale	IV
Wenning, 2004 [37]	40 MSA	cross-sectional	Rating scale for MSA	III
Higo, 2005 [12]	21 MSA	case series	Dysphagia instrumental features; videofluoroscopy; swallowing function scale	IV
Alfonsi, 2007 [30]	9 MSA, 9 PSP, 28 PD, 24 HC	cross-sectional	Dysphagia instrumental features; EMG	III
Kollensperger, 2008 [3]	57 MSA, 116 PD	cross-sectional	Differential diagnosis between MSA-P and PD; diagnostic role of dysphagia	II
Alfonsi, 2010 [49]	5 MSA	cross-sectional	EMG features predict the response to treatment/ dysphagia score	IV
Isono, 2015 [34]	7 MSA, 6 SCA3	cross-sectional	Differential diagnosis between MSA-P and PD; videofluoroscopy; swallowing function scale	III
Taniguchi, 2015 [23]	16 MSA, 16 ALS	cross-sectional	Dysphagia instrumental features; videofluorography	III
Sulena, 2017 [29]	22 MSA, 26 PD, 25 PSP, 20 HC	cross-sectional	Dysphagia instrumental features; 3-ounce water swallow test	III
Umemoto, 2017 [24]	61 MSA	case series	Dysphagia instrumental features; videofluoroscopic swallowing study	IV
Claus, 2018 [27]	10 MSA, 10 PD, 10 PSP, 10 HC	cross-sectional	Dysphagia instrumental features; high resolution manometry; fiberoptic endoscopic evaluation of swallowing	III
Lee, 2018 [21]	59 MSA	cohort	Dysphagia instrumental features; videofluoroscopic swallowing study	IV
Miki, 2019 [5]	203 MSA	cohort	Differential diagnosis between MSA-P and PD; prevalence and latency of dysphagia; dysphagia as milestone	IV
Warnecke, 2019 [22]	8 MSA	case series	Dysphagia instrumental features; flexible endoscopic evaluation of the swallowing	IV
Ueha, 2018 [28]	25 MSA	case series	Dysphagia instrumental features; high-resolution manofluorography	IV
Do, 2020 [25]	59 MSA	cohort	Dysphagia instrumental features; videofluoroscopic swallowing study; videofluroscopic dysphagia scale	IV

Abbreviation: MSA = Multiple system atrophy, PSP =Progressive supranuclear palsy, PD = Parkinson's disease, HC = Healthy control, yr = year.
Each study was classified according to various descriptors, including topic domain, sample size, design, presence of diagnostic criteria of the syndrome, and level of evidence according to the Classification of Evidence Schemes of the Clinical Practice Guideline Process Manual of the American Academy of Neurology [19]. Each study was graded according to its risk of bias from Class I to Class IV (with I highest quality and IV lowest quality). Risk of bias was judged by assessing specific quality elements (i.e., study design, patient spectrum, data collection, and masking) for each clinical topic (diagnostic accuracy, prognostic accuracy, and treatment).

Table 2
Primary studies that form the basis of the statements on prognosis with their level of evidence.

First author, yr	N. of patients	Study design	Topic	Level of evidence class
Muller, 2001 [8]	15 MSA	cohort	Dysphagia predicts shorter survival: 15 months after the onset of dysphagia	III
Higo, 2003 [20]	29 MSA	case series	Swallowing dysfunctions and aspiration	IV
Higo, 2003 [35]	36 MSA	case series	Swallowing dysfunctions and aspiration	IV
Higo, 2005 [12]	21 MSA	case series	Swallowing dysfunctions and aspiration	IV
Krim, 2007 [6]	86 MSA	cohort	Dysphagia predicts shorter survival both in univariate and multivariate models	II
Papapetropoulos, 2007 [13]	21 MSA, 21 PD	case-control	Acute aspiration, bronchopneumonia and causes of death in MSA	III
Tada, 2007 [9]	49 MSA	cohort	Acute aspiration, bronchopneumonia and causes of death in MSA	III
O'Sullivan, 2008 [2]	83 MSA, 110 PSP	cohort	Dysphagia as outcome (milestone)	II
Taniguchi, 2015 [23]	16 MSA, 16 ALS	case-control	Swallowing dysfunctions and aspiration	IV
Flabeau, 2017 [51]	28 MSA	cohort	Acute aspiration, bronchopneumonia and causes of death in MSA	II
Lee, 2018 [21]	59 MSA	case series	Swallowing dysfunctions and aspiration	IV
Zhang, 2018 [50]	131 MSA	cohort	Acute aspiration, bronchopneumonia and causes of death in MSA	II
Do, 2020 [25]	59 MSA	cohort	Swallowing dysfunctions and aspiration	IV
Lieto, 2019 [10]	66 MSA	cohort	Dysphagia does not predict shorter survival	III

