UNIVERSITÀ DEGLI STUDI DI MILANO

DOCTORAL PROGRAMME IN NUTRITIONAL SCIENCE

DYSPHAGIA IN NEURODEGENERATIVE DISEASES: SWALLOWING PROFILES AND NUTRITIONAL RISK

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Abstract

ABSTRACT

The PhD dissertation focuses on the topic of dysphagia in neurodegenerative diseases. The first aim was to investigate the frequency of dysphagia in 55 patients with different stages of Huntington's disease through an instrumental assessment of swallowing. Dysphagia was found in 30% of the patients in the early stage, in 90% of patients in the moderate stage, and in all patients in the advanced stage. Diagnostic accuracy of a neurological clinical scale was investigated and a cut-off was identified to guide the neurologists in the referral to the swallowing team. A second study analyzed the association between maximum tongue pressure and signs of dysphagia during fiberoptic endoscopic evaluation of swallowing in patients with Amyotrophic Lateral Sclerosis. Results showed that patients with residue in the pyriform sinus had lower maximum tongue pressure. Measuring maximum tongue pressure in patients with Amyotrophic Lateral Sclerosis may provide additional information on swallowing function and may potentially represent a marker for eating-related fatigue. Chapter 4 describes the development and validation of the Mealtime Assessment Scale (MAS), a clinical protocol to assess swallowing safety and efficacy during meal. Finally, the association between dysphagia and risk of malnutrition was investigated in 162 patients with neurodegenerative diseases (Huntington's disease, Parkinson's disease, and Amyotrophic Lateral Sclerosis). Age, type of oral intake, residue in the valleculae with semisolids, penetration with liquids, swallowing safety during meal, number of masticatory cycles, and oral phase duration were significantly associated with risk of malnutrition in three neurodegenerative diseases, but only age and swallowing safety during the meal were independent predictors of malnutrition risk. Clinical implications of the studies are discussed.

Riassunto

RIASSUNTO

La tesi di dottorato si focalizza sul tema della disfagia nelle malattie neurodegenerative. Il primo obiettivo è stato di indagare, tramite valutazione strumentale, la frequenza della disfagia in 55 pazienti con Malattia di Huntington in diversi stadi. La presenza di disfagia è stata riscontrata nel 30% dei pazienti in stadio precoce, nel 90% dei pazienti in stadio moderato e in tutti i pazienti in stadio avanzato. L'accuratezza diagnostica di una scala clinica neurologica è stata calcolata ed è stato identificato uno specifico cut-off per guidare i neurologi nell'invio dei pazienti ad una valutazione deglutitoria specialistica. Il secondo studio ha analizzato l'associazione tra la massima pressione linguale e la presenza di segni di disfagia alla valutazione endoscopica della deglutizione nei pazienti con Sclerosi Laterale Amiotrofica. I risultati hanno mostrato una massima pressione linguale minore nei pazienti con ristagno nei seni piriformi rispetto ai pazienti senza ristagni post-deglutitori nella medesima sede. La misurazione della massima pressione linguale può fornire informazioni aggiuntive sulla funzionalità deglutitoria nei pazienti con Sclerosi Laterale Amiotrofica e potrebbe, potenzialmente, rappresentare un marker di affaticamento al pasto. Il capitolo 4 descrive il processo di creazione e validazione della Mealtime Assessment Scale, un protocollo clinico per la valutazione della sicurezza e efficacia deglutitoria durante il pasto. Infine, è stata studiata l'associazione tra disfagia e rischio di malnutrizione in 162 pazienti con una diagnosi di malattia neurodegenerativa (Malattia di Huntington, Malattia di Parkinson e Sclerosi Laterale Amiotrofica). L'età, il tipo di dieta orale, la presenza di ristagni nelle vallecule con i semisolidi, la presenza di penetrazione con i liquidi, la sicurezza deglutitoria al pasto, il numero di cicli masticatori e la durata della fase orale sono risultati essere significativamente associati al rischio di malnutrizione, ma soltanto l'età e la sicurezza deglutitoria al pasto sono fattori predittivi indipendenti. Le implicazioni cliniche degli studi sono discusse all'interno della tesi.

Contents

CHAPTER 1

General Introduction and Outline

1.1 Dysphagia in neurodegenerative diseases

1.1.1 Dysphagia: definition, manifestation, and complications

Swallowing involves a rapid and highly coordinated sequence of neuromuscular actions that ensures the passage of any substance (food, liquid, saliva, mucus, drugs) from the mouth to the stomach via the pharynx and the esophagus. Dysphagia is the term used to describe any difficulties in swallowing. Oropharyngeal dysphagia (OD) refers to any alterations of the bolus transit from the mouth to the esophagus.

Different diseases, neurological and non-neurological, may lead to OD. Two aspects of swallowing are typically impaired in OD: swallowing safety and swallowing efficacy[1]. Safety is defined as "the patient's ability to ingest all needed calories and water with no respiratory complications,"[1] typically measured as the ability to transfer the bolus without laryngeal penetration or tracheal aspiration. Efficacy is defined as "the patient's ability to ingest all the calories and water he or she needs to remain adequately nourished and hydrated,"[1] typically measured as the ability to transfer the bolus without post-swallow pharyngeal residue. Along with pharyngeal signs of OD, other signs of swallowing impairment include, for instance, oral residue, food leakage from the lips during mastication, prolonged oral preparation, prolonged meal durations.

The importance in recognizing and managing OD lies in the fact that, irrespective of the disease, OD can lead to severe complications such as aspiration pneumonia, malnutrition and dehydration that severely impact patient's survival, clinical management and health costs[2-3]. Moreover, psychosocial consequences of OD are likewise important. Patients with OD may report diminished self-esteem, fear, anxiety, frustration, and depression. OD may lead to social isolation and increase caregiver's burden[4-5].

The dissertation will focus on OD in three neurodegenerative diseases, Huntington's disease, Parkinson's disease, and Amyotrophic Lateral Sclerosis.

1.1.2 Dysphagia in Huntington's disease

Huntington's disease (HD) is a rare incurable and progressive autosomal dominant neurodegenerative disorder caused by a CAG expansion in the *IT-15* gene, which encodes the mutated protein huntingtin. The progression is generally slow and leads to death on average 15-20 years after the onset[6]. Pneumonia has been reported to be the major cause of death in HD patients[7-8]; Hamilton and colleagues have retrospectively investigated pneumonia's etiology in this population and, although data were available only for a limited number of subjects, the 65.8% of patients showed signs related to aspiration pneumonia[9].

Presence of OD in HD has been reported[10-12]. Studies showed a prevalence ranging between 85 to 100%[13-14]. Despite it, little has been published on the topic and the experience from the clinical practice suggests that many patients with HD never access to a swallow examination within the course of the disease. The etiopathogenesis of OD in HD is quite complex and probably is correlated with motor dysfunctions caused by basal ganglia circuitry changes. Motor symptoms are heterogeneous and usually start as involuntary movements like chorea or choreo-athetosis and later progress with voluntary movement deficits including incoordination, bradykinesia, and ideomotor apraxia. When these heterogeneous movement disorders involve oropharyngeal musculature, OD arises. In addition, the behavioral and cognitive dysfunctions cause a scarce controlled and impulsive consuming of food that contributes to eating difficulties.

1.1.3 Dysphagia in Parkinson's disease

Parkinson's disease (PD) is a chronic, progressive neurodegenerative disorder resulting from the loss of neuronal cells, specifically the dopaminergic neurons of the midbrain in the substantia nigra. The main symptoms are tremor, muscular rigidity, bradykinesia and postural instability. As PD progresses, a variety of other symptoms arises, including dysphagia, dysarthria impaired gastrointestinal motility and gastroparesis, fatigue, depression and cognitive impairment. Mortality due to pneumonia is common[15-16].

Prevalence of OD reaches the 95% in the advanced stage PD[17]. The pathophysiology of OD is not clearly understood. Concerning underlying neural mechanisms, OD development seems to be mainly ascribable to the dysfunction of the central pattern generator of swallowing and the degeneration of the substantia nigra with disturbances of nondopaminergic neural networks. Typically, patients with PD exhibit impaired oral phase of swallowing in the early stages, while pharyngeal signs of OD arise with disease progression[18-19]. Rigidity, bradykinesia, and hypokinesia lead to altered timing of swallowing events both in the oral and the pharyngeal stage of swallowing[19-23].

1.1.4 Dysphagia in Amyotrophic Lateral Sclerosis

Amyotrophic Lateral Sclerosis (ALS) is a neurodegenerative disorder characterized by progressive loss of motor neurons[24]. The etiology of ALS is multifactorial. Increased oxidative stress, glutamate toxicity, mitochondrial dysfunction, inflammation and

apoptosis have been implicated in its pathogenesis[25]. Life expectancy ranges from 2 to 5 years and is largely dependent upon disease onset type.
Regardless of the site of onset, OD occurs at some point throughout ALS progression in 85% of the patients[26]. OD in ALS is the result of different pathological mechanisms: rigidity and/or weakness of muscles directly involved in pharyngeal swallowing (facial, tongue, pharyngeal, and laryngeal muscles), weakness of respiratory muscles, sensory impairment[27-29]. Analogously to PD, alterations of all phases of swallowing have been reported, although OD is usually characterized by an initial impairment of the oral phase and subsequent impairment of the pharyngeal phase[30-33].

1.2 Dysphagia and nutritional status

Malnutrition is defined as "a state resulting from lack of intake or uptake of nutrition that leads to altered body composition (decreased fat free mass) and body cell mass leading to diminished physical and mental function and impaired clinical outcome from disease"[34]. Malnutrition is commonly considered a possible complication of OD. The guidelines of the European Society for Clinical Nutrition and Metabolism (ESPEN) on clinical nutrition in neurology recognize the major role of OD in malnutrition development in the neurological setting[35]. However, the relationship between OD and malnutrition is debated in literature, mainly because of the different measures of OD and nutritional status applied in the studies.
In patients with stroke, a systematic review from 2009 concluded that the odds of malnutrition were increased in elderly, frail and institutionalized persons, in patients with excessive polypharmacy, general health decline, cognitive decline, eating dependencies, and OD[36]. However, only five of the eight studies included in the review reported a significant association between OD and malnutrition, and the pooled analysis revealed a significant effect only for trials conducted several weeks following stroke. More recently, Crary and colleagues reported a significant association between clinically assessed OD and hydration status but not with nutritional status[37].
Many studies have focused on the relation between OD and nutrition in the elderly. Older patients with OD were at higher risk of malnutrition[38-40], had lower body mass index (BMI)[38,41], but it was not related to lower intake of calories[39,42].
More recently, the bidirectional causal relationship between OD and malnutrition has been underlined. Carrión et al reported that malnutrition may further impairs swallowing in older patients with chronic OD of different etiology[43]. They found that residue at spoon-thick viscosity was increased in patients with poor nutritional status compared to those with adequate nutritional status. In a study by Saito et al, the risk of malnutrition was a independent predictor of penetration and aspiration[44]. The authors suggested the existence of a triangular link between malnutrition, neuromuscular dysfunction, and OD: OD increases the risk of malnutrition, malnutrition affects muscle and nerve function impairing force of contraction and rate of relaxation of muscle fibers, neuromuscular dysfunction additionally impairs swallowing function.

The association between OD and malnutrition in neurodegenerative disease has been poorly explored and was only based on self-reported OD. Early weight loss was found to be mainly associated with presence of OD in ALS, but a subgroup of spinal onset patients without OD at diagnosis still exhibited a severe early weight loss, similarly to bulbar patients[45]. The only study investigating the relation between OD and nutritional status in HD found that patient-reported swallowing difficulties were not associated with BMI[46]. In PD, evidence is contrasting. Sheard and colleagues showed that swallowing difficulties (patient-reported) were significantly related to malnutrition[47], whereas other authors reported that OD was not independently associated with nutritional risk or weight changes[48-49].

1.3 Aims and outline

The first aim of the PhD was to investigate swallowing function in patients with HD. As reported in the scoping review in **chapter 2**, OD is a serious health issue in HD but none of the studies evaluated the frequency and the characteristics of OD in the different stages of the disease. Therefore, a cross-sectional study was conducted to investigate whether OD affects patients with HD already at an early disease stage and whether the onset and severity of OD correlates with the onset and severity of specific motor disorders. The study on 43 patients with HD, reported in **chapter 2**, provides an insight on OD onset and progression in HD to guide the definition of a standard clinical care for OD. In **chapter 3**, the role of tongue pressure in swallowing function was investigated in 55 patients with ALS. Maximum tongue pressure is known to be a marker of disease progression and of bulbar involvement, as well as a poor prognostic factor for survival in ALS, but its association with signs of OD is not fully understood in this population. **Chapter 4** describes the development and validation of the Mealtime Assessment Scale (MAS), a clinical protocol to assess swallowing performance during meal. Instrumental assessment of swallowing is the gold standard for diagnosis of OD. However, swallowing safety and efficacy during meal consumption may not overlap swallowing safety and efficacy assessed during instrumental evaluation as other factors (e.g. environmental, cognitive, motor factors) may positively or negatively influence swallowing performance. In clinical practice, it is important to assess the patient also during meal, as it may better reflect swallowing performance in daily living than standard clinical or instrumental evaluation. Because of the lack of validated tools to document it, the MAS was developed. Finally, the study in **chapter 5** aimed to analyse the association between OD and risk of malnutrition in 162 patients with neurodegenerative diseases. Patients had a diagnosis of HD, PD, and ALS. A comprehensive swallowing examination including fibreoptic endoscopic evaluation of swallowing, oral phase efficiency assessment, and meal observation was performed. Swallowing profiles of the three groups of patients were delineated.

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CHAPTER 2

Dysphagia in Huntington's disease

SCOPING REVIEW Accepted for publication in Neurological Sciences

PhD candidate's role: Conceptualization, review design, literature search, studies' selection and data extraction, data analysis, paper writing, submission process, review and editing

ORIGINAL CONTRIBUTION Under review (Brief report)

PhD candidate's role: Conceptualization, study design, data collection, data curation, data analysis, data interpretation, paper writing

2.1 MANAGEMENT OF DYSPHAGIA IN HUNTINGTON'S DISEASE: A SCOPING REVIEW

ABSTRACT

Background. Huntington's disease (HD) is a rare neurodegenerative disorder of the central nervous system characterized by involuntary choreatic movements, cognitive, behavioral and psychiatric disturbances. Most HD suffer from oropharyngeal dysphagia (OD) and aspiration pneumonia is the leading cause of death. However, little is known about dysphagia management in HD.

Objective. A revision of the literature was conducted to depict the state-of-art on the assessment (timing and methods) and treatment of OD in HD.

Methods. Literature search was performed on PubMed and EMBASE. Study selection and data extraction were performed by two independent researchers. Disagreements were resolved by consensus. Original studies were excluded if they did not provide information on the management of OD, included patients with mixed etiologies or were included in a previous review from 2011.

Results. 507 records were identified and 24 studies were included: 16 cross-sectional studies, 2 case reports, 2 case series, 2 open-label trials, 1 pre-post study, and 1 randomized controlled trial.

Conclusions. Based on the studies retrieved, OD seems to occurs from the early stage of the disease, although no data from instrumental assessment are available. The presence of some clinical markers may alert on the need of a swallowing assessment. Timing for OD re-assessment should be based on the recommendation of the swallowing experts on a case basis. Instrumental assessment of swallowing by videofluoroscopy or fiberoptic endoscopy is feasable and recommended to diagnose dysphagia in patients with HD. Clinical assessment tools and patient-reported outcome measures may be used to complete the swallowing examination, but not to replace instrumental assessment.

The impact of pharmacological and rehabilitative treatments on OD in HD has been little studied in literature. While the effect of tetrabenazine on swallowing is still controversial, compensatory strategies seems to be applicable and efficacious. To date, there are no well-proven rehabilitative strategies to improve swallowing function in patients with HD. The topic of OD in HD remains poorly studied compared to its clinical relevance.

INTRODUCTION

Huntington's Disease (HD) is a rare neurodegenerative disorder of the central nervous system, caused by the expansion of the CAG triplet in the huntingtin gene[1,2]. It is a monogenic autosomal dominant disease that occurs in carriers of a CAG-sequence longer than 35 repeats, and its age at onset inversely correlates with CAG elongation. HD is clinically characterized by progressive motor dysfunction (mainly chorea), cognitive decline and psychiatric disturbances, such as changes in personality and depression[1-3].

Chorea, the most common and characteristic motor disturbance in HD patients, is usually present from the early stages of the disease; however, all patients develop, during the course of the disease, more or less severe parkinsonism[3]. This combination of hyperkinetic and hypokinetic disorders not only occurs in the extremities and trunk but when affect oropharyngeal muscles[4,5] causes symptoms as dysarthria and oropharyngeal dysphagia (OD)[6]. These symptoms are just part of a more complex condition that can impact on eating in general: other involuntary movements such as neck and trunk hyperextension also compromise the safety of eating as they can make eating-posture challenging to maintain[5], therefore contributing to increase the risk of aspiration during meals. Moreover, along with motor disturbances, also cognitive symptoms of HD may impact eating behavior. Tachyphagia (excessively rapid eating) is observed in patients with HD due to the lack of cognitive inhibition that regulates feeding rate[4], and usually, an increase in appetite is common in HD patients regardless of the presence of a depressive disorder.

To date, pneumonia is the leading cause of death in HD[7,8], and death occurs mostly from aspiration pneumonia, which is known to be promoted by severe impairment in swallowing function. OD contributes to increase caregiver's burden and to reduce QOL[9]. Despite its clinical relevance, little is known about OD in HD. In 2011, Heemskerk and Roos published a literature review on OD in HD in the years 1985-2009[10]. The authors retrieved only 5 studies investigating swallowing function in HD and 2 of those studies were case-reports. The review synthesized available information on the characteristics of OD in HD showing that abnormalities of swallowing in HD are found in both the preparatory, oral and pharyngeal phases of swallowing[4,5]. Moreover, the retrieved studies provided preliminary evidence on the applicability of the videofluroscopic study of swallowing (VFSS) and the efficacy of mealtimes interventions in this population. As 10 years have passed since the literature search, this scoping review aims to provide an update on current knowledge about OD in HD. In particular, the review aims to identify and summarize the existing evidence on 3 clinical questions related to the management of OD in this population: 1) When should OD be assessed in patients with HD?; 2) How should OD be assessed in patients with HD?; 3) Can pharmacological and rehabilitative treatments influence OD in HD?

METHODS

Literature searches were performed using PubMed and EMBASE. The exact search string on PubMed was ((“Huntington Disease”[Mesh]) OR ((“Huntington's Disease”) OR (“Huntington Disease”) OR (“Huntington's chorea”) OR (“Huntington chorea”) OR

(HD))) AND ((“Deglutition Disorders”[Mesh]) OR ((“Deglutition Disorder”) OR (“Deglutition Disorders”) OR (“Swallowing Disorders”) OR (“Swallowing Disorder”) OR (Dysphagia))). The search string on EMBASE was ((Huntington* AND chorea) OR (Huntington* AND disease)) AND ((swallowing) OR (dysphagia) OR (deglutition)). Language filter was applied to allow understanding of the contents of the manuscripts by the researchers. Records needed to be published in English, Italian, French, German or Spanish. The review protocol was not registered. Literature searches were executed on June 15th, 2019. No time filter was used.

A speech and language therapist (SLT) and a resident otorhinolaryngologist independently conducted study selection. Disagreements were resolved by consensus among the two raters. Papers have been selected based on their titles and abstracts, and afterward on full-text, when available. Only papers reporting original studies were included. Exclusion criteria were: studies on HD not linked to OD or not answering to the three clinical questions identified in the aims; studies including patients with mixed etiologies with no possibility to extract data on HD from those of other populations; studies already included in the review by Heemskerk and Roos[10]. In order to give an extensive overview of current knowledge on OD in HD, also grey literature and abstract on congress proceedings were included, if not duplicated in peer-reviewed publications. During full-text analysis, reference lists were screened to identify additional studies not retrieved through database searching.