Abbreviation: MSA = Multiple system atrophy, PD = Parkinson's disease, PSP = progressive supranuclear palsy, ALS = amyotrophic lateral sclerosis, yr = year. Each study was classified according to various descriptors, including topic domain, sample size, design, presence of diagnostic criteria of the syndrome, and level of evidence according to the Classification of Evidence Schemes of the Clinical Practice Guideline Process Manual of the American Academy of Neurology [19]. Each study was graded according to its risk of bias from Class I to Class IV (with I highest quality and IV lowest quality). Risk of bias was judged by assessing specific quality elements (i.e., study design, patient spectrum, data collection, and masking) for each clinical topic (diagnostic accuracy, prognostic accuracy, and treatment).

swallowing and resting [23,27,28].

Patients with PD and MSA had a similar pattern of dysphagia, but dysphagia occurred earlier in the disease course and was symptomatic in a higher proportion of patients with MSA than in those with PD [20, 29–31]. The electrophysiological evaluation of the oral-pharyngeal swallowing in PD, MSA-P, and PSP patients showed a prolonged duration of laryngeal–pharyngeal mechanogram in all groups, suggesting that bradykinesia may be the main cause of swallowing difficulties.

Table 3
Primary studies that form the basis of the statements on treatment with their level of evidence.

First author, yr	N. of patients	Study design	Topic	Level of evidence class
Higo, 2003 [35]	36 MSA	case series	Tracheotomy negatively influences swallowing	IV
O'Sullivan, 2008 [2]	83 MSA, 110 PSP	cohort	PEG as milestone of MSA	IV
Ogawa, 2009 [57]	1 MSA	case report	PEG/PEG-J/PEJ	IV
Alfonsi, 2010 [49]	5 MSA	case series	Botulinum toxin	IV
Ueha 2016 [56]	18 MSA	before-after study	Tracheostomy/laryngeal closure/surgical decision-making flow-chart	IV
Perry, 2018 [54]	1 MSA	case report	Biofeedback in strength and skill training	IV

Abbreviation: MSA = Multiple system atrophy, PSP = progressive supranuclear palsy, PEG = percutaneous endoscopic gastrostomy, J = jejunal, yr = year.
Each study was classified according to various descriptors, including topic domain, sample size, design, presence of diagnostic criteria of the syndrome, and level of evidence according to the Classification of Evidence Schemes of the Clinical Practice Guideline Process Manual of the American Academy of Neurology [19]. Each study was graded according to its risk of bias from Class I to Class IV (with I highest quality and IV lowest quality). Risk of bias was judged by assessing specific quality elements (i.e., study design, patient spectrum, data collection, and masking) for each clinical topic (diagnostic accuracy, prognostic accuracy, and treatment).

However, MSA-P and PSP patients frequently presented a distinct finding early in the disease course, which is an opening deficit of the UES during the transit of the bolus from the pharynx to the esophagus. This deficit corresponds to the reduction or absence of the normal EMG silence of the cricopharyngeal muscle during the pharyngeal phase of swallowing [30].

Although studies addressing the pathophysiology of dysphagia in MSA are lacking, results of the above study suggest a common phathophysiological mechanism causing dysphagia in PD, MSA-P, and PSP, mainly related to the degeneration of cholinergic neurons of the pedunculopontine tegmental nucleus. However other brainstem central pattern generators of swallowing are probably involved in MSA and PSP, and could explain the earlier occurrence and the higher severity of dysphagia in these disorders [30,32,33].