The same two researchers that assessed study eligibility independently conducted the data extraction. Disagreements were resolved by consensus. For each study, design, aim, number and characteristics of participants, methods, and key findings related to the clinical question were extracted. All selected studies were summarized in tables based on the clinical question they provided an answer to. Studies were included in more than one table if they responded to two or more clinical questions.

The review was reported according to PRISMA reporting guidelines’ extension for scoping review (see Appendix 1).

RESULTS

The flow-chart for literature search, record screening and study selection is reported in Figure 1. Overall, 497 records were identified from database searching and 10 records from reference lists of full-text articles. Finally, 24 studies were included in the review. Included studies were published between 2009 and 2018. Sixteen are cross-sectional studies, 2 are case reports, 2 are case series, 2 are open-label trials, 1 is a pre-post study, and 1 is a randomized controlled trial (RCT). Among the 24 studies, 10 are papers published in peer-reviewed journals, 13 are abstract of oral or poster presentations at congresses, and 1 is an unpublished paper retrieved from an institutional repository.

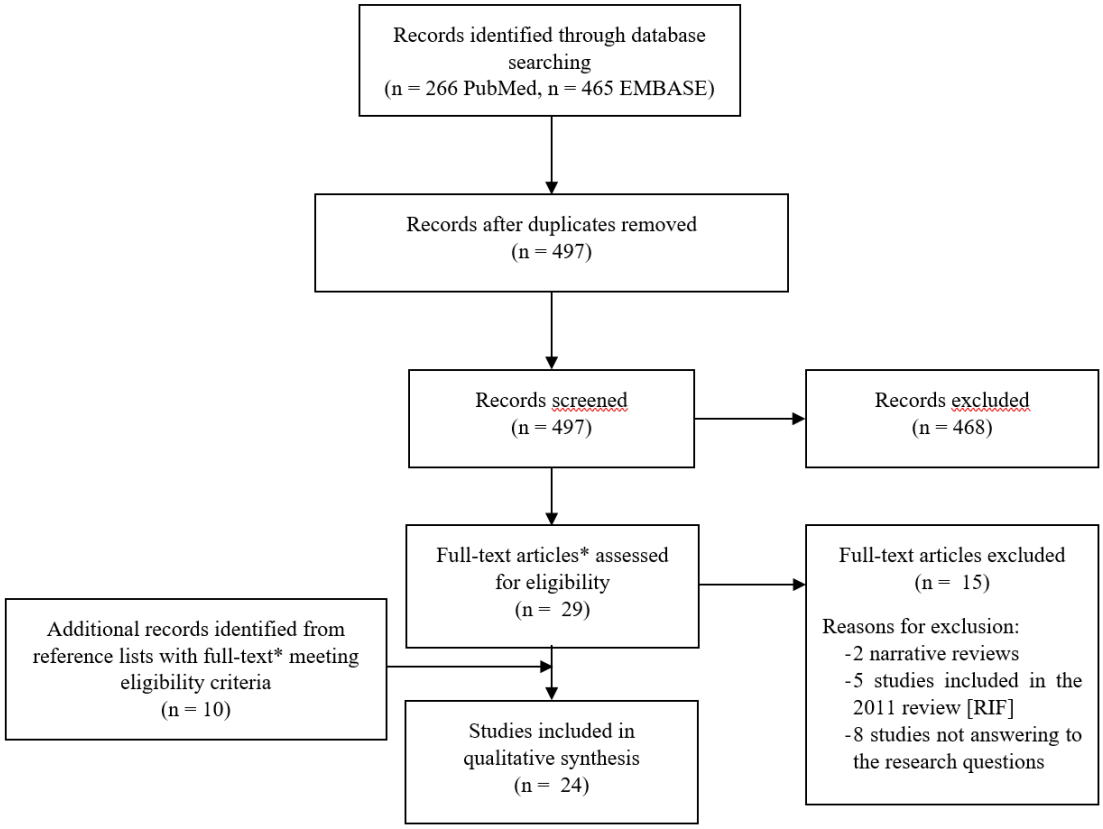
Sample sizes were relatively small for most of the studies. Indeed, 14 (58.3%) studies had a sample size <50. Apart from case-reports, the sample size of the studies assessing dysphagia through instrumental evaluation ranged from a minimum of 13 subjects to a maximum of 86. The greatest samples examined were made of 224[9] and 509[11] participants, but only included patient-reported swallowing outcomes.

Complete characteristics of included studies are listed in Tables 1 to 3. Table 1 reports 10 studies (9 cross-sectional studies and 1 case series) providing information useful to

identify OD assessment timing. Table 2 synthesized 13 studies (11 cross-sectional studies and 2 case reports) on OD assessment tools in HD. Table 3 includes 7 studies (2 case series, 2 open-label studies, 1 RCT, 1 pre-post study, and 1 cross-sectional study) investigating the effect of pharmacological and rehabilitative treatments on swallowing function in patients with HD.

Figure 1. Flow chart of study selection

*Full-text only for published articles in peer-review journals



DISCUSSION

The present review provides an updated overview of the current knowledge on the assessment and treatment of OD in HD. A previous review, conducted on the years 1985-2009 by Heemskerk and Roos, retrieved only 5 studies[10]. These studies provided information on the characteristics of OD in HD, with a description of how each swallowing phase is impacted by the disease and, preliminary evidence of the efficacy of swallowing compensatory strategies and of the applicability of the VFSS to instrumentally assess OD in this population[10]. Since 2009, the number of studies investigating OD in HD has increased and 24 studies have been included in the present review in addition to those of the previous review. However, only 10/24 studies were published in peer-reviewed journals. Thus, these data reflects the growing awareness of the scientific and clinical community on OD in HD, but the topic is still poorly explored compared to its clinical relevance in this population.

Table 1. Timing of swallowing assessment

Authors, year [study design]	Purpose of the Study	Participants	Examinations	Main Results
Dello Monaco *et al*, 2014 [13] [cross-sectional, abstract]	To investigate swallowing function in HD and provide appropriate management	N=38 HD patients	• Swallowing evaluation (*nfd*) • Clinical neurological assessment (UHDRS) • Classification according to disease stage: early, middle, late stage	• Early stage: 11% had swallowing difficulties; required compensatory strategies and diet restrictions • Middle stage: 11% had swallowing difficulties • Late stage: 26% had severe OD
Mariscal *et al*, 2014 [9] [cross-sectional, abstract]	To determine the prevalence of dysphagia in HD	N=224 HD patients	• Eating Assessment Tool-10 (EAT-10) for dysphagia symptoms • SumaCare for caregiver burden • Total Functional Capacity (TFC) for functional capacity • UHDRS for disease severity • Problem Behaviors Assessment-short form (PBA-s) for psychiatric status • Body Mass Index (BMI) for nutritional status • 36-Item Short Form Health Survey (SF36) for quality of life	• 88% of sample completed EAT-10: 37% of them complained of dysphagia symptoms (equal frequency between women and men) • Patients with OD: - were older - had higher UHDRS motor score - had lower cognitive scores and lower level of education - had lower TFC score
Schradt *et al*, 2014 [14] [cross-sectional, abstract]	To determine dysphagic symptoms by FEES according to HD-stage	N=29 HD patients	• Clinical Swallowing Assessment • FEES with different consistencies (puree, water, thickened liquid, bread, apple, and pill): morphological data and functional data for spilling, residuals, penetration and aspiration • Comparison of morphological data with functional data to characterize dysphagia in HD and to define predictors in clinical swallowing assessment	• Significant difference between HD-stages in Percutaneous Endoscopic Gastrostomy recommendation • Dysarthria, dysphonia, gag reflex and voluntary cough distinguished dysphagic from non-dysphagic patients in FEES
de Tommaso *et al*, 2015 [15] [cross-sectional]	To evaluate OD in HD in view of motor, cognitive and functional decline	N_1=37 HD patients N_2=39 controls	• Neurological and psychological examination (UHDRS) • Bedside Swallowing Assessment Scale (BSAS) • Water test: 10 mL and 60 mL bolus • Supplementary evaluations: ingestion of different food consistencies, respiratory status study, nutrition, oral health (*nfd**) • Dysphagia Outcome and Severity Scale (DOSS) on clinical evaluation by SLTs	• Motor UHDRS scores were significantly different among the 3 severity groups • DOSS scores and main clinical features (age, disease duration, motor impairment, dysarthria, tongue protrusion) significantly correlated (r = 0.315-0.542)

Authors, year [study design]	Purpose of the Study	Participants	Examinations	Main Results
Calasans dos Santos *et al*, 2016 [16] [cross-sectional, abstract]	To correlate swallowing parameters with cognitive assessment and CAG repeats	N=19 patients (13 HD and 6 controls)	• Clinical evaluation of swallowing • VFSS • Montreal Cognitive Assessment • Genetic analysis of CAG repetition	Cognitive and genetic aspects are significantly correlated to swallowing parameters in HD
Schradt *et al*, 2016 [6] [cross-sectional, abstract]	To collect data of OD features in HD To identify risk factors for severity of dysphagia in HD	N=86 HD patients (61 investigated retrospectively and 25 prospectively)	• Clinical swallowing examination • FEES • Swallowing-Quality of Life (SWAL-QOL) questionnaire	• Subclinical OD was found at all stages of the disease • Dysarthria and dysphonia were identified as predictors for the risk of aspiration
Manor *et al*, 2018 [20] [cross-sectional]	To characterize swallowing deficits in HD patients and to evaluate its relation to cognition, duration of illness and severity	N=14 HD patients	• UHDRS • Montreal Cognitive Assessment • Swallowing Disturbances Questionnaire (SDQ) • Swallowing-Quality of Life (SWAL-QOL) questionnaire • FEES	Significant correlations were found between: - volitional cough strength, ability to initiate volitional swallow and cognitive status - volitional cough and disease duration - diadochokinetic task rate and numbers of CAG repeats
Schradt et al, 2018 [17] [case series, abstract]	To study predictors of OD in HD	N = 73 HD patients	• Clinical swallowing examination • FEES • Penetration-aspiration scale (PAS)	Dysarthria and voice-change after swallow were sensitive, but not very specific predictors of penetration and aspiration. Tongue movement disorder predicted penetration/aspiration with a sensitivity>86%.
Schumann et al, 2018 [47] [cross-sectional, abstract]	To define clinical risk factors for HD-associated OD	N = 21 HD patients	• UHDRS • Clinical swallowing examination • FEES	• FEES showed penetration or aspiration in 80%. • No significant correlations were found between OD severity and any of the clinical markers (motor score, cognition, functional assessment, age, CAG).

LEGEND: nfd = not further defined; UHDRS = Unified HD Rating Scale

When to assess swallowing in HD

In the studies retrieved by Heemskerk and Ross, no data on OD in different stages of the disease were available. Based on the results of the studies included in this review, OD was found in all stages of the disease[6]. Dello Monaco and colleagues reported that 11% of the patients with HD in the early stage were judged dysphagic based on a clinical swallow examination[13]. However, because silent aspiration may occurs, clinical examination may have underestimated the prevalence of OD in the early stage of the disease. Data on the prevalence of OD in the different stages of the disease based on instrumental assessment are lacking or currently not accessible (abstracts from conference proceedings)[14].

Different authors tried to identify clinical predictors of OD, that may alert the neurologist on the necessity of a swallowing assessment. Although results are heterogeneous because of different assessment methodologies, the following clinical markers were reported to be associated with OD in more than one study:

- old age[9,15]
- high Unified Huntington's Disease Rating Scale (UHDRS) motor score[9,15]
- poor cognitive status[9,16]
- dysphonia[6,14]
- dysarthria[6,14,15,17]
- tongue movements alterations[15,17].

Yet, there are no specific cut-offs of this clinical signs that might be used to recognize for newly-reported OD or worsening of severe OD that could become life-threatening.

Thus, although different studies led to contrasting results, OD should be assessed despite the stage of the disease, in particular in case of the presence of the above-mentioned clinical markers. Re-assessment of OD should be based on the recommendation of swallowing experts and customized on the individual case. Longitudinal studies on the evolution of swallowing function are required to guide the definition of general recommendation on the timing of swallowing re-assessment.

How to assess OD in HD

Different techniques are used to assess OD, either clinical or instrumental or both. Instrumental assessment of swallowing using VFSS or fiberoptic endoscopic evaluation of swallowing (FEES) is the "gold standard" for the diagnosis of OD. The two methods for instrumental assessment have been demonstrated to yield comparable sensitivity and specificity to signs of OD and, therefore, are considered complimentary[18]. The previous review reported a first study using VFSS in patients with HD[10]. In the present review, the majority of the studies included assessed OD instrumentally. Beside VFSS, FEES was applied in some of the studies, pointing out the feasibility to perform this procedure in the population of HD[19-20]. Therefore, there is evidence that both FEES and VFSS can be used to diagnose OD in patients with HD. No study has compared FEES and VFSS in this population, nor

Table 2: Tools for swallowing assessment in HD

Authors, year [study design]	Purpose of the Study	Participants	Examinations	Main Results
SELF-ASSESSMENT				
Heemskerk *et al*, 2014 [33] [cross-sectional]	To develop and validate a self-assessment questionnaire for OD in HD	N= 55 HD patients	• Huntington's Disease Dysphagia Scale (HDDS) • Swallowing Disturbance Questionnaire (SDQ)	• Final version of the HDDS made up of 11 items • Cronbach's alpha = 0.728 • Correlation with SDQ for construct validity: r = 0.734 • Inter-rater reliability: Intraclass Correlation Coefficient = 0.754
Carlozzi *et al*, 2017 [34] [cross-sectional]	To develop a patient-reported outcome measure to assess the impact of speech and swallowing difficulties in HD	N=507 prodromal or manifest HD patients	• Huntington Disease Health-Related Quality of Life (HDQLIFE) measurement system • UHDRS	Two separate unidimensional sets of item were created: Speech difficulties (27 items) and Swallowing difficulties (16 items)
Carlozzi et al, 2018 [11] [cross-sectional]	To determine whether and at what stage cognitive impairment and HD disease progression may limit the utility of PRO measures	N = 509 patients with premanifest, early-stage, or late-stage HD	• Huntington Disease Health-Related Quality of Life (HDQLIFE) measurement system • UHDRS • Total Cognition Score = Stroop Color Word Test score + symbol digit modalities test score	For the HDQLIFE Swallowing, Total Cognition Scores <179 and <134 reduced reliability to <0.80 (from good to acceptable) and <0.70 (from acceptable to inadequate)
Boileau et al, 2018 [48] [cross-sectional, abstract]	To determine clinical validity of the HDQLIFE Speech and Swallowing PRO measures	N_1= 31 patients with premanifest, early-stage, or late-stage HD N_1= 31 controls	• Huntington Disease Health-Related Quality of Life (HDQLIFE) measurement system	HDQLIFE Swallowing Difficulties showed a Cronbach's alpha =0.89 (internal consistency) and was able to differentiate between controls, premanifest, early-HD, and late-HD participants (known groups validity).
CLINICAL ASSESSMENT				
Schradt *et al*, 2014 [14] [cross-sectional, abstract]	To investigate clinical assessment diagnostic accuracy compared to FEES in HD	N=29 HD patients	• Clinical Swallowing Assessment including 90-mL water swallow test • FEES with different consistencies (puree, water, thickened liquid, bread, apple and pill): morphological data and functional data for spilling, residuals, penetration and aspiration	The 90-mL water swallow test is not a sufficient diagnostic test to exclude OD in HD

Authors, year [study design]	Purpose of the Study	Participants	Examinations	Main Results
de Tommaso *et al*, 2015 [15] [cross-sectional]	To evaluate OD in HD in view of motor, cognitive and functional decline	N=37 HD patients	• Neurological and psychological examination (UHDRS) • Bedside Swallowing Assessment Scale (BSAS) • Water test: 10 mL and 60 mL bolus • Supplementary evaluations: ingestion of different food consistencies, respiratory status study, nutrition, oral health (*nfd*) • Dysphagia Outcome and Severity Scale (DOSS) on clinical evaluation by SLTs	According to BSAS: 35.1% had relevant/serious swallowing difficulties
INSTRUMENTAL ASSESSMENT				
Vogel *et al*, 2011 [49] [retrospective cross-sectional, abstract]	To describe frequency and nature of swallowing deficits in HD using VFSS	N=45 HD patients	• Retrospective analysis of 45 VFSS during ingestion of liquid and solid boluses as per established clinical protocols (*nfd*) • Bethlehem Assessment Scale used to describe the first 3 phases of swallow: oral-preparatory, oral and pharyngeal	• 100%: reduced tongue capacity to collect and propel bolus • 100%: reduced elevation of soft palate • 100%: delayed swallow reflex initiation • 89%: valleculae pooling • 91%: reduced pharyngeal peristalsis • 55%: aspiration on at least one texture • Preserved function of lips, jaw, cricopharyngeal muscles and clearance of pyriform sinuses • Severity of deficits varied as a function of texture
Lee *et al*, 2012 [22] [case report]	To assess oropharyngeal and esophageal dysphagia in HD using HRIM	N=1 HD patient, age = 65 years CAG=44 repeats illness duration=10 years, 5 years history of progressive dysphagia;	High Resolution Impedance Manometry (HRIM) 10x5 mL saline swallows + 10x5 mL viscous swallows	Incomplete relaxation of lower esophageal sphincter; spastic esophageal motility; normal upper esophageal sphincter relaxation, irregular and simultaneous contractions between velopharyngeal- and meso-hypopharyngeal zone;
Süssmuth *et al*, 2012 [50] [cross-sectional, abstract]	To evaluate OD in HD by FEES	N=23 HD patients	FEES testing puree, liquid and solid boluses	• 19/23 patients: disturbances of the pre-oral, oral, and pharyngeal stage of swallowing • 10/19 patients: OD with aspiration or risk of aspiration

Authors, year [study design]	Purpose of the Study	Participants	Examinations	Main Results
Heemskerk *et al*, 2015 [12] [cross-sectional]	To identify specific OD features in HD using VFSS	N=45 HD patients from three clinical stages	VFSS protocol: - thin liquid: 3mL (x1) and 10 mL (x1) - thick liquid: 5 mL (x1) - a piece of barium bread	• 77.8% (35/45) diagnosed as dysphagic • 45-50% of patients had residues in valleculae and pyriform sinuses • Aspiration and residues more pronounced with larger boluses (10 mL) • Significant shorter duration of the oropharyngeal transit time and the velopharyngeal closure
Alves *et al*, 2016 [51] [case report]	To describe swallowing endoscopic findings of the pharyngeal phase in HD	N=2 HD patients from the same family	• Clinical assessment of swallowing • FEES: volumes of 3-10 mL of consistent liquid, nectar and puree. Presence or absence of posterior oral spillage, pharyngeal residue, penetration, aspiration	• Clinical assessment: difficulties in labial sealing, oral incoordination, compensatory head movements, impaired oral transit • FEES: - Posterior oral spillage (for liquid and nectar bolus) - Pharyngeal residue in small quantities • Absence of penetration and/or aspiration
Schindler *et al*, 2017 [19] [cross-sectional, abstract]	To analyze applicability of FEES for evaluation of OD in patients with HD	N=14 HD patients	• Assessments included BMI and FEES (with ingestion of thin liquid, semisolid and solid) • Quantitative analysis of dysphagia through FEES: - Penetration-Aspiration Scale (PAS) - Yale Pharyngeal Residue Severity Rating Scale (YPRSRS) - Dysphagia Outcome and Severity Scale (DOSS)	• VFSS was never required to improve diagnostic accuracy of OD • FEES can be easily applied in everyday clinical practice for swallowing assessment in HD patients
Manor *et al*, 2018 [20] [cross-sectional]	To characterize swallowing deficits in HD patients To evaluate FEES feasibility in HD To study the relation between FEES findings and self-reported dysphagia	N=14 HD patients	• UHDRS • Montreal Cognitive Assessment • FEES • Swallowing Disturbances Questionnaire (SDQ) • Swallowing Related Quality Of Life (SWAL-QOL) questionnaire	• FEES was well tolerated in 4 patients, with mild difficulty in 8 patients, and with moderate difficulty in 2 patients • The SWAL-QOL significantly correlated with bolus flow time in FEES

LEGEND: UHDRS = Unified HD Rating Scale; nfd = not further defined

investigated the effects of choreic movements on the accuracy of the instrumental examination. Therefore, analogously to other population at risk of OD, the choice of the instrumental assessment method should rely on their availability as well as on the specific advantages and limitations of each method[21].

For the first time, Lee and colleagues used Pharyngeal High Resolution Impedance Manometry (HRIM) in a patient with HD[22]. Pharyngeal HRIM is a method for evaluating swallowing using quantitative measurements of swallowing pressure and bolus flow related to pharyngeal function, upper esophageal sphincter function, and flow timing[23]. The advantage of HRM over FEES and VFSS is that it provides an objective assessment of swallowing biomechanics, potentially enhancing the understanding of OD pathophysiology and the definition of a treatment program. The procedure requires the insertion of a catheter through the nostril and up to the esophagus. Pharyngeal HRIM was tested on a single patient with HD[22]. Beside HRIM, needle and surface EMG swallowing assessment have been applied in other neurological populations to study pathophysiological mechanisms of OD and to detect early swallowing abnormalities[24-26]. EMG allows the measurement of the amplitude and the timing of muscles' activation during swallowing. Based on the literature review, no study used needle or surface EMG to assess swallowing function in HD. Potential barriers to EMG swallowing assessment in this population are represented by the involuntary movements of the head and neck because of the interferences in the recording of muscles' activation and the difficulties in needle placing. Thus, the feasibility of pharyngeal HRIM and EMG swallowing assessment in patients with HD and the criteria for the selection of candidates to assess with these instrumental methods still have to be explored.

As previously stated, the instrumental assessment of swallowing, with either VFSS or FEES, represents the "gold standard". However, VFSS and FEES' availability is often limited and they are minimally invasive procedures. Therefore, the clinical pathway of swallowing assessment generally includes a screening and a clinical assessment of swallowing function before the access to instrumental assessment. Their sensitivity depends on the disease of the population being tested because of the different rate of silent aspiration[24]. The only study addressing this issue in patients with HD shows that the 90ml Water Swallow Test does not have a sufficient diagnostic accuracy to exclude dysphagia in HD when compared to FEES[14]. Concerning clinical assessment tools, only de Tommaso and colleagues[15] applied a standardized bedside swallowing assessment checklist[28] in patients with HD. The same checklist was previously used in patients with acute stroke and was found to have a sensitivity ranging from 47% to 70% and a specificity from 66% to 86% for the detection of aspiration[28]. No specific data were gained for patients with HD. A variety of screening and clinical swallow examination tools have been developed in the past years for neurological disorders[29-30]. While data on their diagnostic accuracy in HD are lacking, the selection of the most suitable tool may rely on several factors: diagnostic accuracy in other neurological disorders (especially if not limited to stroke patients), psychometric properties, availability of an instrumental assessment, number of trained staff, workload, and time constraints[30].

Patient-reported outcome (PRO) measures can be used as screening tools for the detection of a swallowing impairment as well. In OD literature and clinical practice, the Eating-Assessment tool (EAT-10) is a widely used self-administered questionnaire for

the detection of patients at risk for OD[31], although its psychometric properties have been recently debated[32]. Two PRO measures have been specifically developed for patients with HD: the Huntington's Disease Dysphagia Scale (HDDS)[33], an 11-item self-assessment questionnaire, and the Huntington Disease Health-Related Quality of Life (HDQLIFE)[34], a questionnaire investigating the impact of swallowing and speech difficulties on quality of life (QOL). These questionnaires represents essential tools to understand patient's perception of swallowing function as well as the impact of OD on QOL, however can not replace the instrumental assessment of swallowing for the diagnosis of OD in this population. Indeed, none of the questionnaires have been validated against instrumental procedures. Additionally, anosognosia for OD was previously reported[4] uncovering the issue of unreliable self-reporting of symptoms. This finding was more recently investigated by Carlozzi and colleagues, who identified specific cognitive scores that dramatically reduce the reliability of the PRO swallowing outcomes, as assessed trough the HDQLIFE Swallowing tool[11].

Finally, assessing OD in HD cannot leave a general and neurological examination out of consideration, as it is essential to define the level of motor, cognitive, functional impairments and thus the stage of the disease. History – such as dietary choices and feeding habits[4] –, orolingual functions and other features during ingestion need to be evaluated, such as position and respiratory control, quantity and rapidity of food intake[1].

Table 3: Treatments affecting swallowing in HD

Authors, year [study design]	Purpose of the study	Participants	Treatment	Outcome Measures	Main Results
PHARMACOLOGICAL TREATMENTS					
Frank, 2009 [38] [open-label]	To study the adverse effects of TBZ therapy in HD	N=75 HD patients	Use of TBZ	Adverse effects reported by the patients	3 patients reported OD onset as an adverse effect of TBZ therapy
Shen *et al*, 2013 [39] [open-label]	To study the adverse effects of TBZ therapy in HD	N=98 HD patients	Use of TBZ	Adverse effects reported by the patients	19 patients reported OD onset as an adverse effect of TBZ therapy
de Tommaso *et al*, 2015 [15] [cross-sectional]	To investigate the effect of neuroleptics on swallowing function	N_1=37 HD patients (10 patient treated with neuroleptics)	Use of neuroleptics (*nfd*)	• Bedside Swallowing Assessment Scale (BSAS) • Dysphagia Outcome and Severity Scale (DOSS) on clinical evaluation by SLTs	BSAS and DOSS scores were not significantly different between patients using and not using neuroleptics
REHABILITATIVE TREATMENTS					
Reyes *et al*, 2015 [42] [RCT]	To examine the effects of respiratory muscle strength training on pulmonary and swallowing function, exercise capacity and dyspnea in HD	N=18 HD patients	Both patients' groups received a 4-month home-based inspiratory and expiratory muscle strength training (5 sets of 5 repetitions for both muscle groups, 6 times a week): - *Control group*: fixed resistance of 9 cm H_2O - *Experimental group*: progressively increased resistance from 30% to 75% of each patient's maximum respiratory pressure	Measures were assessed at baseline, 2 and 4 months after training: - spirometric indices - maximum inspiratory pressure - maximum expiratory pressure - 6-min walk test - dyspnea - water-swallow test - Swallowing-Quality of Life (SWAL-QOL) questionnaire	Respiratory training: - improved pulmonary function - had small effects on swallowing function, dyspnoea and exercise capacity
Kerkdijk et al, 2018 [43] [case series, abstract]	To study the applicability and the patient experience of a sEMG-based biofeedback swallowing program	N=7 HD patients	SilverFit Rephagia – training program with a series of swallowing exercises by using a biofeedback system with sEMG electrode	• Feasability (technical issues, time) • Patient feedback	• sEMG electrode stays in place • Automatic swallowing movement recognition could not be applied • Patients were sufficiently concentrated • Patients finished the exercise session within 45 minutes • Patient reported the program enlarged their motivation to practice swallowing exercises

Authors, year [study design]	Purpose of the study	Participants	Treatment	Outcome Measures	Main Results
COMPENSATORY TREATMENTS					
Heemskerk, 2016 [40] [pre-post, abstract]	To study the effectiveness of the Masako and the Mendelsohn maneuver in HD	N=30 HD patients with dysphagia	Masako and Mendelsohn maneuvers	• Patient reported outcome • VFSS in 1 patient	• Most patients could perform at least one swallowing maneuver • Most patients reported that they benefit from the treatment
Schradt et al, 2018 [17] [case series, abstract]	To study efficacy of compensatory strategies for OD in HD	N =73 HD patients	Chin tuck posture and diet adaptation	• FEES • Penetration-aspiration scale • Clinical Swallow Examination	Chin tuck swallowing as well as individual diet adaptation were effective in all stages of HD

LEGEND: nfd = not further defined; RCT = randomized controlled trial; TBZ = Tetrabenazine

Treatments influencing swallowing function in HD

Two types of treatments may impact on swallowing function: pharmacological treatment for HD and rehabilitative treatment for swallowing. Concerning pharmacological treatment, only symptomatic therapies are currently available for HD. Neuroleptics and antidepressants are administered when psychosis symptoms or mood disorders occur[35]. Neuroleptics also can improve chorea[35], and in choreic HD patients with psychosis or irritability, they can be used to treat both. Well-known side effects of treatment with classic and also atypical neuroleptics are orofacial dyskinesia and hypokinetic disorders that could potentially worsen swallowing[36]. In the present review, one study[15] acknowledges that the use of neuroleptics shows no significant difference in OD symptoms and severity. This result is in accordance with the study by Leopold & Kagel[4], included in the 2011 review[10]. However, the effects of neuroleptics on swallowing function was not the primary aim of none of the studies. Because OD can be a side effect of the pharmacological treatment as well as a symptom of HD, it is difficult to extrapolate the influence of neuroleptic on swallowing without having pre- and post-treatment data on the same cohort of patients. Thus, the present review do not provide any additional information on this issue.

On the motor function side, tetrabenazine (TBZ) have been reported to suppress choreiform movements[37]. Some consideration should be made about OD in HD regarding the use of TBZ, as there is discussed evidence accompanying its adverse effects. The drug is overall well-tolerated[37-38], but for what concerns bucco-lingual and oro-pharyngeal coordination, reports of dysarthria and OD have appeared[38-39]. It is difficult to establish whether OD symptoms are increased because of TBZ use or are a result of the natural progression of the disease, and the drug is diffusely used. Therefore, since there is conflicting evidence about TBZ side-effects, its outcomes on swallowing need to be better understood. Even though anti-choreic and anti-psychotic treatments are useful to control motor and behavioral symptoms in HD and positively impact on patients' QOL, their use in mid-late stage HD patients with OD should be cautious.

Swallowing therapy by speech and language therapists is based on two mechanisms: rehabilitation and compensation. The results of the previous review suggested that compensatory strategies (i.e. postures, maneuvers, diet modifications) may be applicable and efficacious in reducing the risk of lower airways' invasion in patients with HD. Since then, other two studies confirmed this findings[17,40]. In particular, Heemskerk and colleagues trained 30 patients with HD and OD on the use of Masako and Mendelsohn maneuvers[40]. The ability to perform a swallowing maneuver highly depends on motor coordination and cognitive functions (i.e. executive function skills)[41], which are both affected by the disease. Most of the patients recruited in the study could perform at least one maneuver and reported that they benefit from their application[40]. Therefore, the use of compensatory strategies is recommended in case of patients with HD and OD, after having tested their applicability in the individual patient and their efficacy during instrumental assessment and/or meal observation.

Concerning rehabilitative strategies, the literature in HD is still scarce. The only randomized controlled trial examined the effects of a 4-month respiratory muscles training on pulmonary and swallowing functions – assessed by a water swallow test and swallowing-related QOL questionnaires – on two groups of 9 patients with HD[42].

Resistance respiratory training was applied to the two groups. Although pulmonary function seemed to be improved in the experimental group, there was no significant difference between them in swallowing function and exercise capacity. The absence of an instrumental assessment of swallowing is a severe limitation of the study. Recently, another study (abstract in conference proceeding) reported preliminary evidence of the feasibility of swallowing program based on biofeedback in patients with HD[43]. Therefore, to date, the possibility to modify swallowing function through rehabilitative strategies in patients with HD, by improving it or delaying OD onset, is still unknown. However, results on the feasibility of swallowing rehabilitative programs seems to be promising. Studies assessing the efficacy of strength- or skill-based rehabilitative interventions for swallowing in patients with HD, using a rigorous methodology and adequate outcome measures, are needed.

Lastly, no study has analyzed the effect of percutaneous endoscopic gastrostomy (PEG) on survival in patients with HD. As literature shows that PEG placement may have profoundly different outcomes in different neurological populations[44-46], data on the risks of PEG placement, its impact on the development of nutritional and pulmonary complications, and the best timing in HD are of highest importance.

Limitations

Some limitations can be identified in the present review. Firstly, the literature search was conducted only on two databases (PubMed and EMBASE) and language filters were applied. Although MEDLINE and EMBASE are the largest database of biomedical journals and the majority of the studies are written in English, some studies may have been missed. Reference lists' search of full-text articles may have, at least partially, overcome this limitation. Secondly, also grey literature and abstract of congress proceedings were included in order to provide a comprehensive overview of the current knowledge. However, no peer-review was performed on these type of publication, and limited information was provided on the abstract of oral and poster presentations, restricting the possibility to critically analyze the results. Lastly, being a scoping review, the risk of bias of the included studies was not assessed, and results were not weighted accordingly. As stated, it was beyond the objectives of the review, aiming to provide a general overview of the knowledge on the management of OD in HD. However, the readers should be aware that the quality of the evidence was heterogeneous and was not depicted in the present review.

Conclusions

The present review provides an overview on the literature of the last 10 years on the management of OD in HD. The number of studies retrieved reflects a growing interest on the topic, which however remains poorly studied compared to its clinical relevance. Moreover, the majority of the studies have not been published as full-text articles, which is important to promote an evidence-based practice on the management of OD in this population. Relevant gaps in literature have been identified.

Based on the studies retrieved, OD should be assessed, especially when specific clinical markers occurs, despite the stage of the disease. Timing for OD re-assessment should be based on the recommendation of the swallowing experts on case basis. Instrumental

assessment of swallowing by VFSS or FEES is feasible and recommended to diagnose OD in patients with HD. Clinical assessment tools and PRO measures may be used to complete the swallowing examination, but not to replace instrumental assessment.
The evidence on the detrimental effects of anti-choreic and anti-psychotic pharmacological treatments on swallowing function is controversial. Thus, their use in mid-late stage HD patients with OD should be cautious. Compensatory strategies (diet modification, head postures, swallowing maneuvers) seems to be applicable and efficacious. To date, there are no well-proven rehabilitative strategies to improve swallowing function in patients with HD.

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2.2 DYSPHAGIA IN EARLY TO ADVANCED STAGE HUNTINGTON'S DISEASE

Abstract

Background. Huntington's disease (HD) is a neurodegenerative disorder characterized by motor disturbances, cognitive decline, and behavior changes. A well-recognized feature of advanced HD is oropharyngeal dysphagia (OD), which leads to malnutrition and aspiration pneumonia, the latter being the first cause of death in HD. Data on the prevalence of OD in the different stages of the disease based on instrumental assessment or on the possible correlation between OD severity and disease are lacking.

Objective. The study aimed to assess the frequency and the severity of OD in different stages of HD.

Methods. A cross-sectional study was performed on 43 patients with different stages of HD (20 early, 10 moderate, and 13 advanced) and 27 age-matched healthy volunteers. OD was evaluated by fiberoptic endoscopic examination of swallowing. Disease severity was assessed with the Unified Huntington's Disease Rating Scale (UHDRS). OD severity, penetration and aspiration, and pharyngeal residue were rated through validated ordinal scales and were compared (i) between patients and healthy volunteers and (ii) among different HD stages. Dysphagia severity was correlated to UHDRS total motor score (TMS).

Results. OD was noted in 30% of early-stage, in 90% of moderate-stage, and 100% of advanced-stage patients with HD. Patients significantly differed from healthy volunteers for all the swallowing variables. A progressive increase of the severity of OD and penetration-aspiration, but not of pharyngeal residue, was found in patients with more severe HD stages. OD severity significantly correlated to UHDRS-TMS (r=-0.63). A UHDRS-TMS>37 was able to identify patients with OD with 82% sensitivity and 73% specificity.

Conclusions. The study findings improve our understanding of OD onset and development in HD, contributing to the definition of standards for recognition, management, and care of HD patients with OD.

INTRODUCTION

Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder caused by a CAG expansion in the *IT-15* gene; its prevalence in the Caucasian population is estimated to be 7-11 per 100,000[1]. HD is characterized by motor, cognitive, and behavioural symptoms that have their onset usually between age 30 and 50 years and then slowly progress for 15-20 years until death. Most HD patients with moderate to advanced stages of disease complain of swallowing difficulties. Severe oropharyngeal dysphagia (OD) often leads to aspiration pneumonia, the main cause of death in HD[2]. The pathophysiology of OD in HD is still unclear. Neuropathological changes in HD include prominent loss of striatal GABAergic neurons and progressive involvement of the cerebral cortex, pallidum, thalamus, brainstem, and cerebellum[3]. Such widespread brain neurodegeneration leads to chorea, dystonia, incoordination, parkinsonism, and ideomotor apraxia. Heterogeneous movement disorders involving the oropharyngeal musculature give rise to OD. Feeding difficulties are further worsened by both the behavioural and cognitive dysfunctions accompanying poorly controlled and impulsive food consumption.

OD in HD has been variously described in case reports and series[2,4-6]. The largest study to date evaluated OD using a videofluoroscopic swallowing study (VFSS) in a cohort of 35 HD patients with moderate to advanced stage disease[7]. More recently, fiberoptic endoscopic evaluation of swallowing (FEES) has been described in a case report and in another study in a cohort of 14 HD patients with OD[6,8]. While the studies highlighted the importance of the symptom, they did not evaluate OD in the different stages of disease. One study correlated neurological features and dysphagia severity based on clinical swallow examination[9]. However, clinical examination may have underestimated the severity of OD because of silent penetration or aspiration events. So whether OD affects HD patients already at an early disease stage is unclear and whether the onset and severity of OD correlates with the onset and severity of specific motor disorders unknown. A better understanding of OD onset and progression in HD may guide the definition of standard clinical care for OD, its recognition, and management.

The study aimed to assess the frequency and the severity of OD using FEES in different stages of HD and to identify correlations with specific motor symptoms that could be used as red flags for OD in this population. The hypothesis were that OD occurs since the early stage of the disease in a certain percentage of patient with HD and that OD severity increases in more advanced stages.

METHODS

Study Population

A cross-sectional prospective study was conducted in a cohort of patients with HD and a cohort of healthy volunteers. The study, which is part of a larger study on OD in neurodegenerative diseases, was carried out according to the Declaration of Helsinki and approved by the Institutional Review Board of the Luigi Sacco Hospital and the Ethics Committee of the Istituto Auxologico Italiano IRCCS. Written, informed consent was obtained from participants or their caregivers. The study was reported according to STROBE guidelines (see Appendix 1).

Patients were consecutively recruited over a 2-year period (May 2016-May 2018) in two neurological centers of Northern Italy during their first or follow-up neurological visit. Patients with genetically confirmed HD (CAG≥39) were recruited. Exclusion criteria were: use of enteral nutrition, history of head and neck cancer, other neurological diseases, self-reported, or documented OD prior to HD diagnosis. Data on age, gender, number of CAG repeats, age of onset, and duration of the disease were collected for all patients.

For the control group, FEES of age-matched healthy volunteers were selected from a database previously collected by the researchers using the same FEES protocol. Inclusion criteria were: age >20 years, no medical history of voice, swallowing, gastroenterological, respiratory, neurologic, metabolic, hematologic, or neoplastic disorders. Healthy volunteers underwent evaluation by a phoniatrician and completed a medical history questionnaire to screen for potential comorbidities.