A single case series study compared dysphagia in MSA-C with dysphagia in hereditary spinocerebellar ataxia type 3, and found an earlier onset and a faster progression of dysphagia in the MSA-C group [34].

Signs and symptoms of oropharyngeal dysphagia should be investigated in the clinical history of patients with MSA. These included choking or coughing during or immediately after swallowing, or in some cases a fear of swallowing, food leaking from the oral cavity, drooling, and a sensation of food being stuck in the throat [11,21,29]. Functional deficits of the upper aerodigestive tract can result in the presence of residual food in the oral cavity, pharynx and laryngeal vestibule, adding voice hoarseness or a wet and gurgly voice to other vocal changes related to the disease [11,12,35]. Drooling is linked to bradykinesia/-hypokinesia involving the oral preparatory and propulsive phases of swallowing but pharyngeal/orofacial dystonia may play an additional role [3,11,30]. Changes in posture during oral food intake, changes in eating habits (e.g., avoidance of a particular food consistency), unusual prolongation of mealtimes and weight loss are also signs that deserve clinical attention [11,36]. Frequent fever of unexplained origin, coughing, bronchitis and pneumonia may be investigated as possible consequences of aspiration.

A first step in screening for dysphagia includes the use of questionnaires or scales. A simple clinical assessment is included in the Unified MSA Rating Scale (UMSARS) [37]. Self-administered questionnaires are routinely used for screening for the presence of dysphagia in general neurological conditions (e.g. Eating Assessment Tool-10 questionnaire) [38] or specifically in PD (the swallowing disturbance questionnaire and the Munich Dysphagia test-PD) [39,40] but are not validated in MSA. An alternative or next step should be the use of specific clinical evaluations like the Mann Assessment of Swallowing Ability, the Test of Masticating and Swallowing Solids and the volume-viscosity swallow test, which is validated in PD patients against VFSS and measures the volume that can be swallowed with one swallow in a stepwise manner (5, 10, 20 ml) for multiple consistencies [41–43].

Alternately, the simplified cough test is also a useful means of detecting silent aspiration in patients with neurological disorders reporting symptoms of dysphagia [44].

The VFSS and FEES are considered the two reference instrumental methods for objectively investigating swallow dysfunction and have been used to detect the presence and the severity of dysphagia in MSA patients [11,20,22,35]. The severity is measured with rating scales tailored for instrumental investigations like the Penetration-Aspiration Scale [45], the Yale Pharyngeal Residue Rating Scale [46], the Normalized Residue Ratio Scale [47], and the Dynamic Imaging Grade of Swallowing Toxicity scale [48]. Recently, a standardized FEES protocol for MSA was applied in a small cohort of patients and although results should be confirmed in prospective studies on larger samples, this protocol may help to assess relevant swallowing dysfunctions and identify specific abnormalities in MSA patients [22].

High-resolution manometry is useful to assess disorders of esophageal peristalsis [20,23,27,28]. Also, electrokinesigraphic studies of the oropharyngeal phases of swallowing have been used to evaluate pathophysiological mechanisms of oropharyngeal dysphagia in MSA [30,49].

As dysphagia in MSA occurs early and develops progressively, it is prudent to screen patients both at the time of diagnosis and periodically thereafter to prevent complications and improve disease management [23,25,34].

3.2.1. *Statements on the diagnosis of dysphagia*

Statements are based on core literature consisting of Class II to IV studies (Table 1) and on expert adaptation of knowledge from the literature on dysphagia, selected by applying the analogy principle [3,5,12,20–25,27–30,34,37,49].

- Patients should be screened at the time of diagnosis and periodically thereafter.
- The clinical history should include:
  - Coughing/choking during/after eating or drinking
  - Wet/gurgly voice after eating or drinking
  - Hoarse voice
  - Perception of food or pills stuck in the throat
  - Food modifications or posturing adopted spontaneously
  - Prolonged meal duration
  - Fatigability during meals
  - Drooling or food falling from mouth
  - Recurrent pneumonia
  - Recurrent episodes of fever of unknown origin
  - Unexplained weight loss
- A simple clinical assessment of dysphagia is included in UMSARS.
- The evaluation of dysphagia comprises a screening questionnaire and clinical and instrumental assessment (VFSS, FEES and manometry).
- VFSS and FEES assess both presence and severity of dysphagia and the result can be documented using a scale.