Neurological assessment

Patients were evaluated by neurologists with expertise in HD and assessed with the Unified Huntington's Disease Rating Scale (UHDRS)[10]. The UHDRS is a clinical rating scale for HD comprising 6 subscales: Part I total motor score (TMS), Part II cognitive assessment, Part III behavioural assessment, Part IV functional assessment, Part V independence scale, and Part VI total functional capacity (TFC).

In particular, UHDRS Part I (TMS) assesses for the presence and severity of typical motor symptoms of HD. It consists of 31 items rated on a scale from 0 to 4; the higher the score, the more severe the motor impairment. The maximum possible total score is 124.

UHDRS Part VI (TFC) provides a measure of functional limitations in 5 domains (occupation, finances, domestic chores, activity of daily living, and care level). The total score ranges from 0 to 13; the lower the score, the higher the functional limitation. Disease stage can be determined based on UHDRS Part VI, as previously established in literature[11-12].

Instrumental assessment of swallowing

All recruited patients and healthy volunteers were assessed for swallowing function at the same Phoniatric Unit of a university hospital of Northern Italy. Fiberoptic endoscopic examination of swallowing (FEES) was conducted with liquids (3 trials x 5-10-20 cc of blue dyed water), semisolids (3 trials x 5-10-20 cc of pudding), and solids (2 trials x half cracker) using an Olympus Evis Exera II 18 endoscopy system and an Olympus ENF VQ trans-nasal flexible endoscope (Olympus Corporation, Tokyo, Japan). Each FEES was video-recorded, de-identified, and assessed by a speech and language therapist (SLT) blinded to the diagnosis and the disease stage. For inter-rater analysis, 50% of the patients' FEES were independently assessed by a second rater. OD severity, swallowing safety, and swallowing efficacy were rated with validated ordinal scales.

The Dysphagia Outcome and Severity Scale (DOSS) was used to assess OD severity[13]. The DOSS levels, ranging between 7 (normal swallowing) and 1 (severe dysphagia), are based on the signs of OD, the need of diet modifications, and the type of nutrition required. Levels 7 and 6 correspond to swallowing within functional limits (dysphagia severity stage 0), levels 5 to 3 to mild-moderate OD requiring diet modifications

(dysphagia severity stage 1), levels 2 and 1 to severe OD requiring tube feeding (dysphagia severity stage 2). For the present study, the DOSS was independently translated into Italian and adaptated to FEES by three operators. The three versions were compared and a final version was drafted by consensus. Afterwards, backtranslation from the Italian version was made, translated by two native English speakers who talked Italian fluently. The two versions were compared with the original version of DOSS. No substantial differences were identified. The adapted version of the DOSS in reported in Appendix 2.

For the safety analysis, laryngeal penetration and aspiration were assessed through the Penetration-aspiration scale (PAS)[14]. The scoring, ranging from 1 (no penetration and aspiration) to 8 (silent aspiration), takes in account three variables: the presence of penetration or aspiration, the level of airway invasion and the ability to eject substances from the airways. The worst PAS score for each subject was considered for statistical analyses. A PAS score ≥3 represents presence of penetration, a PAS score ≥6 represents presence of aspiration, and a PAS score =8 represents presence of silent aspiration.

Pharyngeal residue, as a measure of swallowing efficacy, was rated according to the Yale Pharyngeal Residue Severity Rating Scale (YPRSRS)[15]. The scale provides two score based on the amount of post-swallow residue in the valleculae and in the pyriform sinuses. The score ranges from 1 (no residue) to 5 (severe residue).The worst YALE scores for each subject were considered for statistical analyses.

Statistical analysis

All data are presented as the mean±SEM or absolute (relative) frequency..

Inter-rater agreement for FEES outcomes was calculated using the linear weighted kappa coefficient. The weighted kappa values was considered poor (0), slight (0.00–0.20), fair (0.21–0.40), moderate (0.41–0.60), substantial (0.61–0.80), and almost perfect agreement (0.81–1)[16].

D'Agostino & Pearson omnibus normality test was used to test data for normality and Brown-Forsythe test and Bartlett's test were used to verify the assumption of homogeneity of group variances. In the case test for normality and equal variance were satisfied, data were analyzed with parametric test: two-tailed unpaired t-test to compare differences between two groups and Analysis of variance (ANOVA) with Tukey test or Holm-Sidak's multiple comparisons test to compare more than two groups. In the case test for normality and equal variance were not satisfied, data were analyzed by Mann Whitney test or Kruskal-Wallis test followed by Dunn's multiple comparisons test. Data distribution were analyzed by Chi-Square test. Correlations were assessed by Pearson or Spearman test. Receiver operating characteristic (ROC) curves with area under the curve, sensitivity and 1-specificity were created to determine the diagnostic accuracy of the UHDRS I TMS to detect dysphagia. Dysphagia presence was defined for DOSS scores ≥5.

RESULTS

Study sample

Forty-three patients with HD were recruited. In particular, 20 patients were staged as having early (TFC score 13-7; Shoulson-Fahn stage 1-2), 10 as having moderate (TFC

score 6-4; Shoulson-Fahn stage 3), and 13 as having advanced-stage HD (TFC score 3-0; Shoulson-Fahn stage 4-5)[11-12]. For the control group, 27 age-matched volunteers were retrieved from the database. Age distribution of healthy volunteers and patients with HD is depicted in Figure 1. Demographic, genetic, and clinical data are reported in Table 1.

Table 1. Demographic, genetic, and clinical data of all the subjects enrolled in the study

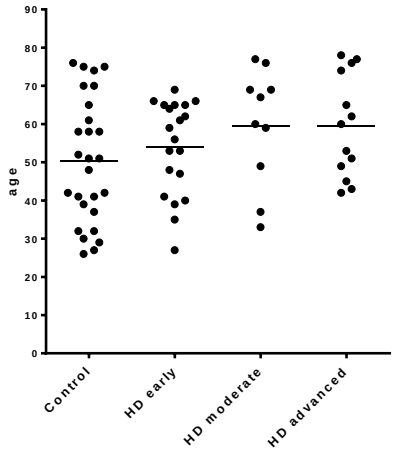
	Controls		HD patients							
	n=27		all patients n=43		early-stage n=20		moderate-stage n=10		advanced-stage n=13	
Characteristic	**Mean ± SEM**	**Range**	**Mean ± SEM**	**Range**	**Mean ± SEM**	**Range**	**Mean ± SEM**	**Range**	**Mean ± SEM**	**Range**
Demographic information										
Gender (M/F)	14/13		18/25		7/13		4/6		7/6	
Age (years)	50.4 ± 3.2	26-76	57.0 ± 2.0	27-78	54.1 ± 2.8	27-69	59.6 ± 4.9	33-77	59.6 ± 3.7	42-78
Genetic and clinical data										
CAG repeats on upper allele			43.5 ± 0.6	39-59	43.6 ± 1.0	40-59	43.5 ± 1.2	41-51	43.5 ± 0.8	39-48
Age at onset (years)			49.2 ± 1.9	23-71	48.4 ± 2.6	23-62	52.5 ± 4.4	30-71	47.8 ± 3.5	32-69
Duration of illness (years)			7.9 ± 0.7	1-19	5.8 ± 0.7	1-12	7.1 ± 1.0	3-12	11.8 ± 1.2	5-19
UHDRS										
UHDRS I			49.1 ± 3.7	7-106	31.6 ± 2.7	7-52	45 ± 3.3	33-65	79.3 ± 4.7	52-106
UHDRS II			123.4 ± 10.6	0-286	149.1 ± 12.7	86-286	104 ± 9.0	58-150	25 ± 25	0-75
UHDRS III			23.3 ± 2.5	2-44	23.4 ± 4.6	2-44	24.3 ± 4.8	11-44	22.4 ± 4.1	6-38
UHDRS IV			13.7 ± 1.2	1-25	19.3 ± 0.8	12-25	12 ± 0.7	9-15	3.7 ± 0.8	1-8
UHDRS V			68.7 ± 2.6	30-100	79.7 ± 2.1	70-100	68 ± 1.9	60-80	46.1 ± 3.3	30-60
UHDRS VI			6.4 ± 0.6	1-13	10.2 ± 0.4	7-13	5.4 ± 0.3	4-6	1.3 ± 0.2	1-3

UHDRS I = Total motor score; UHDRS II = Cognitive scale; UHDRS III = Behavioural scale; UHDRS IC = Functional scale; UHDRS V = Independence scale; UHDRS VI = Total function capacity

Inter-rater agreement

Inter-rater agreement was tested on 22 (51%) FEES of patients with HD. Inter-rater agreement was substantial for DOSS (weighted kappa=0.75; SEM 0.10), PAS (weighted kappa=0.61; SEM 0.10), and YPRSRS valleculae (weighted kappa=0.63; SEM 0.06), while it was moderate for YPRSRS pyriform sinus (weighted kappa=0.52; SEM 0.07).

Figure 1. Age of healthy volunteers and patients with HD in different disease stages



No statistically significant differences were found between the groups (Mean ± SEM, Controls 50.4 ± 3.2, early-stage HD 54.1 ± 2.8, moderate-stage HD 59.6 ± 4.9, advanced-stage HD 59.6 ± 3.7, one-way ANOVA p=0.1870)

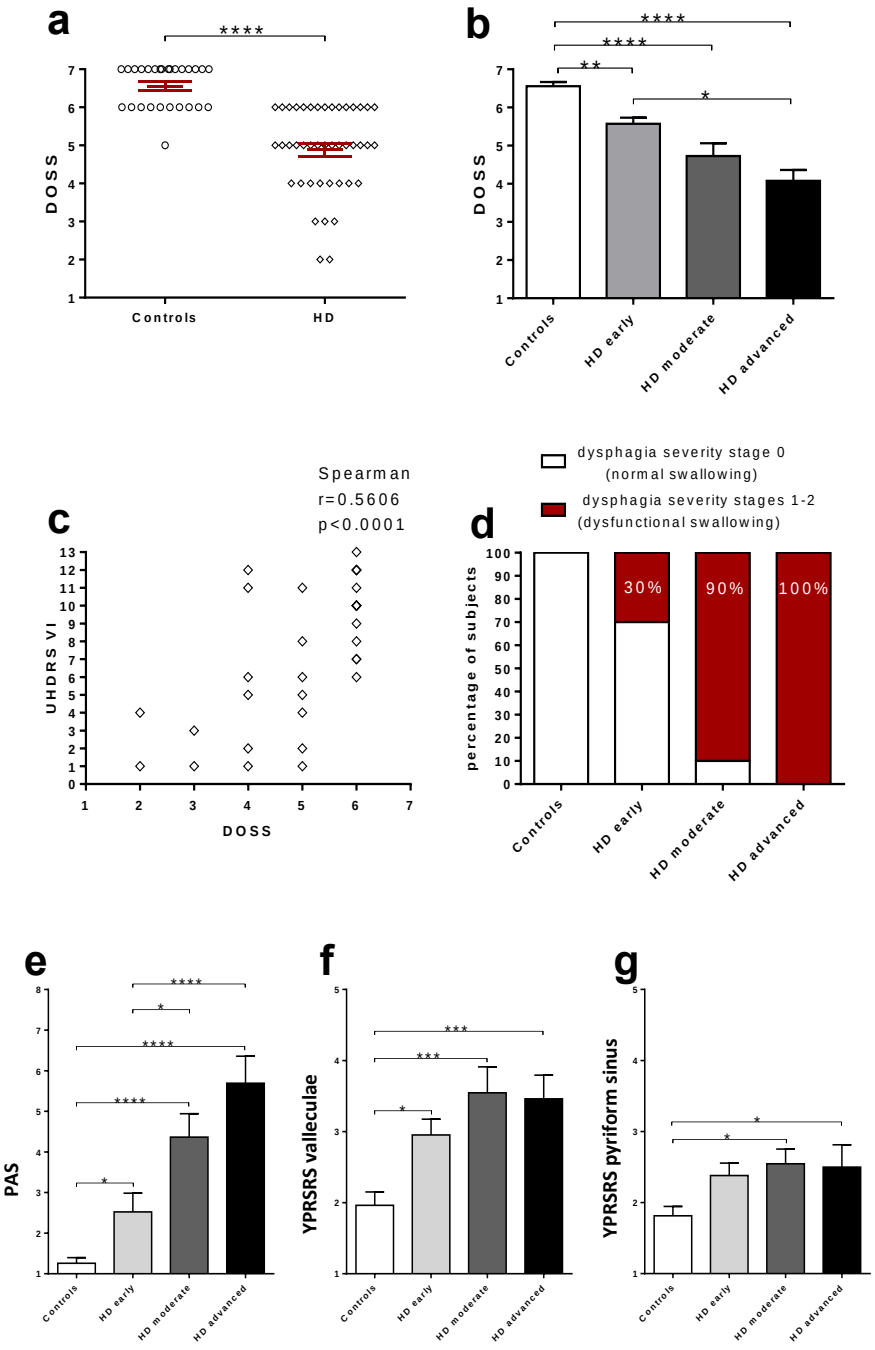
Dysphagia assessment in the controls and the HD patients

FEES was well tolerated by both the HD patients and healthy controls.

OD severity was graded according to the DOSS. DOSS scores were lower in the HD patients than the controls (HD 4.88±0.17 vs. controls 6.56±0.11; Mann-Whitney test, $p<0.0001$; Fig.2a). To determine whether OD was already present among the patients with early-stage HD, patients were stratified according to disease stage[11,17] and reanalysed the DOSS scores. DOSS scores were significantly lower (i) for the patients than for the controls at all disease stages and (ii) for advanced-stage than for early-stage HD patients (controls 6.56±0.11, early-stage HD 5.57±0.17, moderate-stage HD 4.73±0.33, advanced-stage HD 4.08±0.29, Kruskal-Wallis and Dunn's test, controls vs. early-stage HD $p<0.01$; controls vs. moderate-stage HD $p<0.001$; controls vs. advanced-stage HD $p<0.0001$; early-stage vs. advanced-stage HD $p<0.05$; Fig.2b). Furthermore, a significant correlation was found between UHDRS Part VI, assessing TFC, and DOSS scores (Spearman, $r=0.56$, $p<0.001$; Fig.2c).

To quantify the frequency of OD at each HD stage, the number of subjects with normal swallowing (DOSS score 7-6 denotes dysphagia severity stage 0) versus dysfunctional swallowing (DOSS score ≤5 denotes dysphagia severity stages 1-2) was analysed and compared. OD was present in 30% of those with early-stage, 90% of those with moderate-stage, and 100% of those with advanced-stage HD ($p<0.001$, df=3, chi-square=48.75; Fig.2d).

Figure 2. Dysphagia parameters in n=27 control subjects, and n= 43 HD patients including n=20 HD early, n=10 HD moderate and N=13 HD advanced



a. Comparison of the Dysphagia Outcome and Severity Scale (DOSS) in HD and control subjects. DOSS values were lower in HD patients as compared to controls (mean±SEM of DOSS values: Controls 6.56±0.11, HD 4.88±0.17. Data were analysed by Mann Whitney test: ****p<0.0001).

b. DOSS values were lower in early-moderate-advanced HD patients as compared to controls (mean ± SEM of DOSS values: Controls 6.56±0.11, HD early 5.57±0.17, HD moderate 4.73 ± 0.33, HD advanced 4.08 ± 0.29. Data were analysed by Kruskal-Wallis test and Dunn's multiple comparisons test: Controls vs HD early **p<0.01, Controls vs HD moderate ****p<0.0001, Controls vs HD advanced ****p<0.0001, HD early vs HD advanced *p<0.05, HD early vs HD moderate p>0.05, HD moderate vs HD advanced p>0.05).

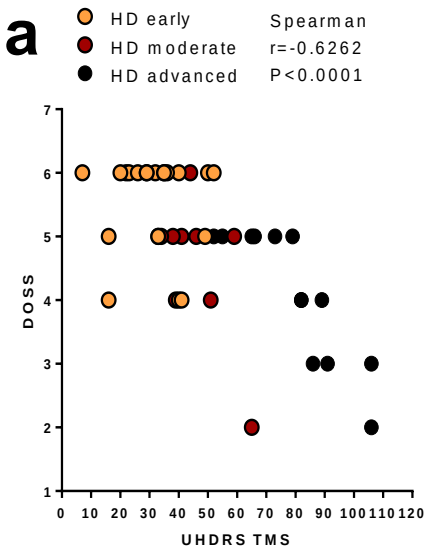
c. Correlation between DOSS values and the functional capacity (UHDRS VI) values in HD patients. A positive correlation was found between the two parameters. Spearman correlation coefficient was r=0.5606, p<0.0001.

d. Distribution of dysphagia frequency. 30% of the HD early patients showed OD vs 90% of the HD moderate and 100% of the HD advanced ($p<0.0001$, df = 3, Chi-square = 48.75).
e. Comparison of Penetration-Aspiration Scale (PAS) scores. PAS values were higher in HD patients as compared to controls (mean ± SEM of PAS scores: Controls 1.26 ± 0.14, HD early 2.52 ± 0.46, HD moderate 4.36 ± 0.58, HD advanced 5.69 ± 0.66. Data were analysed by one-way ANOVA followed by Holm-Sidak's multiple comparisons test: Controls vs HD early *$p<0.05$, Controls vs HD moderate ****$p<0.0001$, Controls vs HD advanced ****$p<0.0001$, HD early vs HD moderate *$p<0.05$, HD early vs HD advanced ****$p<0.0001$, HD moderate vs HD advanced $p>0.05$).
f. Comparison of YPRSRS scores in the valleculae. YPRSRS values were higher in HD patients as compared to controls (mean ± SEM of YPRSRS valleculae scores: Controls 1.96 ± 0.19, HD early 2.95 ± 0.22, HD moderate 3.55 ± 0.37, HD advanced 3.46 ± 0.33. Data were analysed by one-way ANOVA followed by Tukey's multiple comparisons test: Controls vs HD early *$p<0.05$, Controls vs HD moderate ***$p<0.001$, Controls vs HD advanced ***$p<0.001$, HD early vs HD moderate $p>0.05$, HD early vs HD advanced $p>0.05$, HD moderate vs HD advanced $p>0.05$).
g. Comparison of YPRSRS scores in the pyriform sinuses. YPRSRS values were higher in HD patients as compared to controls (mean ± SEM of YPRSRS pyriform sinus scores: Controls 1.82 ± 0.13, HD early 2.39 ± 0.18, HD moderate 2.55 ± 0.21, HD advanced 2.50 ± 0.31. Data were analysed by one-way ANOVA followed by Tukey's multiple comparisons test: Controls vs HD moderate *$p<0.05$, Controls vs HD advanced *$p<0.05$, Controls vs HD early $p>0.05$, HD early vs HD moderate $p>0.05$, HD early vs HD advanced $p>0.05$, HD moderate vs HD advanced $p>0.05$).

To better characterize OD, swallowing safety and efficacy were assessed based on the PAS and the YPRSRS scales, respectively. PAS scores were significantly higher (i) for the patients with HD than the controls and (ii) for the patients in the HD moderate and advanced-stage than patients in the HD early stage (controls 1.26±0.14, early-stage 2.52±0.46, moderate-stage 4.36±0.58, advanced-stage HD patients 5.69±0.66. One-way ANOVA and Holm-Sidak's test, controls vs. early-stage $p<0.05$; controls vs. moderate-stage $p<0.001$; controls vs. advanced-stage HD patients $p<0.001$; early-stage vs. moderate-stage $p<0.05$; early-stage vs. advanced-stage HD patients $p<0.001$; Fig.2e). Penetration (PAS ≥3) and aspiration (PAS ≥6) were present in all stages of disease (penetration in 25% of early-stage, 90% of moderate-stage, 85% of advanced-stage HD patients; aspiration in 10% of early-stage, 20% of moderate-stage, 54% of advanced-stage HD patients). Silent aspiration (PAS =8) was observed in 10% of early-stage, 10% of moderate-stage, and 31% of advanced-stage HD patients.
The YPRSRS scores in the valleculae and the pyriform sinuses were significantly higher for patients with HD than the controls, while are comparable across the various stages of disease (Fig.2f YPRSRS valleculae scores: controls 1.96±0.19, early-stage 2.95±0.22, moderate-stage 3.55±0.37, advanced-stage HD patients 3.46±0.33. One-way ANOVA and Tukey's test: controls vs. early-stage $p<0.05$; controls vs. moderate-stage $p<0.001$; controls vs. advanced-stage HD $p<0.001$. Fig.2g YPRSRS pyriform sinus scores: controls 1.82±0.13, early-stage 2.39±0.18, moderate-stage 2.55±0.21, advanced-stage HD patients 2.50±0.31, controls vs. moderate-stage $p<0.05$; controls vs. advanced-stage HD $p<0.05$).

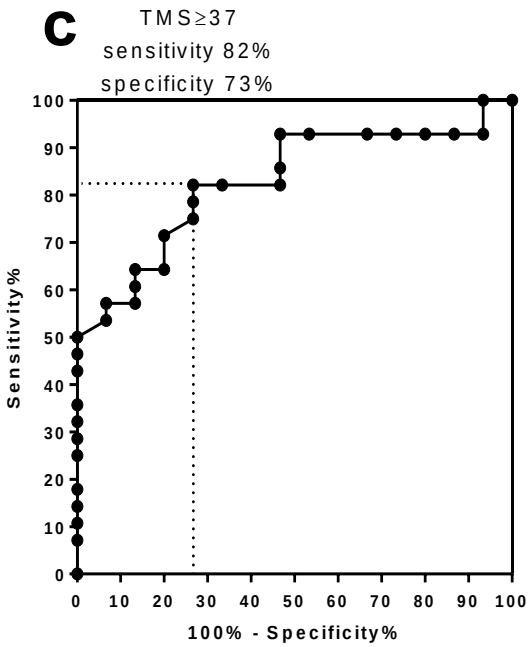
Correlations between dysphagia and HD features
We wondered which genetic or clinical factors could predict the severity of OD. DOSS scores did not correlate with age and CAG values (Spearman, $p>0.05$), however, they did correlate with duration of illness (Spearman duration of illness $r=-0.40$, $p=0.009$).
Because OD arises when motor disturbances involve the oropharyngeal musculature, it was hypothesized that OD would run parallel with worsening of motor symptoms. A significant negative correlation was found between UHDRS I-TMS and DOSS scores (Spearman, $r=-0.63$, $p<0.001$; Fig.3a). Also the UHDRS I-TMS subitems correlated with DOSS scores (Fig.3b).

Figure 3. Correlations between dysphagia severity parameters and disease progression



b

Parameter	Spearman r	p value
Ocular pursuit	-0.4997	**0.0006**
Saccade initiation	-0.5260	**0.0003**
Saccade velocity	-0.5285	**0.0003**
Dysarthria	-0.5435	**0.0002**
Tongue protrusion	-0.4281	**0.0042**
Finger taps	-0.5859	**<0.0001**
Pronate/supinate hands	-0.6051	**<0.0001**
Luria	-0.5276	**0.0003**
Rigidity-arms	-0.4760	**0.0013**
Bradykinesia-body	-0.4250	**0.0045**
Maximal dystonia	-0.4732	**0.0014**
Maximal chorea	-0.2870	0.0620
Gait	-0.4996	**0.0006**
Tandem walking	-0.5227	**0.0003**
Retropulsion pull test	-0.4571	**0.0021**



a. Correlation between DOSS values and the total motor score in HD patients. A negative correlation was found between the two parameters. Spearman correlation coefficient was r=-0.63, p<0.001.
b. Correlations between DOSS values and the subitems of UHDRS I. All the parameters but chorea negatively correlated with DOSS values.
c. Receiver operating curve (ROC) of gain-of-function mutations and control mutations (nABN and hSNPs) as a function of UHDRS Part I total motor score (TMS). Using the cut-off value TMS=37 that maximizes sensitivity and specificity, TMS correctly classified 11 out of 15 HD patients as having normal swallowing (DOSS≥6) and 23 out of 28 of HD patients as having dysfunctional swallowing (DOSS≤5), yielding 82% sensitivity and 73% specificity. The area under the curve is 0.83 (95% Confidence Interval=0.71 to 0.96).

Moreover, it was hypothesized that the TMS might provide enough sensitivity and specificity to distinguish between HD patients with normal swallowing (DOSS 7-6) and those with dysfunctional swallowing (DOSS ≤5). The area under the curve was 0.83 (95% Confidence Interval=0.71-0.96). Using a cut-off of TMS 37, which maximizes sensitivity and specificity, we were able to correctly classify 11 out of 15 HD patients with having normal swallowing (DOSS score 7-6) and 23 out of 28 of HD patients with dysfunctional swallowing (DOSS score ≤5), yielding 82% sensitivity and 73% specificity (Fig.3c). This suggested that a TMS > 37 is indicative of the onset of OD.

DISCUSSION

This study is the first study describing the frequency and the severity of OD in different stages of HD using FEES. Results shows that OD occurs in all stages of the disease and its frequency and severity increase in more advanced stages. Swallowing function of patients in the early stage of HD significantly differs from that of healthy controls. OD severity correlates with the severity of motor symptoms.

Swallowing alterations were detected in a relevant percentage (30%) of HD patients with early-stage disease. This finding complements a previous study that investigated dysautonomic symptoms via questionnaire and found swallowing difficulties in pre-manifest HD mutation carriers[18]. Since 10% of the early-stage HD patients in our cohort displayed silent aspiration, monitoring of swallowing function in HD is warranted starting already at an early stage of disease.

In the present cohort, OD progressively worsened in more severe stages of the disease. In the moderate-advanced stages, almost all HD patients were noted to exhibit OD. To the best of our knowledge, this is the first study to highlight such a high frequency of severe OD in moderate- and advanced-stage HD patients. OD severity was found to be significantly correlated with both disease severity (assessed by the UHDRS VI TFC) and the severity of motor symptoms (assessed by the UHDRS I TMS). Moreover, OD severity correlated with all UHDRS I TMS subitems, except for maximal chorea. This evidence supports the hypothesis that movement disorders eliciting OD stem from the impairment of several motor control systems quantifiable by UHDRS I. The absence of a correlation between DOSS and maximal chorea score, already reported in a previous study using clinical swallowing examination[9], probably reflects the well-known reduction in chorea described in advanced stages of HD.

Swallowing function was characterized based on two dimensions: swallowing safety (based on the presence and severity of penetration and aspiration) and swallowing efficacy (based on the presence and severity of pharyngeal residue). FEES findings in the study cohort suggest that swallowing safety decreases while the disease severity progresses, whereas the impairment of swallowing efficacy remains generally stable. Concerning pathophysiological mechanisms, these findings seems to support the hypothesis that tongue and pharyngeal weakness, contributing to pharyngeal residue, may be responsible of OD onset in the initial stages, while altered coordination and timing of pharyngeal events of swallowing, secondary to difficulties in motor planning, become prevalent in the more advanced stages. However, this hypothesis should be verified in future studies exploring pathophysiological mechanisms of OD in HD.

Because swallowing assessment is often not included in the standard clinical evaluation of patients with HD, the study searched for genetic or neurological clinical features predictive of OD onset. A UHDRS I TMS>37 detected OD presence with a 82% sensitivity and 73% specificity. Therefore, a UHDRS I TMS>37 can be used as a criteria for the referral to the swallowing team. Its implementation in neurological clinical practice, together with the use of dysphagia-specific self-reported questionnaires such as the Huntington Disease (HDDS)[19], may enhance a multidisciplinary approach to HD symptoms and contribute to the definition of clinical care standards for the recognition and management of OD in this disease.

In the present study, FEES was feasible in all patients with HD. Instrumental assessment with the FEES or videofluoroscopy is essential, along with the bedside evaluation, to identify patients with penetration or clinically silent aspiration. Furthermore, this study provides evidence for the usefulness of early assessment via FEES of the swallowing function in HD to identify and treat early changes in function, possibly preventing malnutrition or severe respiratory complications before their occurring.

Limitations and Future perspectives

Limitations of the current study include the sample size and the cross-sectional design. Indeed, although the study describes swallowing function in the largest sample of patients with HD investigated using FEES, the sample size within each disease stage is small with a potential impact on statistical power. OD was compared among patients in different disease stages but the evolution of dysphagia within the same patient was not examined. Further studies in larger cohorts of HD patients and with a longitudinal design are needed to confirm the present results.

Additionally, patients with enteral nutrition were excluded from the study, being part of a larger study including nutritional outcomes. Therefore, the inclusion of these patients may highlight additional significant differences in swallowing function among different HD stages. The FEES was found to be feasible in all recruited patients, however, this finding may not be generalized to patients with more severe HD symptoms requiring enteral nutrition.

FEES recordings were assessed using validated ordinal scales. However, interpretation of FEES images is subjective, and therefore influenced by several factors such as the rater and the bolus consistency[20]. To control for subjectivity, inter-rater agreement was analyzed on 50% of the patients' sample, but data on intra-rater agreement are lacking. The DOSS was used to provide a score of the overall severity of dysphagia. The scale was developed and validated for the use in videofluoroscopy[13]. Later, the DOSS was applied to FEES in several studies[21-23]. For the present study, the DOSS was adapted to FEES and showed substantial inter-rater agreement. However, a formal validation of the DOSS to its use in FEES is currently not available.

Results of the study support the importance of a swallowing assessment event in the early stages of HD. Future studies should analyze the impact of an early OD recognition and management on its health and psychosocial consequences.

CONCLUSIONS

In conclusion, 30% of patients in the early-stage of HD exhibit OD during FEES and 10% shows silent aspiration. Thus, swallowing assessment is warranted starting already from stage of the disease. OD frequency and severity increase in the moderate and advanced stages and OD severity strongly correlated with motor function. In particular, a UHDRS TMS≥37 can be used as a clinical cut-off for referral to the swallowing team. Results of the present study contribute to the definition of clinical care standards for OD recognition and management in patients with HD, aiming to limit its health and psychosocial consequences.

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CHAPTER 3

Association between Maximum Tongue Pressure and Swallowing Safety and Efficacy in Amyotrophic Lateral Sclerosis

Under review

PhD candidate's role: Conceptualization, study design, project administration, supervision, formal analysis, data interpretation, visualization, paper writing, submission process, review and editing

Abstract

Background. Oropharyngeal dysphagia (OD) is a common finding in ALS, with reduction of swallowing safety and efficacy. The tongue has an important role in swallowing function for oral processing and bolus propulsion through the pharynx.

Objective. The cross-sectional study aims to analyze the association between signs of OD and maximum tongue pressure (MTP) in patients with ALS.

Methods. Patients with ALS referred for FEES were recruited. FEES was conducted to test swallowing function with liquid (5ml, 10ml, and 20ml), semisolid (5ml, 10ml, and 20ml), and solid. FEES recordings were assessed for swallowing safety, using the Penetration Aspiration Scale (PAS), and for swallowing efficacy, using the Yale Pharyngeal Residue Severity Rating Scale (YPRSRS). PAS scores >2 were suggestive of penetration, PAS scores >5 of aspiration, and YPRSRS scores >2 of residue. MTP was measured using the Iowa Oral Performance Instrument. Tongue pressure measurements were compared between patients with and without signs of OD.

Results. Fifty-five patients with ALS were included. Patients with residue in the pyriform sinus had a significantly lower MTP than patients without residue in the pyriform sinus with semisolids 10ml ($p=0.011$) and 20 ml ($p=0.032$). No significant differences were found for residue in the valleculae and penetration/aspiration.

Conclusions. MTP is significantly associated with an impairment of swallowing efficacy in patients with ALS. The association was found with larger volumes and more viscous consistencies.

INTRODUCTION

Amyotrophic Lateral Sclerosis (ALS) is a neurodegenerative disease characterized by progressive degeneration of upper and lower motor neurons[1]. Regardless of the site of onset, OD occurs at some point throughout ALS progression in 85% of the patients[2]. OD in ALS is the result of different pathological mechanisms: rigidity and/or weakness of muscles directly involved in pharyngeal swallowing (facial, tongue, pharyngeal, and laryngeal muscles), weakness of respiratory muscles, and sensory impairment[3-5]. Alteration of all phases of swallowing have been reported, although OD is usually characterized by initial impairment of the oral phase in the early stage and subsequent impairment of the pharyngeal phase[6].

The tongue plays an important role in swallowing function. During the oral phase of swallowing, the tongue contributes to bolus formation, placement, and transportation within the oral cavity. In the pharyngeal phase, the tongue generates a driving force for bolus propulsion through the pharynx and into the upper esophageal sphincter (UES)[7]. In the elderly and in patients with Parkinson's disease, reduced tongue pressure has been reported to be associated with OD, aspiration, and oral intake[8-10].

To date, the association between maximum tongue pressure (MTP) and pharyngeal signs of OD is poorly studied in patients with ALS. Hiraoka et al reported a reduced MTP in patients with ALS with post-swallow pharyngeal residue compared to patients without post-swallow pharyngeal residue[11], but the investigation was limited to patients with spinal onset and with 3ml semisolid bolus. To the best of our knowledge, no data is available on other consistencies and signs of lower airway invasion. Understanding the association between tongue pressure and signs of OD may shed light on the role of the tongue in the development of pharyngeal OD in patients with ALS and provide information to guide OD management in this population.

The study aimed to investigate the association between tongue pressure measurements (MTP and tongue endurance) and signs of OD in patients with ALS with a variety of consistencies and bolus volumes. The hypothesis was that MTP and tongue endurance would be decreased in patients with ALS exhibiting signs of OD, particularly with more viscous consistencies and bigger volumes which requires higher pressure generation during swallowing. The secondary aim of the study was to characterize OD in patients with ALS using different bolus types.

METHODS

The cross-sectional study was carried out according to the Declaration of Helsinki and was previously approved by the Institutional Review Board of the Luigi Sacco Hospital (n.2016/ST/262) and from the Ethics Committee of Istituti Clinici Scientifici Maugeri IRCCS. All participants provided written informed consent. The study was reported according to STROBE guidelines (see Appendix 1).

Subjects

Patients were consecutively recruited among inpatients and outpatients referred for fiberoptic endoscopic evaluation of swallowing (FEES) in two ALS Center from March 2017 to December 2018. Inclusion criteria were a diagnosis of definite, possible, clinically probable, or clinically probable laboratory-supported ALS based on the Revised El Escorial criteria[12], full oral nutrition, age 18-90 years. Exclusion criteria were a history of head and neck cancer, known gastrointestinal diseases, or other concomitant neurological diseases, missing data on FEES or tongue pressure or FEES and tongue pressure measurements conducted in different days. Age, gender, age of onset, site of onset were recorded for all included patients.

Neurological assessment

All patients were functionally rated by a neurologist using the ALS Functional Rating Scale-Revised (ALSFRS-R)[13]. The ALSFRS-R is a functional rating system of independence in activities of daily living for patients with ALS. The scale is made up of 12 items, divided into 4 domains (bulbar, upper limb, lower limb, and respiratory functions). The bulbar domain includes 3 items (speech, salivation, and swallowing). Each item is rated on a 5-points scale from 0 (total loss of function) to 4 (no loss of function). The total score ranges from 0 to 48, while the bulbar score from 0 to 12.

Tongue pressure measurement

MTP and tongue endurance were measured with the Iowa Oral Performance Instrument (IOPI) (model 2.3; IOPI Medical LLC, Carnation, WA). The IOPI measures the amount of pressure exerted on an air-filled bulb. The previous study reported a high inter- and intra-rater reliability of the IOPI device for tongue measurements[14-15]. Calibration of the device was checked and adjusted, if necessary, before obtaining measures.

MTP was measured by asking the participants to obtain maximal tongue elevation pressure. The bulb was placed in the patient's oral cavity by the clinician. The standard placement of the bulb was along the central groove of the tongue blade just posterior to the upper alveolar ridge and patients were asked to rest their incisors on the tubing of the IOPI bulb, according to previous literature[16]. To ensure the same positioning among different trials, a mark was made on the tube of the bulb just anterior to the incisors. Then, patients were instructed to "push the bulb against the roof of your mouth as hard as you can." All trials were motivated by verbal encouragement from the examiner. The measurement was repeated 3 times, with a resting period of 30 seconds after each trial. The highest measurement was recorded. MTP is expressed in kPa.

Tongue endurance was defined as the time the patients are able to sustain 50% of their MTP. The examiner manually set the pressure, based on the MTP results. The bulb was placed in the same position as the MTP trials. Patients were instructed to sustain the target pressure for as long as possible. A series of LED lights alerted the patients when they reached the target pressure. Time was measured using the stopwatch incorporated in the IOPI device. Timing starts when the pressure meets the target pressure and stops

when the pressure drops steeply, the pressure is maintained between 40 and 50 % of MTP for 2 seconds or more, or the pressure stays below 40 % of MTP for at least 0.5 seconds[16]. The measurement was repeated 3 times, with a resting period of 2 minutes between the trials. The longer performance was recorded. Endurance is expressed in seconds.
All measures were acquired at least 1 hour after meals and before FEES to avoid potential fatigue effects secondary to meal consumption.

Fiberoptic endoscopic evaluation of swallowing
Fiberoptic endoscopic examination of swallowing (FEES) was conducted with liquids (3 trials x 5-10-20 cc of blue-dyed milk), semisolids (3 trials x 5-10-20 cc of apple sauce), and solids (2 trials x half cracker) during the same day of tongue pressure measurements. The protocol was reduced in case a consistency or a volume was not considered safe to be administered. Each FEES was video-recorded, de-identified, and assessed by 2 independent speech and language therapists (SLTs) after a 5-hour training using validated ordinal scales for swallowing safety and efficacy. A 3rd rater with >5-year experience on FEES assessed the videos and decided on disagreements in case: (i) a score difference >1 or (ii) a score difference =1 changing the categorization of the patient occurred between the 2 raters.
Swallowing safety was assessed using the Penetration-aspiration scale (PAS)[17]. The ordinal scale scores from 1 to 8. In particular, scores 1 and 2 represents no or minimal penetration within functional limits, scores 3 to 5 represents laryngeal penetration, and scores 6 to 8 represents tracheal aspiration.
Swallowing efficacy was assessed according to the Yale Pharyngeal Residue Severity Rating Scale (YPRSRS)[18]. The scale provides two scores based on the amount of post-swallow pharyngeal residue in the valleculae and the pyriform sinuses. The score ranges from 1 (no residue) to 5 (severe residue). For the present study, a score >2 was suggestive of the presence of clinically relevant residue.
Before FEES examination, typical oral intake was recorded with the Italian version of the Functional Oral Intake Scale (FOIS)[19]. The FOIS is a 7-point ordinal scale describing the functional level of oral intake of food and liquid. Level 7 represents full oral diet with no restrictions, levels 6-4 indicate a full oral diet with restrictions, levels 3-2 describe a mixed oral and tube intake, while level 1 represents a totally tube-dependent intake.

Statistical analysis
Data are reported as absolute (relative) frequency and mean±sd or median (IQR), according to the variable's distribution. Statistical analysis was performed with the IBM SPSS Statistics 25.0® package for Windows (SPSS Inc, Chicago, IL) and MedCalc Version 19.1.3.
Inter-rater agreement for FEES outcomes between the 2 independent raters was calculated using the linear weighted kappa coefficient. The weighted kappa values was

considered poor (0), slight (0.00–0.20), fair (0.21–0.40), moderate (0.41–0.60), substantial (0.61–0.80), and almost perfect agreement (0.81–1)[20].