3.3. Prognostic value of dysphagia

Two studies found an association between dysphagia and survival in patients with MSA [6,8]. A retrospective study of an unselected cohort of 86 MSA patients enrolled throughout the Aquitaine region (France) with prospective follow-up on mortality ascertained by telephone calls found that the presence of dysphagia, whose degree of severity was not assessed, predicts shorter survival with a relative risk of 2.56 [6]. In a retrospective study from 7 centers that analyzed the medical records of 15 pathologically confirmed MSA cases, the latency to complaint of dysphagia was highly correlated with total survival time (median time to death after dysphagia onset: 15 months, 6–68) [8].

A retrospective chart review of 83 pathologically confirmed MSA patients showed that severe dysphagia and other milestones of disease progression did not independently predict survival in MSA. However, the time to reach any of the seven milestones of disease advancement predicted disease duration until death [2]. Indeed, the authors point out that "when patients with MSA and early autonomic dysfunction develop severe dysphagia, there is a shorter interval from this point to death."

In a recent retrospective study including only MSA-C patients (N = 66), the prevalence of dysphagia at last visit, which was 78%, was not an independent predictor of survival (HR 0.98 [0.41 to 2.32], p = 0.964) but nor was any other clinical sign or symptom [10]. The contrasting results of these two studies are probably due to differences in the severity of dysphagia and in the observed population limited to MSA-C in one study.

Dysphagia caused by delays in the oral and pharyngeal phases of swallowing, in combination with laryngeal (airway and sensory) and esophageal sphincter disturbances, may lead to both acute aspiration and aspiration pneumonia [12]. One third of 21 pathologically confirmed patients with MSA had reported recurrent episodes of aspiration and PEG insertion did not prevent them [13]. Studies evaluating whether specific features of dysphagia affect overall survival in MSA are lacking. However, swallowing dysfunction in the oral and pharyngeal phase, aspiration and food stagnation within the esophagus were instrumentally observed in MSA [12,20,21,23,35] and may lead to bronchitis, pneumonia and choking [25]. Acute aspiration and bronchopneumonia, which may result from silent aspiration, are leading causes of death in MSA [9,13,50,51].

Dysphagia can be distressing for patients and caregivers and impair quality of life as observed in patients with PD [52]. However, the impact of dysphagia on quality of life in MSA remains to be determined. Similarly, whether dysphagia has a different prognostic significance between MSA-P and MSA-C in terms of quality of life and survival has not been evaluated.

3.3.1. Statements on the prognostic value of dysphagia

The following statements are based on core literature consisting of Class II to IV level studies (Table 2) and on expert adaptation of knowledge from the literature on dysphagia, selected by applying the analogy principle [2,7–10,12,13,20,21,23,25,35,50,51].

- There is evidence that dysphagia is associated with poor survival.
- Aspiration is a consequence of dysphagia that affects survival.
- There is no evidence that specific features of dysphagia affect survival.
- Dysphagia can be distressing for patients and caregivers and can lead to pulmonary complications and malnutrition.
- The impact of dysphagia on health-related quality of life remains to be determined.

3.4. Treatment of dysphagia

The aim of oropharyngeal dysphagia treatment is to improve the transport of food and liquids to prevent respiratory complications, malnutrition and dehydration. There are no known specific effective procedures for the treatment of dysphagia in patients with MSA.

Despite the high prevalence of oral symptoms in MSA, treatment strategies for these symptoms are not recommended, since no study has addressed them systematically or investigated a potential therapeutic approach to date.