The normality assumption of the tongue pressure measurement was verified with the Kolmogorov-Smirnov test. MTP was compared among patients with signs of OD (clinically relevant residue in the valleculae, clinically relevant residue in the pyriform sinus, penetration, aspiration), without signs of OD, and not assessed for each bolus type using the one-way ANOVA and post-hoc Tukey test for multiple comparisons or the independent-samples t-test, according to the number of categories observed. Significance was set at $p<0.05$.

RESULTS

Subjects

Overall, 65 patients with ALS meeting inclusion criteria were assessed during the recruitment period. However, 3 patients were excluded because they did not undergo a FEES during hospitalization, 4 patients were excluded because tongue pressure measurements could not be performed due to severe tongue fasciculations, while 3 patients were excluded because the FEES and the tongue measurements were not performed within the same day. Thus, 55 patients with a diagnosis of ALS and referred for FEES assessment were included in the study. Demographic and clinical characteristics of the sample are shown in Table 1.

Table 1. Demographic and clinical characteristics of the patients

Variable		Mean ± sd or n (%)
AGE *years*		67.8 ± 10
GENDER	*M*	30 (54.5%)
	F	25 (45.5)
SITE OF ONSET	*Spinal*	39 (70.9%)
	Bulbar	16 (29.1%)
AGE OF ONSET *years*		63.5 ± 10
DISEASE DURATION *years*		4.2 ± 4.8
ALSFRS-R	*Total*	27.4 ± 8.6
	Bulbar	8.4 ± 3
DIET TYPE	*FOIS 7*	16 (29.1%)
	FOIS 6	15 (27.3%)
	FOIS 5	11 (20%)
	FOIS 4	13 (23.6%)

FOIS = Functional oral intake scale. FOIS 7 = total oral intake with no restrictions; FOIS 6 = total oral intake with restriction to specific foods or liquid items; FOIS 5 = total oral intake of multiple consistencies requiring special preparation; FOIS 4 = total oral intake with homogeneous pureed diet

Inter-observer agreement

Results of inter-rater agreement between the 2 independent raters on FEES outcomes is shown in Table 2. Inter-rater agreement ranged from moderate to substantial for all the FEES scales and bolus type, except for YPRSRS scores in the valleculae with 5ml and 10ml liquids (PAS linear weighted kappa =0.46-0.71; YPRSRS valleculae linear weighted kappa =0.35-0.65; YPRSRS pyriform sinus liner weighted kappa =0.41-0.71)

Table 2. Linear weighted kappa (SEM) for inter-rater agreement on FEES outcomes

Consistency	Volume	PAS	YPRSRS valleculae	YPRSRS pyriform sinus
LIQUIDS				
	5ml	0.69 (0.06)	0.35 (0.09)	0.45 (0.07)
	10ml	0.71 (0.07)	0.38 (0.10)	0.46 (0.08)
	20ml	0.58 (0.10)	0.41 (0.11)	0.41 (0.09)
SEMISOLIDS				
	5ml	0.53 (0.09)	0.57 (0.07)	0.71 (0.06)
	10ml	0.54 (0.09)	0.52 (0.09)	0.56 (0.06)
	20ml	0.46 (0.09)	0.56 (0.07)	0.55 (0.08)
SOLIDS				
	3.15g	0.66 (0.10)	0.65 (0.06)	0.65 (0.08)

FEES findings

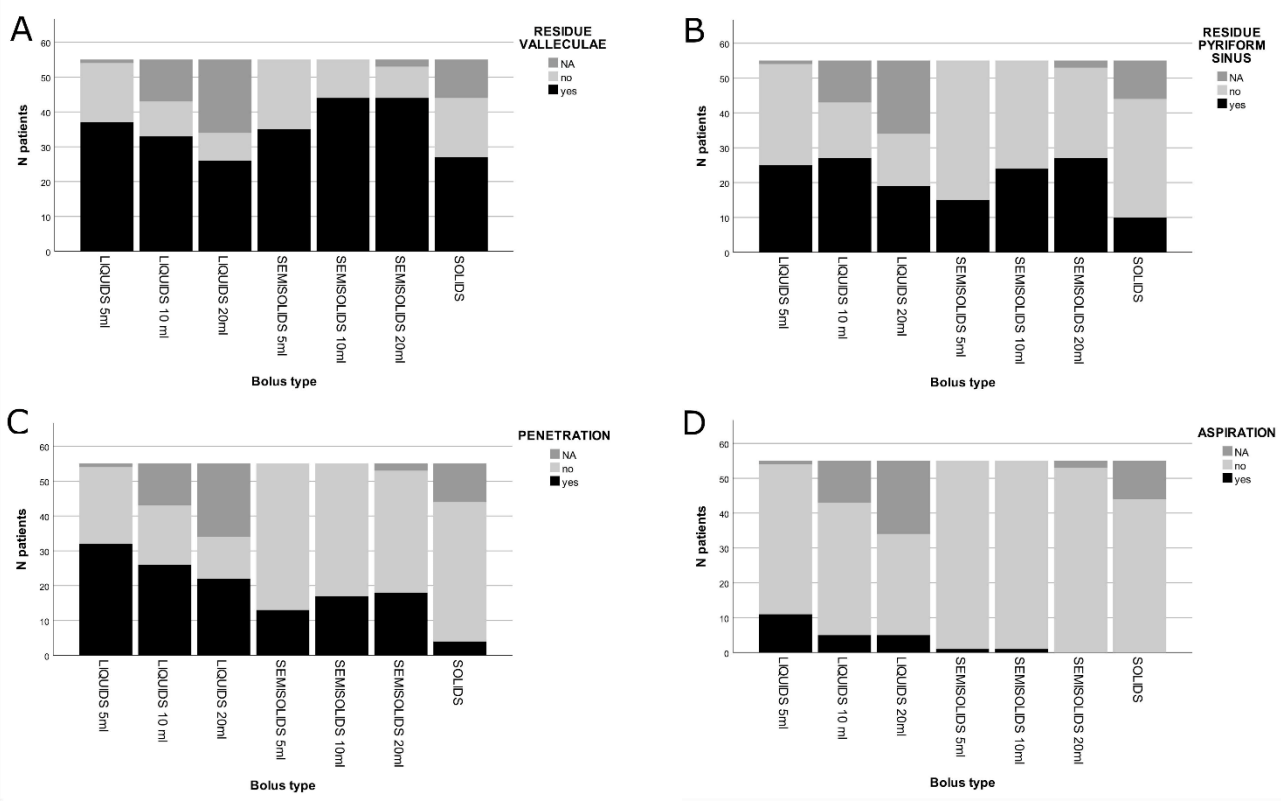
The frequency of signs of OD detected on FEES is depicted in Figure 1.

Liquids were not tested in 1, 12, and 21 patients for the 5ml, 10ml, and 20 ml, respectively. All patients were tested with semisolids 5 and 10 ml, whereas 20 ml semisolids were not administered in 2 patients, while solids were not offered in 11 patients.

Residue in the valleculae (YPRSRS valleculae>2) was the more common findings, occurring in >60% of the patients tested with all the bolus types. Residue in the pyriform sinus (YPRSRS pyriform sinus>2) was similar to liquids and semisolids at the same volume, occurring from 37.5% to 62% of the patients tested, while was lower with solids (22.7%). Penetration (PAS≥3) mainly occurred with liquids (59-64%), while its frequency decreased with semisolid (24-34%) and solids (10%). Finally, aspiration (PAS≥6) occurred in <20% of the patients and mostly with liquids.

Analyzing the association among different signs of OD on FEES, swallows exhibiting residue in the pyriform sinus (147/338, 43.5%) also exhibited residue in the valleculae (129/147, 87.8%). On the contrary, residue in the valleculae occurred in 246/338 (72.8%) swallows, but only 119/246 (48.4%) swallows showed also residue in the pyriform sinus. Penetration occurred in 119/246 (48.4%) of the swallows with residue in the valleculae and in 86/147 (58.5%) of swallows with residue in the pyriform sinus.

Figure 1. Frequency of signs of dysphagia during FEES with different bolus consistencies and volumes



A. Residue in the valleculae; B. Residue in the pyriform sinus; C. Penetration; D. Aspiration.
LEGEND. NA = Bolus type not administered

Association between tongue pressure and swallowing safety and efficacy

MTP was on average 29.7 ± 14 kPa. Median tongue endurance was 10 seconds (IQR 4-16). The tongue endurance measurements were highly skewed, with 29/55 (52.7%) patients being <10 seconds. Thus, no correlation or comparison was performed for this variable.

MTP was compared among patients with signs of OD, without signs of dysphagia, and not assessed for safety reasons during FEES for each bolus type. Results of the comparisons are reported in Table 3. Patients with residue in the pyriform sinus had a significantly lower MTP than patients without residue in the pyriform sinus with semisolids 10 ml and 20 ml (p=0.011 and p=0.014, respectively). No statistical significant different MTP was found between patients with or without other signs of OD. Concerning the comparison with patients not assessed for safety reasons, they showed significantly lower MTP than patients without signs of OD for the following consistencies: 10 ml liquids (except for aspiration), 20 ml liquids (except for residue in the valleculae and penetration), and solids.

Table 3. Comparison of MTP between patients (i) not assessed, (ii) with, and (iii) without signs of dysphagia for each bolus type

		NOT ASSESSED		PRESENT		ABSENT		p
Bolus type	**Sign of dysphagia**	**N**	**Mean ± sd**	**N**	**Mean ± sd**	**N**	**Mean ± sd**	
LIQUID 5ml‡								
	Residue valleculae	1	10	37	30 ± 13.2	17	30.1 ± 15.7	.994
	Residue pyriform sinus	1	10	25	29.1 ± 12.5	29	30.8 ± 15.1	.657
	Penetration	1	10	32	27.1 ± 13.1	22	34.3 ± 14.1	.060
	Aspiration	1	10	11	27.5 ± 13.2	43	30.7 ± 14.1	.495
LIQUID 10ml†								
	Residue valleculae	12	**21.3 ± 12.1**	33	32.9 ± 13.2	10	**29.1 ± 16.4**	.044*
	Residue pyriform sinus	12	**21.3 ± 12.1**	27	29.2 ± 13.2	16	**36.8 ± 13.7**	.012*
	Penetration	12	**21.3 ± 12.1**	26	30.8 ± 12.4	17	**33.8 ± 15.7**	.047*
	Aspiration	12	21.3 ± 12.1	5	35.4 ± 11.3	38	31.6 ± 14.1	.050
LIQUID 20ml†								
	Residue valleculae	21	23.6 ± 2.7	26	35.6 ± 12	8	26.3 ± 17.9	.096
	Residue pyriform sinus	21	**23.6 ± 2.7**	19	32.2 ± 13.1	15	**34.9 ± 15.2**	.033*
	Penetration	21	23.6 ± 2.7	22	32.7 ± 14.1	12	34.6 ± 14.1	.036*
	Aspiration	21	**23.6 ± 2.7**	5	33.4 ± 9.4	29	**33.4 ± 14.7**	.039*
SEMISOLID 5ml‡								
	Residue valleculae	0	-	35	28.6 ± 12.6	20	31.6 ± 16.4	.458
	Residue pyriform sinus	0	-	15	25.3 ± 13.7	40	31.3 ± 13.9	.162
	Penetration	0	-	13	27 ± 13.4	42	30.5 ± 14.3	.437
	Aspiration	0	-	1	12 ± 0	54	30 ± 13.9	.206
SEMISOLID 10ml‡								
	Residue valleculae	0	-	44	30.3 ± 13.6	11	27.3 ± 16.2	.531
	Residue pyriform sinus	0	-	24	**24.3 ± 12.4**	31	**33.8 ± 14**	.011*
	Penetration	0	-	17	27.8 ± 13.7	38	30.5 ± 14.3	.518
	Aspiration	0	-	1	12 ± 0	54	30 ± 13.9	.206
SEMISOLID 20ml†								
	Residue valleculae	2	21 ± 15.6	44	30.2 ± 13.6	9	29.1 ± 16.6	.666
	Residue pyriform sinus	2	21 ± 15.6	27	**25.4 ± 12.5**	26	**34.8 ± 14.1**	.032*
	Penetration	2	21 ± 15.6	18	29.3 ± 16	35	30.4 ± 13.1	.657
	Aspiration	2	21 ± 15.6	0	-	53	30 ± 14	.378
SOLID†								
	Residue valleculae	11	**19.6 ± 15.4**	27	31.1 ± 11.5	17	**33.9 ± 14.5**	.021*
	Residue pyriform sinus	11	**19.6 ± 15.4**	10	27.5 ± 8	34	**33.6 ± 13.5**	.012*
	Penetration	11	**19.6 ± 15.4**	4	25.5 ± 7	40	**32.9 ± 12.9**	.015*
	Aspiration	11	**19.6 ± 15.4**	0	-	44	**32.2 ± 12.6**	.007*

† One-way ANOVA with post-hoc Tukey test for multiple comparisons

‡ Independent-sample t-test

*p<0.05. Statistically significant post-hoc comparisons are reported in bold.

NOTE: Residue valleculae = YPRSRS valleculae >2; Residue pyriform sinus = YPRSRS pyriform sinus >2; Penetration = PAS ≥3, Aspiration = PAS ≥6.

DISCUSSION

The present study aimed to clarify the association between MTP and OD in patients with ALS. MTP, tongue endurance and swallowing function were assessed in a sample of 55 consecutive patients with ALS. For the first time, OD in ALS was characterized using a variety of consistencies and volumes during the instrumental assessment of swallowing. Swallowing efficacy was more impaired than swallowing safety. A reduced MTP was associated with residue in the pyriform sinus, but not with residue in the valleculae and penetration/aspiration.

In ALS, MTP is recognized to be a marker of disease progression[21] and of bulbar involvement[11], as well as a poor prognostic factor for survival[22]. In other populations, MTP was reported to be associated with OD, mealtime performance, and malnutrition[9]. The measurement of MTP is associated with the concept of functional reserve. The functional reserve is defined as the difference in pressures generated in maximum isometric tasks compared to swallowing tasks[23]. As MTP reduces and tongue-to-palate pressure required for swallowing remains constant, a reduction of the functional reserve may potentially result in a disruption to the swallowing process. In the sample of patients recruited in the study, MTP was on average 29.7 ± 14 kPa, with 44% (24/55) of the patients showing an MTP below previously reported normal values[16]. In a previous study a cut-off of 21 kPa was determined for MTP as a marker of onset of bulbar symptoms[11], as clinically detected by the neurologist. One third (18/55) of the patients in the present study exhibited a MTP <21 kPa, but the mean MTP of patients with signs of dysphagia during FEES was generally higher than the cut-off. However, in the current study, MTP was measured with the IOPI, while the cut-off reported in the previous study was derived using a different tongue pressure manometer. Thus, it is not possible to compare the data.

Tongue endurance was <10 seconds and below normal values[16] in the majority of the patients with ALS tested in the study. Reduced tongue endurance represents an important finding. Endurance is related to physical fatigue, which is a frequent symptom and is associated with poor quality of life in patients with ALS[24]. To date, the importance of tongue endurance for swallowing function is not fully understood. When considering single swallows, the ability to sustain tongue-to-palate pressure for several seconds is probably not clinically relevant. However, tongue endurance may be important to reduce fatigability during meal consumption. Kays and colleagues analyzed the effect of dining on MTP and tongue endurance in healthy subjects and reported a significant reduction of both measures despite the age of the subject[25]. As patients with ALS were found to exhibit a reduced baseline functional reserve (MTP) and tongue endurance, meal consumption may further reduce tongue pressure measures and, consequently, exacerbate swallowing difficulties.

Patients with residue in the pyriform sinus with 10ml and 20ml semisolids had significantly lower MTP. Although not significant, a trend for lower MTP in patients with residue in the pyriform sinus was also observed for solids. Therefore, the hypothesis of a stronger association between MTP and signs of OD with more viscous

consistencies and big volumes, requiring stronger muscle contraction, was confirmed. Concerning the physiopathological mechanism explaining the association with residue in the pyriform sinus, one hypothesis may be related to the mylohyoid muscle involvement in MTP generation. Indeed, Palmer and colleagues[26] quantified the contribution of different muscles on tongue-to-pressure generation. Posterior fibers of the genioglossus and mylohyoid muscle accounted for the majority of the tongue pressure. Mylohyoid muscle is involved in laryngeal elevation during swallowing and, thus, influence UES opening. Therefore, reduced MTP may be secondary to weakness of the mylohyoid muscle, leading to reduced laryngeal elevation, reduced UES opening, and accumulation of post-swallow residue in the pyriform sinus. Another possible explanation may be that reduced MTP reflects a more generalized weakness of bulbar muscles leading to other pathophysiological mechanisms associated to residue in the pyriform sinus (e.g. pharyngeal constriction)[27]. Future study should provide a better insight into this association.

Interestingly, no association was found between the MTP and the residue in the valleculae. This finding was unexpected due to the role of the tongue in bolus propulsion through the pharynx. A possible explanation is related to the fact that MTP was investigated in the anterior portion of the tongue, as it was previously reported as a marker of disease progression and OD. Indeed, a difference between the anterior and the posterior MTP is known[16], mainly secondary to the different composition in the fibers' type. Thus, different results may be found for posterior MTP in ALS. Another possibility is that the high prevalence of residue in the valleculae, reaching 83% of the patients with semisolids, did not allow to detect differences in MTP because of the reduced number of patients with no residue in the valleculae. Based on the present result, residue in the valleculae seems to be an early onset sign of OD in the disease progression of ALS. Indeed, residue in the valleculae was found as an isolated sign of OD in around half of the sample and was associated less with penetration than residue in the pyriform sinus. This finding is in accordance with the previous study by Waito et al, who interpret that as a sign of rostrocaudal pattern of ALS bulbar disease progression[27].

Impairment of swallowing efficacy (pharyngeal residue) was found to be a prominent feature of OD in ALS, with a higher prevalence than impairment of swallowing safety (penetration/aspiration). Previous studies have mainly focused on signs of swallowing safety, but assessing both aspects is relevant to address both pulmonary and nutritional complications of dysphagia[28]. Not surprisingly, signs of swallowing unsafety mainly occurred with liquids, whereas signs of swallowing inefficiency with more viscous consistencies. Only another study investigated swallowing function in ALS using 3 types of consistencies (liquids, semisolids, and solids)[29]. The present study added the analysis on different volumes. Observing the relative frequency of signs of OD in patients tested during FEES, the frequency of residue seems to increase from 5ml volumes to 10ml volumes, with no further increase between the 10ml and 20ml, while penetration seems to remain stable among different volumes within the same consistency. However, the

number of not assessed patients due to perceived safety issues increased with larger volumes and these patients exhibited significantly lower MTP than patients with no sign of dysphagia for many of the assessed parameters (Table 1). Therefore, the frequency of signs of OD with larger volumes and their association with MTP may be underestimated.

Implications for clinical practice

The existence of an association between MTP and signs of OD in patients with ALS have an impact on both the assessment and the management of OD in this population. Firstly, it suggests that, when possible, including MTP measures during swallowing assessment provides additional information on swallowing function, being, for instance, a potential outcome measure of eating-related fatigue. Secondly, the fact that the association was found with larger volumes and more viscous consistencies has implications for diet recommendation in patients with ALS. In case of a reduction of MTP, smaller volumes should be recommended. Moreover, if swallowing safety is preserved, less viscous consistencies may be preferable. Finally, the lingual resistance training program may represent a potential rehabilitation strategy to slow the progression of OD. Lingual resistance training was found to be effective in contrasting sarcopenia in patients with presbyphagia, improving tongue strength, hyoid elevation, UES opening, and reducing residue in the pyriform sinus[30]. Although the applicability of strengthening program in patients with ALS is controversial, a progressive shift of the paradigm on rehabilitation in ALS toward the possibility to use low-load exercise, also to improve bulbar functions, was observed in the last decade[31-32]. However, the feasibility and efficacy of lingual resistance training in ALS need to be tested in future studies.