To treat the component of dysphagia in MSA related to parkinsonism, the same strategies used for PD could be adopted. Evidence- and consensus-based guidelines of the European Society for Clinical Nutrition and Metabolism have provided recommendations for nutritional disorders and malnutrition in PD [53]. However, there is no strong evidence in the literature for compensatory and rehabilitative practices for dysphagia in PD and most traditional dysphagia therapies in the treatment of stroke patients were not confirmed to be effective for PD patients [31,53].

The following compensatory treatments were selected in the present Consensus based on expert opinion:

1) Modifications of the texture of liquids and foods (i.e. to jelly or thickened liquids) or of bolus volume.
2) Postural adjustment by chin down movement (chin-tuck maneuver) when attempting to swallow (this postural adjustment is thought to be effective against aspiration during swallowing because gravity helps the food bolus to pass easily through the esophagus, reduces horizontal movement of the hyoid bone, facilitates vertical movement of the epiglottic base, and narrows the airway entrance). In MSA patients with antecollis, this postural compensation technique is not applicable. In these cases attempts can be made to correct the antecollis by injecting botulinum toxin into the flexor muscles of the neck, although the technique is effective only in a few cases.
3) Supraglottic swallow maneuvre during swallowing (a technique aiming to close the vocal cords and the supraglottic structures to protect the upper airways well in advance of the bolus arriving).
4) Enhancement of oral/dental care and proper positioning of the patient's head, both after meals and during sleep (to reduce the risk of aspiration pneumonia).

Studies on dysphagia rehabilitation in MSA are lacking. A single case report showed improvement of swallowing functions in an MSA-C patient using biofeedback in strength and skill training, a task-specific swallowing rehabilitation that targets motor control and swallowing precision by providing feedback regarding the timing and strength of muscle contractions [54].

If a patient is aspirating even only small amounts of food but does not cough efficiently, or exhibits serious aspiration and suffers from aspiration pneumonia and compensatory treatments fail to resolve the aspiration, non-oral feeding techniques such as gastrostomy tube feeding are usually performed, although evidence of their impact on survival are lacking [2].

The injection of BTX into the UES was shown to subjectively improve dysphagia, evaluated two months after treatment through the dysphagia severity scale, in 5 out of 6 MSA patients presenting UES opening deficit due to cricopharyngeal muscle hyperactivity [49,55].

A single study evaluating the relationship between vocal fold motion impairment in MSA patients and swallowing dysfunction did not find significant differences in swallowing function between patients with and without vocal fold motion impairment suggesting that vocal fold motion impairment alone does not warrant change to non-oral feeding techniques [35]. In the same study, tracheotomy negatively influenced swallowing as the three patients who underwent tracheotomy then required tube feeding or laryngectomy [35]. Similar results were reported in a subsequent study, where 7 out of 11 MSA patients after tracheotomy for airway narrowing or for dysphagia showed worsening or no improvement of swallow function, assessed by the penetration aspiration scale [56].

Finally, in cases of severe dysphagia and esophageal dysmotility, alternative nutritional support can be provided. For instance, in a

patient with MSA who had experienced recurrent aspiration pneumonia while receiving PEG nutrition due to gastroesophageal reflux, a jejunal extension to PEG was applied; then, following subsequent jejunal tube occlusion, a percutaneous endoscopic jejunostomy was placed for nutrition [57].

3.4.1. Statements on dysphagia treatment

The following statements are based on core literature consisting of Class IV level studies (Table 3) and expert adaptation of knowledge from the literature on dysphagia, selected on the basis of the analogy principle [2,35,49,54,56,57].

- Dysphagia in MSA needs to be managed by a multidisciplinary team including otorhinolaryngologists, phoniatrists, speech and language pathologists, dieticians, and neurologists. Periodic follow-up is required as dysphagia worsens with disease progression.
- There is no evidence of effective treatment for dysphagia in patients with MSA.
- Compensatory strategies (i.e. diet modification, swallowing maneuvers and head postures) should be applied when possible.
- In specific cases of isolated UES hyperactivity, BTX injections may be effective.
- PEG feeding may be applied when there is a severe risk of malnutrition, dehydration, and pulmonary complications.
- There is no evidence that PEG improves survival or quality of life in MSA.

4. Research needs

The present Consensus Conference represents the first effort to systematically review literature and to provide statements on dysphagia, a frequent and disabling symptom in MSA that could impact on the disease course causing serious consequences. Despite its clinical relevance, few studies in the literature have focused on diagnosis, prognosis and treatment of dysphagia in MSA, most of them of class III-IV quality, leading to statements necessarily being based on expert opinion. Several research gaps emerged during the consensus meeting concerning dysphagia in MSA.

One main challenge is the early diagnosis of dysphagia in these patients. To date, ad hoc questionnaires for the screening and follow-up of dysphagia in MSA are lacking. The description of dysphagia given in UMSARS part I [37] appears incomplete and fails to highlight disease-specific aspects such as the role of parkinsonism, autonomic symptoms and cerebellar disorders in determining dysphagia in the various forms of MSA. Thus, it is recommended that experts design MSA-specific clinical screening questionnaires and scales or validate for MSA existing questionnaires specific for PD, such as the Swallowing Disturbance Questionnaire scale for PD [39].

FEES and VFSS are the two reference instrumental investigations for assessing the presence of dysphagia and its severity. Standardized FEES or VFSS protocols for MSA should be applied in prospective studies on large samples to verify their utility in identifying specific swallowing abnormalities in MSA patients [22]. Electrokinetic study of swallowing is a new instrumental method for studying the pathophysiological mechanisms of the oropharyngeal phases of swallowing, and could allow the development of a rational and standardized treatment method in MSA patients with dysphagia [30,49]. Its diagnostic accuracy should be compared with FEES and VFSS in a multicenter prospective study.

Moreover, esophageal dysmotility causing dysphagia in MSA should be evaluated in a large sample of patients to establish whether there are differences between the MSA-P and MSA-C phenotypes, whether the onset of esophageal dysmotility is related to particular phases in the disease course, and whether specific clinical features and the severity of dysphagia might be related to esophageal dysmotility.

Concerning the anatomical and pathophysiological correlates of dysphagia in MSA, further studies analysing correlations between neuroimaging or neurofunctional techniques (e.g. magnetic resonance imaging, functional magnetic resonance imaging, positron emission tomography, and magnetoelectroencephalography) and aspects of MSA dysphagia (its presence, characteristics and severity) should be perfomed.

Currently, there are no specific guidelines for managing dysphagia in MSA, with much of the current treatment adapted from recommendations for PD. Longitudinal evaluation of different compensatory therapies and rehabilitation strategies like speech therapy interventions should be investigated. In this regard, it would be useful to assess whether voice treatments can provide significant advantages in MSA dysphagia, as is the case of the Lee Silverman Voice Treatment for PD [53].

Proposed treatments, such as BTX injection into the cricopharyngeal muscle, require verification with longitudinal controls; it also needs to be evaluated whether the effectiveness of this treatment is enhanced by specific speech therapy designed to improve UES opening during swallowing [55].

No studies have examined the effects of peripheral stimulation (of neuromuscular structures or of the pharyngeal mucosa) or central neurostimulation (of the motor or premotor cortex, cerebellum) in dysphagia in MSA patients.

Studies to determine at which disease stage PEG placement is appropriate are warranted in order to guide physicians. Finally, it is unknown whether this nutritional modality has different effects on prognosis in MSA-P and MSA-C. By combining instrumental methods with reliable rating scales, it might prove possible to identify the most appropriate time (if any) for PEG placement, establishing factors on which to base this decision, as well as the impact of PEG on survival and quality of life.

The development of these studies and of guidelines on diagnosis and treatment of dysphagia in MSA, will benefit from the involvement of several professional figures, neurologists, otorhinolaryngologists, phoniatrists, speech and language pathologists and dieticians.

This literature review, and the emergence of several research gaps on diagnosis, prognosis and treatment for dysphagia, emphasizes the need for prospective multicenter studies with a large number of patients and randomized-controlled design to provide a high level of evidence on the management of dysphagia in patients with MSA.

Author contributions

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Declaration of competing interest

The authors declare that they have no known competing interests or personal relationships that could have appeared to influence the work reported in this paper.

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