Limitations and Future perspectives

The study has some limitations. The sample size of 55 patients is relatively limited, with a potential reduction of the power of the study. However, ALS is a rare disease and the sample size is in line with or even greater than the majority of the studies instrumentally assessing dysphagia in this population. Total and bulbar score of the ALSFRS shows a homogeneous distribution among the different scores levels, suggesting that the present sample is representative of a wide range of disease severity. However, patients with enteral nutrition were excluded from the study. Nevertheless, it may have resulted in the exclusion of patients with more severe OD. FEES interpretation is subjective and, therefore, can be influenced by several factors such as the rater and bolus consistency[33]. To control for the subjectivity, two independent raters were involved in FEES assessment and inter-rater agreement was analyzed. Inter-rater agreement was poor for residue in the valleculae using liquids, analogously to previous findings[33]. To overcome this limitation, a 3rd rater was involved to resolve disagreements. Data are lacking on intra-rater agreement. Finally, FEES was used to assess swallowing as it allows to test a high number of boluses, allowing to test several consistencies and volumes. Moreover, FEES is more sensitive to residue than videofluoroscopy[34]. However, during FEES the white-out obscures the visualization of tongue base retraction during swallow. Conversely,

videofluoroscopy and high-resolution manometry may better explain the association between MTP and residue in the pyriform sinus found in the current study by visualizing tongue performance or measuring the pressure generated at tongue level during swallow and studying physiopathological mechanisms. Thus, future studies may be designed to overcome these limitations.

CONCLUSIONS

In patients with ALS, MTP is significantly associated with an impairment of swallowing efficacy. The association was found with larger volumes and more viscous consistencies, providing indications for diet recommendation in this population.

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CHAPTER 4

Mealtime Assessment Scale (MAS): Development and Validation

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4.1 THE MEALTIME ASSESSMENT SCALE (MAS): I. DEVELOPMENT OF A SCALE FOR MEAL ASSESSMENT

Abstract

Background. Safety and efficacy of swallowing in instrumental assessment may not overlap safety and efficacy of swallowing during meal, as personal and environmental factors can influence the performance.

Objective. The study aims to develop a scale to assess safety and efficacy of swallowing during meal.

Methods. A working group discussed the latent construct, target population and purposes of the scale. Items were generated based on the International Classification of Functioning framework. Thirty-nine items were created and divided into 4 subscales. A pilot test was conducted on 40 patients, assessed by a speech and language therapist (SLT) while consuming a meal. In 10 patients, meal observation was simultaneously conducted by 2 SLTs to assess inter-rater agreement. Criteria for identification of items candidate for exclusion or revision were defined.

Results. Twelve items were "not assessable" in at least 10% of the patients. An inter-item correlation $r>0.7$ was found in 2 cases and a discrimination index equal to 0 in 7/22 items. Inter-rater agreement was satisfactory (average deviation index<0.66). After items revision, the Mealtime Assessment Scale (MAS) was created, including 26 items divided into 4 subscales.

Conclusions. The MAS was developed to assess the safety and efficacy of swallowing during meal. A validation process should be conducted.

INTRODUCTION

Swallowing disorder is defined as an alteration in the bolus transit from mouth to stomach[1] and represents a common clinical condition in both acute and long-term care settings[2-3]. Several conditions can interfere with the swallowing process, such as neurological disorders and damages, oncological diseases and the aging process[4]. Swallowing disorders may reduce patients and caregivers' quality of life (QOL)[5]; moreover, swallowing disorders may lead to severe complications, such as aspiration pneumonia, malnutrition, and dehydration[6]. Therefore, the identification and the accurate assessment of patients at risk for swallowing disorders are of primary importance, to reduce the complications and to improve QOL.

Several bedside screening tools have been validated to identify patients at risk for aspiration or unsafe swallowing[7-8]. Standard protocols for clinical assessment have been introduced in daily practice[9]. Videofluoroscopy (VFS) and fiberoptic endoscopic evaluation of swallowing (FEES) are considered the two gold standard methods of instrumental assessment: bolus flow measures have been developed[10-11], and both methods demonstrated to have a good and comparable validity and reliability[12-13]. Finally, the growing attention to the impact of a specific impairment on patient's daily living has led to the introduction of self-evaluation and swallowing-related QOL questionnaires, such as the SWAL-QOL and the EAT-10[5,14]. In summary over the last decades, several tools for both clinical and instrumental assessment of swallowing disorders have been developed. Quantification of swallowing impairment relies on two major components: safety and efficiency[15-17]. Safety refers to a bolus transfer without penetration or aspiration into the airway, and its impairment health effect is aspiration pneumonia; efficiency refers to a bolus transfer without residue, and its impairment health effect is the nutritional compromise.

In the management of patients with swallowing disorders, the goal of treatment is not only improving swallowing function but also enhancing eating as an activity of daily living. With the introduction of the International Classification of Functioning, Disability and Health (ICF), the World Health Organization (WHO) has stressed the importance of considering, and therefore assessing, not only the body structures and functions, but also the activity, the participation and environmental and personal factors of a person[18]. Currently used clinical and instrumental assessment tools aim to investigate only the swallow physiology and pathophysiology; little attention has been paid to the related activities: eating and drinking and, in particular, eating and drinking during a meal. There are several differences between a swallow and a meal assessment; swallowing assessment is usually shorter than meals, it is carried out in standard conditions, and it allows testing only a few boluses for a limited number of consistencies[19]. Besides, during VFS and FEES, patients may be asked to assume an unnatural position and are controlled to maintain the requested position during the assessment; patients are also asked to eat foods with unfamiliar taste and texture[20]. Moreover, the safety and efficacy of a single swallowing act do not overlap with the safety and efficacy of swallowing during the meal, like other personal and environmental factors (e.g., setting, food variability, fatigue, eating desire, eating autonomy) can influence these aspects during mealtime. Previous studies showed that factors not strictly related to swallowing disorder impact on the management and outcome of patients with dysphagia. Steele et al. examined

eating-related difficulties in a multicare level facility for elderly persons; they reported that 87% of residents experienced mealtime difficulties, but only 68% presented signs of swallowing impairment[21]. In two studies, Langmore et al. investigated the factors that contribute to the development of aspiration pneumonia in elderly patients[22-23]. The role of swallowing disorders was controversial: indeed, the presence of dysphagia was found to be a significant risk factor for pneumonia only in the study of 2002, but not in the study of 1998. The difference in findings may be attributed to the different populations (patients from 3 different settings in the study of 1998 vs. only patients in nursing home in the study of 2002) and the different modality used to identify the presence of a swallowing impairment (instrumental assessment vs. observation of the patient eating, respectively). Conversely, both studies highlighted that dependence on eating is a significant predictor. Walton and colleagues assessed meal-related environmental factors increasing the risk of malnutrition in long-stay elderly hospitalized patients and reported that eating environment and eating independence or availability of assistance during meals were major factors affecting the dietary intakes[24]. Finally, factors other than swallowing disorders per se impact on treatment prescription; one of these is compliance with clinician prescriptions, as diet recommendation and swallowing compensation strategies. Patients with swallowing disorders with a modified oral diet were demonstrated to show a high level of non-compliance with speech and language therapists' (SLTs) recommendations[25-26]. Therefore, all these data stress the need to develop valid and reliable tools to assess swallowing during meals.

In 2011, Hansen et al. conducted a review of assessment tools measuring elderly dysphagic patient's performance in eating[27]. They identified only two assessment tools demonstrating adequate psychometric properties, the McGill Ingestive Skills Assessment (MISA)[20,28-29] and the Minimal-Eating Observation Form-version II (MEOF-II)[30]. The MISA is a bedside assessment tool for the evaluation of the functional ingestive skills of elderly persons with neurologic impairment. It was initially developed for occupational therapists (OTs) in Canada and afterwards translated, adapted and validated in Danish[31-33]. The MEOF-II is a screening tool typically carried out by nurses that aim to identify meal-time problems among elderly (>65 years) inpatients. The MEOF-II was further developed by combining items describing meal-time problems with items detecting classic signs of undernutrition. The results of these subsequent studies lead to the development of the Minimal Eating Observation and Nutrition Form-version II (MEONF-II)[34-35]. To the best of our knowledge, no other tools for the assessment of meals have been validated. However, although the MISA and the MEOF-II show a good validity and reliability, some limitations can be identified when aiming to assess both the safety and the efficacy of swallowing during the meal. Indeed, being a screening tool, the MEOF-II is made up of only 9 yes-no items, which meet the rapidity criteria but make it little value for a complete assessment of patients' performance during the meal. Concerning the MISA, it mainly focuses on safety and independence, while the efficacy of swallowing during the meal is investigated only by few items, limiting the ability of the tool to appraise the risk of nutritional and respiratory complications.

Therefore, the aims of this study were to (i) develop a scale to assess swallowing safety and efficacy during a meal; (ii) carry out a pilot study to test the scale; (iii) revise the scale. The development of a valid and reliable scale would allow the assessment of

swallowing during the activities of eating and drinking, which should be considered one of the goals of a successful management of patients with swallowing disorders. Swallowing performance during meal could be used as an outcome measure for any swallowing treatment, including surgery, diet modification, postures and maneuvers, sensori-motor training or neuromodulation. Finally, swallowing assessment during meal might more strongly correlate with patients and caregivers' QOL and better predict dysphagia complications than swallowing assessment during instrumental evaluation. Indeed, the ability of instrumental assessment in predicting the risk of aspiration pneumonia has been demonstrated in both neurological[36] and oncological patients[37], while no predictive study has been conducted concerning nutritional complication. Meal observation, assessing a higher number of swallowing acts[38] and including information on factors such as feeding dependency (predicting the risk of aspiration pneumonia and affecting dietary intake)[22-23] and meal duration (correlating with food intake)[39], may be a stronger predictor of swallowing complications.

METHODS

The present study was carried out according to the Declaration of Helsinki. Each patient included in the study gave written informed consent. This first part of the study was divided into three stages: i) scale development; ii) pilot study; iii) scale revision.

Conceptual framework

A working group composed of 2 phoniatricians and 4 SLTs working with individuals with dysphagia in an acute care hospital (inpatient and outpatient care) and a rehabilitation center in Northern Italy was created for the development of the scale.

During the first meeting, the latent construct of the scale was discussed. The latent construct is a variable of an individual that cannot be measured directly but can be assessed by measuring related behaviors, defined by sets of standardized item[40]. Moreover, the latent variable can be influenced by the characteristics of the individual and the environment. The safety and efficacy of swallowing during the meal was unanimously identified as the latent construct of the scale. The definition of the concepts of safety and efficacy established by the group of Clavé in the development of the Volume-Viscosity Swallow Test (V-VST)[15] was assumed. Safety is defined as "the patient's ability to ingest all needed calories and water with no respiratory complications," while efficacy as "the patient's ability to ingest all the calories and water he or she needs to remain adequately nourished and hydrated"[16]. In the original definition of swallowing safety the concept of both efficacy (i.e., the ability to produce the desired result) and efficiency (i.e., the ability to produce the result without wasting time or effort) are incorporated.

The working group individuated as target population all the patients who consume a meal orally regardless of the diagnosis and the setting.

The purposes of the scale were discussed as well, both for clinical practice and research. The primary purpose is the evaluation of swallowing during the meal; and the secondary purpose is the prediction of complications. Potential clinical applications of the scale are: 1) measuring changes of swallowing safety and efficacy during meal over time; 2) assessing swallowing treatments' outcomes regarding the impact on the activities of

daily living; 3) appraising the risk of pulmonary and nutritional complications. Concerning research, the potential applications of the scale are: 1) comparing swallowing safety and efficacy during meal among different populations or within the same population at different moments; 2) assessing treatments' efficacy regarding impact on the activities of daily living.

Scale development

Literature review. A review of the literature was conducted to identify already developed scales for the assessment of meals. A PubMed and PsycINFO search was conducted, and national sector-based journals were consulted. In the free-text search the following terms were used and combined through the boolean operator AND: safety OR safe, efficacy OR efficiency OR efficient, meal OR mealtime, swallowing OR deglutition OR ingestion OR eating, dysphagia OR "deglutition disorder" OR "deglutition disorders," assessment OR evaluation. In PubMed the MeSH headings eating, deglutition and deglutition disorders were searched, while in PsycINFO the subject heading thesaurus ingestion, swallowing and dysphagia were used. The records were firstly selected based on the title, then on the abstract and lastly on the full-text. Moreover, the reference lists of included studies were screened for the presence of any novel citations, which were not identified during the initial search. Four tools for the assessment of the patients during mealtime were identified: the Swallowing Assessment Checklist[41], the McGill Ingestive Skills Assessment (MISA)[20], the Griglia di Osservazione del comportamento durante il pasto del paziente disfagico[42] and the Minimal-Eating Observation Form-version II (MEOF-II)[30]. The Swallowing Assessment Checklist is an instrument of the "Swallowing…on a Plate" (SOAP) training program, developed to teach nurses how to manage patients with dysphagia in nursing homes properly. Filled in by a nurse during the patient's meal, the checklist assesses the oral phase, the pharyngeal phase, the posture, the level of independence in eating and cognitive behaviors influencing swallowing. No data on validity and reliability are available. The MISA is a valid and reliable bedside assessment tool for the evaluation of the functional ingestive skills of elderly persons with neurologic impairment. A 3-point ordinal scale is used to score 43 items, divided into 5 domains: positioning, self-feeding, solid ingestion, liquid ingestion, texture management. The Griglia di Osservazione del comportamento durante il pasto del paziente disfagico ("Mealtime observation checklist for dysphagic patients") is an observation chart for clinical assessment of dysphagia during the meal in Italian. This checklist is divided into two parts: in the first one, demographic information and medical history of the patient are recorded, while the second part includes a checklist of aspects to assess during mealtime. The checklist is made up of 41 yes-no or multiple choices items; moreover, the time needed by the patients to end the meal must be recorded. The MEOF-II is a nursing screening tool for the identification of patients with eating difficulties. It is made up of 9 items dichotomously rated from the ability of the patient to manage without problems different aspects related to three domains: ingestion, deglutition and energy and appetite.

Item generation. Items have been developed and operationalized in the Italian language. A reflective model was used for scale development. In a reflective model, the latent construct causes its visible indicators or items[43-44]. Item generation was firstly based on

the ICF. Two previous papers reporting ICF codes related to dysphagia were consulted[45-46]. Twenty ICF codes from the paper of Threats and 17 ICF codes from the study of Nund et al. were considered relevant for the assessment of meal assumption by the working group, for a total of 24 ICF codes as some ICF codes were the same in the two papers. Moreover, the working group added 8 additional ICF codes which were not included in the studies mentioned above. Therefore, 32 ICF codes were ultimately identified for item generation (Table 1). In particular, 20 codes belonged to Body functions, 5 codes to Activities and Participation, 7 codes to Environmental Factors. No code in the Body structures domain was identified as the assessment of structures is part of the purposes of clinical assessment, but not of mealtime observation. Furthermore, the reason beyond the small number of codes related to Activities and Participation is that the scale does not claim to assess the social impact of dysphagia concerning participation restriction.

Based on the 32 ICF codes, 36 items were formulated. Afterwards, the working group assessed the comprehensiveness of the items and, based on the clinical experience, decided to add 3 items ('Patient's compliance with alimentary instructions,' 'Bolus size' and 'Time period between bites') and to record the total time needed to complete the meal.

The items were grouped into 4 subscales: functions and activities influencing the meal, environmental factors influencing the meal, swallowing safety during the meal, swallowing efficacy during the meal. The subscale functions and activities influencing the meal contained the items related to mental functions, voice functions, neuromusculoskeletal and movement-related functions and activities other than eating and drinking which are not strictly connected with swallowing but may impact on its safety and efficacy during the mealtime. Items related to environmental factors influencing swallowing performance during the meal (e.g., caregiver, food, and liquid characteristics) were allocated to the environmental factors influencing the meal subscale and distinguished according to the fact that the factor analyzed by the item could be a facilitator or a barrier to the safety and efficacy of swallowing during the meal. Items assessing safety and efficacy of swallowing during the meal were divided into the subscales swallowing safety during the meal and swallowing efficacy during the meal, respectively. The working group unanimously accepted items allocation to the subscales. The 39 items divided into the 4 subscales are reported in Table 2. Items are reported both in Italian (original items) and in English to help the reader in understating the scale; no back-translation process was performed.

Table 1. ICF codes related to meal assumption identified by the working group for item generation

BODY FUNCTIONS		ACTIVITIES AND PARTICIPATION		ENVIRONMENTAL FACTORS	
ICF code	**Name of code**	**ICF code**	**Name of code**	**ICF code**	**Name of code**
b110	Consciousness functions[a]	d2302	Completing the daily routine[b]	e1100	Food[a,b]
b1301	Motivation[a,b]	d415	Maintaining a body position	e1101	Drugs[b]
b1302	Appetite[a,b]	d430	Lifting and carrying objects	e1151	Assistive products and technology for personal use in daily living[a,b]
b140	Attention functions[a]	d550	Eating[a,b]	e250	Sound[a]
b144	Memory functions[a]	d560	Drinking[a,b]	e310	Immediate family[a,b]
b147	Psychomotor functions[a]			e340	Personal care providers and personal assistants[a]
b1670	Reception of language[a]			e410	Individual attitudes of immediate family members[a,b]
b176	Mental function of sequencing complex movements				
b310	Voice functions				
b450	Additional respiratory functions[b]				
b455	Exercise tolerance functions				
b5102	Chewing[a,b]				
b5103	Manipulation of food in the mouth[a,b]				
b5104	Salivation[a,b]				
b51050	Oral swallowing[a,b]				
b51051	Pharyngeal swallowing[a,b]				
b530	Weight maintenance functions[b]				
b735	Muscle tone				
b740	Muscle endurance functions				
b760	Control of voluntary movement functions				

[a]ICF code from Threats (2007)

[b]ICF code from Nund et al (2014)

Table 2. Generated items

FUNCTIONS AND ACTIVITIES INFLUENCING THE MEAL (N=9) ***Funzioni e attività che impattano sul pasto***	**ENVIRONMENTAL FACTORS INFLUENCING THE MEAL (N=8)** ***Fattori ambientali che impattano sul pasto***	**SWALLOWING SAFETY DURING THE MEAL (N=11)** ***Sicurezza della deglutizione durante il pasto***	**SWALLOWING EFFICACY DURING THE MEAL (N=11)** ***Efficacia della deglutizione durante il pasto***
Responsiveness *Responsività*	Alternative feeding methods (F) *Metodi di alimentazione alternativi*	Residue in the oral cavity after swallowing *Detersione orale dopo la deglutizione*	Patient's desire to eat *Desiderio di alimentarsi per os*
Linguistic comprehension *Comprensione linguistica*	Food consistency (F) *Consistenza del cibo*	Presence of cough or throat cleaning with semisolids *Presenza di tosse o raclage con i semisolidi*	Ability to complete the meal without exhortations *Capacità di continuare il pasto senza sollecitazioni*
Attention *Attenzione*	Bolus size (F) *Dimensione del bolo*	Presence of cough or throat cleaning with solids *Presenza di tosse o raclage con i solidi*	Shortness of breath while eating *Presenza di affanno durante il pasto*
Memory *Memoria*	Liquid consistency (F) *Consistenza del liquido*	Presence of cough or throat cleaning with liquids *Presenza di tosse o raclage con i liquidi*	Time period between bites *Velocità nell'assunzione del boccone successivo*
Voice quality *Qualità vocale*	Liquids delivery method (F) *Modalità di assunzione del liquido*	Presence of cough or throat cleaning with dual consistencies *Presenza di tosse o raclage con le doppie consistenze*	Fatigue *Affaticabilità*
Patient's compliance with alimentary instructions *Complianza del paziente alle istruzioni alimentari*	Oral medications delivery method (F) *Modalità di assunzione dei farmaci*	Presence of cough or throat cleaning in the distance *Presenza di tosse o raclage a distanza*	Ability to end the whole meal *Capacità di terminare tutte le portate del pasto*
Head-to-trunk control *Controllo del capo e del tronco*	Setting (B) *Setting*	Reflexive cough quality *Qualità della tosse riflessa*	Amount of food eaten *Quantità di cibo assunta alla fine del pasto*
Independence in eating *Autonomia nell'alimentazione*	Possibility to rely on caregiver (B) *Possibilità di far affidamento sul caregiver*	Voice quality post-swallow *Qualità della voce post-deglutitoria*	Control of food leakage while chewing *Efficacia dello sfintere labiale durante la masticazione*
Ability to take food to mouth *Capacità di portare il cibo alla bocca*		Amount of food in the mouth *Quantità di cibo in bocca*	Control of drooling *Controllo orale della saliva*
		Food loss through the cannula *Fuoriuscita di cibo dalla cannula tracheale*	Oral preparation *Preparazione orale*
		Liquids loss through the cannula *Fuoriuscita di liquido dalla cannula tracheale*	Velopharyngeal competence *Continenza velare*

Footnotes. F = facilitator; B = barrier

The original version of the items in Italian is reported in Italics

Scoring development. The working group discussed the scoring of the items and decided to assign the same number of scoring categories to all the items. Moreover, group members agreed to use an even number of scoring categories so that no neutral category exists and the raters would be forced to choose between either side of a moderate level of functioning. Current evidence suggests that generally, people are unable to discriminate much beyond seven levels[47]. However, the use of only 2 scoring categories would lead to a loss of information being less than the rater's ability to discriminate, while using 6 scoring categories was challenging to give a label to each level. According to the ICF classification, it was decided that a higher score would be representative of a more critical problem in the observed variable. Therefore, a 4-point Likert scale, ranging from 0 (normal) to 3 (severely deviant), was used to score each item of the subscales *functions and activities influencing the meal*, *swallowing safety during the meal* and *swallowing efficacy during the meal*. Concerning the scale *environmental factors influencing meal*, the 4-point scoring system was maintained, but the sign + or – was associated to the number according to the fact that the factor analyzed in the item could be considered a facilitator or a barrier to swallowing performance during the meal. An operational definition was given for each score, to reduce the subjectivity of the scoring system (e.g. for the bolus size a score of 0 corresponded to a tablespoon, a score of 1 to a half tablespoon, a score of 2 to a teaspoon, a score of 3 to a half tablespoon). Moreover, the *Not assessable (N.A.)* box was added to be crossed in case that an item was not assessable. The working group decided not to sum the scores of the items from the scales *body functions and activities influencing meal* and *environmental factors influencing meal* because of the clear multidimensionality of these two scales, but their items can be used to interpret the scores of the following two scales. Two scores (a safety score and an efficacy score) resulted from the sum of the scores of the items from the *swallowing safety during the meal* and *swallowing efficacy during the meal* scales; the higher the scores, the more reduced the safety or the efficacy of swallowing during meal. For both the scales, the score ranged from 0 to 33. A percentage score could also be calculated to nullify the impact of not assessable skills, using the following proportion: $Total\ score : [117 - (3 * number\ of\ N.A.items)] = x : 100$. The time the patient needed to end the meal had to be recorded.

Overall, scale development required seven meetings. The scale was named "Mealtime assessment scale" (MAS). An instruction manual was developed to train the staff in the conduction of the assessment.

Pilot study

The developed protocol was tested on 40 patients in a rehabilitation center and a University Hospital. Inclusion criteria were: age over 18, hospitalized, the presence of swallowing disorder in a previous instrumental or clinical assessment. The patients' sample is described in Table 3.

Table 3. Demographic and clinical characteristics of the pilot study's sample

		Median (range) or n/N (%)
Age		78 (28-92)
Gender		
	M	21/40 (52.5%)
	F	19/40 (47.5%)
Diet		
	C1	15/30 (37.5%)
	C2	14/40 (35%)
	C3	1/40 (2.5%)
	C4	10 /40 (25%)
Etiology		
	Ischemic stroke	13/40 (32.5%)
	Hemorrhagic stroke	5/40 (12.5%)
	PD	3/40 (7.5%)
	Vascular Parkinsonism	3/40 (7.5%)
	Encephalopathy	1/40 (2.5%)
	Cerebral hypoxia	1/40 (2.5%)
	MSA	2/40 (5%)
	MS	1/40 (2.5%)
	ALS	2/40 (5%)
	Thyroid cancer	1/40 (2.5%)
	Cranial nerve palsy	1/40 (2.5%)
	Psychogenic	1/40 (2.5%)
	Dysphagia of unspecified etiology	6/40 (15%)

C1 = homogenous puree consistency diet; C2 = soft food diet; C3 = normal diet except for dual consistencies, friable and filamentous foods; C4 = normal diet; PD = Parkinson's disease; MSA = Multiple system atrophy; MS = Multiple sclerosis; ALS = Amyotrophic lateral sclerosis

Each patient was assessed during lunchtime using the MAS by a SLT who was not part of the working group for item development and was instructed to use the scale by reading the developed manual. A specific setting of the evaluation was not established for each patient, and they were assessed where they usually ate meals. Patients were not asked to assume any particular position; some patients already used compensation postures or maneuvers. The whole meal was observed. Ten out of 40 patients were assessed during the same meal by a second SLT who independently scored the MAS to test its inter-rater agreement.

Statistical analysis

Results are reported as median and range or absolute and relative frequencies. Statistical analysis was performed using IBM Statistics SPSS® for Windows software (SPSS Inc,

Chicago, IL). The Cronbach's alpha was used to calculate internal consistency of both the *swallowing safety during the meal* and the *swallowing efficacy during the meal* subscales. Moreover, Cronbach's alpha without an item was computed to identify items to be removed to improve internal consistency. A Cronbach's alpha >0.70 was regarded as "good" internal consistency[48-50]. Corrected item-to-total correlation was calculated; ultimate item-to-total correlation was considered for values between 0.30 and 0.70[51-52]. Non-parametric Spearman correlation test was used to assess inter-item correlation. An inter-item correlation above 0.70 suggests that item are redundant[52]. Significance was set for $p<0.05$. The average deviation index (AD index) was used to test the inter-rater agreement. A good inter-rater agreement was considered for AD index below 0.66[53]. A discrimination index was calculated for each item of the subscales *swallowing safety during the meal* and *swallowing efficacy during the meal*. The discrimination index is the difference between the number of individuals with a total score above the median who scored positive (2 or 3) on the item and the number of individuals with a total score below the median who scored positive on the item divided by the number of individuals above the median. The discrimination index ranges from -1 to +1; values of 0.20 or above are considered desirable, and values of 0.40 or above are regarded as high[54]; a negative discrimination index suggests the need of item revision.

Scale revision

Based on the pilot study results, items were collegially revised by the working group. Criteria for identification of items candidate for exclusion or revision were: 1) percentage of N.A. higher than 10%; 2) increase of the Cronbach's alpha without the item; 3) item-to-total correlation lower than 0.30; 4) inter-item correlation $r>0.7$; 5) inter-rater agreement with an AD index >0.66; 6) negative discrimination index or equal to 0; 7) variance in the scores equal to 0.

RESULTS

Pilot study

Cronbach' alpha was α=-0.088 for the safety scale and α=0.660 for the efficacy scale. The items *presence of cough or throat cleaning with dual* consistencies, *food loss through the* cannula, *liquid loss through the cannula* and *velopharyngeal competence* were not included in the analysis because of the absence of variance between scores or of the high number of not assessable items. Tables 4 and 5 report Cronbach's alpha without the item and item-to-total correlation for the safety and the efficacy scales, respectively. Table 6 shows median scores and range obtained on the MAS by the patients included in the pilot study; absolute frequency and percentage of not assessable items are also reported as well as AD index values for inter-rater agreement and the discrimination indexes. Twelve items were not assessable in at least 10% of the patients. The AD index was <0.66 for all the items, except for 4/39 items for which it was not computable because of the high frequency of not assessable items. Discrimination index was not computable in 3/11 items of the *swallowing safety during the meal* subscale because of the high prevalence of N.A. answers. No items showed a negative discrimination index and a value equal to 0

was found in 2/11 items of the *swallowing safety during the meal* subscale and 5/11 items of the *swallowing efficacy during the meal* subscale.
An inter-item correlation r>0.7 was found in 2 cases. The item "Swallowing medicines" and the item "Alternative feeding methods" showed a correlation of r=0.77 (p=0.003). The item "Patient's desire to eat" strongly correlated with the item "Ability to continue the meal without solicitations" (r=0.92, p<0.001).

Table 4. *Swallowing safety during the meal* subscale – Cronbach's alpha and item-to-total correlation

Item	Cronbach's alpha without the item	Item-to-total correlation
Residue in the oral cavity after swallowing	-0.722	0.866
Presence of cough or throat cleaning with semisolids	-1.000	0.945
Presence of cough or throat cleaning with solids	0.219	-0.500
Presence of cough or throat cleaning with liquids	-0.667	0.327
Presence of cough or throat cleaning in the distance	-0.900	0.000
Reflexive cough quality	0.611	-0.655
Voice quality post-swallow	-0.900	0.000
Amount of food in the mouth	-0.970	0.000

Table 5. *Swallowing efficacy during the meal* subscale – Cronbach's alpha and item-to-total correlation

Item	Cronbach's alpha without the item	Item-to-total correlation
Control of food leakage while chewing	0.518	0.811
Control of drooling	0.580	0.600
Oral preparation	0.672	0.104
Patient's desire to eat	0.666	0.168
Ability to complete the meal without exhortations	0.658	0.187
Shortness of breath while eating	0.630	0.389
Time period between bites	0.643	0.310
Fatigue	0.678	-0.144
Ability to end the whole meal	0.579	0.583
Amount of food eaten	0.675	0.024

Table 6. Median (range) scores, frequency of not assessable items, inter-rater agreement and discrimination index of the items of the first version of the MAS

	Median	range	N.A. (%)	AD index	Discrimination index
Responsiveness	0	0-2	0/40 (0%)	0	-
Linguistic comprehension	0	0-2	1/40 (2.5%)	0.15	-
Attention	0	0-2	1/40 (2.5%)	0.35	-
Memory	0	0-3	3/40 (7.5%)	0.28	-
Voice quality	1	0-3	1/40 (2.5%)	0.15	-
Patient's compliance with alimentary instructions	0	0-2	2/40 (5%)	0.17	-
Head-to-trunk control	0	0-2	0/40 (0%)	0.3	-
Independence in eating	0	0-3	7/40 (17.5%)	0.06	-
Ability to take food to mouth	0	0-3	12/40 (30%)	0.25	-
Alternative feeding methods	0	0-3	0/40 (0%)	0	-
Food consistency	1	0-3	1/40 (2.5%)	0.05	-
Bolus size	0	0-3	2/40 (5%)	0.05	-
Liquids consistency	0	0-3	2/40 (5%)	0	-
Liquids delivery method	0	0-3	13/40 (32.5%)	0.17	-
Oral medications delivery method	2	0-3	28/40 (70%)	N.C.	-
Setting	1	0-2	0/40 (0%)	0.25	-
Possibility to rely on caregiver	0	0-3	0/40 (0%)	0.17	-
Oral cavity detersion after swallowing	1	0-3	2/40 (5%)	0.6	0.26
Presence of cough or throat cleaning with semisolids	0	0-2	10/40 (25%)	0.06	0.07
Presence of cough or throat cleaning with solids	0	0-2	16/40 (40%)	0	0.09
Presence of cough or throat cleaning with liquids	0	0-3	16/40 (40%)	0	0.19
Presence of cough or throat cleaning with dual consistencies	0	0-0	36/40 (90%)	0	N.C.
Presence of cough or throat cleaning in the distance	0	0-1	1/40 (2.5%)	0	0
Reflex cough quality	0	0-2	31/40 (77.5%)	N.C.	0.13
Voice quality post-swallow	0.5	0-2	2/40 (5%)	0.11	0.11
Amount of food in the mouth	0	0-1	1/40 (2.5%)	0.2	0
Food loss through the cannula	0.5	0-1	38/40 (95%)	N.C.	N.C.
Liquids loss through the cannula	0	0-0	39/40 (97.5%)	N.C.	N.C.
Control of food leakage while chewing	0	0-2	2/40 (5%)	0.22	0.17
Control of drooling	0	0-1	1/40 (2.5%)	0	0
Oral preparation	0	0-1	2/40 (5%)	0.14	0
Velopharyngeal competence	0	0-0	1/40 (2.5%)	0	0
Patient's desire to eat	0	0-3	1/40 (2.5%)	0.05	0.39
Ability to complete the meal without exhortations	0	0-2	2/40 (5%)	0.1	0.29
Shortness of breath while eating	0	0-2	2/40 (5%)	0.22	0
Time period between bites	1	0-2	12/40 (30%)	0.38	0
Fatigue	0	0-2	1/40 (2.5%)	0.11	0.17
Ability to end the whole meal	1	0-3	1/40 (2.5%)	0.2	0.72
Amount of food eaten	1	0-3	1/40 (2.5%)	0.18	0.56

N.C. = not computable

Scale revision

The working group discussed the items that were candidates for exclusion or revision based on the criteria previously defined.

Eleven items were removed:

- 6 items which were frequently not assessable (*liquids delivery method, oral medications delivery method, reflexive cough quality, time period between bites, food loss*

from the cannula, liquid loss from the cannula); moreover the item *reflexive cough quality* was removed to improve the Cronbach's alpha of the *safety* scale
- the item *responsiveness* because of the impossibility to conduct a meal observation in case the item was assigned a high score
- the items *setting* and *alternative feeding methods* because they were judged to be improper to score and were maintained in a separate section without a scoring system as variables to be contemplated in the scores interpretation
- the item *velopharyngeal competence* because it scored 0 in all patients
- the item *shortness of breath while eating* because of the high item-item correlation with *fatigue* ($r=0.66$; $p<0.001$).

Other items were revised. Revisions mainly consisted of 1) rephrasing the items and the operational definitions of the scoring levels, using a more specific and univocal terminology and defining, when possible, exact numerical references, such as the frequency of occurrence of a specific behavior; 2) improving the definition of what each item assesses in the instruction manual; 3) unifying items.

Functions and activities influencing the meal. Five items (*linguistic comprehension, attention, memory, patient's compliance with alimentary instructions, head-to-trunk control*) were better defined in the instruction manual; indeed, it was specified that these aspects should be rated based on the performance of the observed meal and not in relation to other information that the SLT may have previously acquired on the patient.
Two items were added to the *functions and activities influencing meal* subscale: the item *teeth* and *voluntary cough*. The item *teeth* belong to the ICF Body structures, which were not included in the scale as stated before. However, because of the variability of this structure in case of removal dental prosthesis, the working group considered essential to assess it during the observed meal. Consequently, the subscale was renamed *structures, functions, and activities influencing the meal*.

Environmental factors influencing the meal. As the *liquids delivery method* was removed, information on the utensils used to take liquids were incorporated in the item *liquids consistency*.

Swallowing safety during meal. The item *amount of food in the mouth* and the operational definitions of the item *residue in the oral cavity after swallowing* were rephrased because of the weak item-to-total correlation but were considered essential to be maintained by the working group. The 5 items related to the presence of cough or throat cleaning were frequently not assessable because mealtime observation often did not allow to observe patient consuming all the food consistencies; therefore, they were unified in a single item *presence of cough or throat cleaning.*

Swallowing efficacy during the meal. The operational definitions of the items *oral preparation, ability to end the whole meal* and *amount of food eaten* were rephrased and improved because of the weak item-to-total correlation, but the working group decided to maintain them. Analogously, relative frequencies of occurrence were added to the operational definitions of the item *control of food leakage while chewing*. The items *patient's*

desire to eat and *ability to complete the meal without exhortations* that showed a high inter-item correlation were both maintained and redefined in the instruction manual; indeed, although the two items include some overlapping aspects, the latter address a broader concept than solely appetite and palatability of the food. Moreover, the items *control of drooling* and *patient's desire to eat* were moved to the *structures, functions, and activities influencing the meal* subscale.

Mealtime Assessment Scale. The revised version of the MAS consists of:

- a first section to record demographic information and medical history of the patient, which may be useful to interpret the scoring of the items.
- the *Structures, functions and activities influencing meal* subscale: it includes 12 items related to mental functions, voice functions, neuromusculoskeletal and movement-related functions and activities other than eating and drinking which are not strictly connected with swallowing but may impact on its safety and efficacy during mealtime.
- the *Environmental factors influencing meal* subscale: it includes 4 items related to environmental factors influencing swallowing performance during the meal. The items are divided into facilitators and barriers based on to the fact that a more deviant score may ease or worsen the safety and efficacy of swallowing during the meal.
- the *Swallowing safety during meal* subscale: it includes 4 items assessing signs of swallowing safety, defined as "the […] ability to ingest all needed calories and water with no respiratory complications". A *safety* score (0-12) can be computed by summing the items' scores.
- the *Swallowing efficacy during meal* subscale: it includes 6 items assessing signs of swallowing efficacy, defined as "the […] ability to ingest all the calories and water he or she needs to remain adequately nourished and hydrated". An *efficacy* score (0-18) can be computed by summing the items' scores.
- a section for the scoring the protocol: in this section the *safety* and *efficacy* scores are computer and the time the patient needed to end the meal is recorded. To nullify the difference in the number of items of the safety and efficacy subscales, for both the *safety* and the *efficacy* sections a percentage can be calculated to quantify the level of impairment in each aspect. The higher the score or the percentage, the less safe or efficacious is the swallowing during the meal.
- an optional section concerning eventual compensations and indications to give to the patient or to the caregiver during the post-assessment counseling.

DISCUSSION

The MAS has been developed to assess the safety and efficacy of meal. Twenty-six items divided into 4 subscales were selected from the original 39 items divided into 4 subscales. The item revision aimed to improve scale reliability, to reduce items' redundancy, to increase the discrimination ability of the tool and its internal consistency, and to remove items that may be not assessable or modify these to guarantee the possibility to score all the items in all situations. The psychometric characteristics of the

revised tool need to be tested to verify if the scale revision reached the above-mentioned aims.

This study represents only the first step in the development and validation of the MAS. The importance of having shared assessment tools stands in the possibility to improve communication among clinicians and to compare results from different studies, contributing building evidence for swallowing treatment. This study laid the groundwork for further development and validation of the MAS, which may support the use of a common language among swallowing expert when assessing swallowing during meals.

The ICF framework was the reference for the item generation process. Other authors have previously recommended the application of the ICF in swallowing assessment to expand the evaluation to aspects other than solely body structures and functions and to better estimate the psychological and social burden derived from dysphagia onset[45-46]. In the ICF classification, eating and drinking are classified as activities and participation, involving different body structures and functions and being influenced by environmental and personal factors[18]. Items selected in the MAS cover several ICF components, including body structures involved in swallowing (e.g., teeth), body functions that directly describe swallowing process (e.g., oral control of the bolus), other body functions that may significantly influence the success in eating and drinking (e.g., attention), activities (e.g., ability to bring food to mouth), environmental factors (e.g., food consistency) and personal factors (e.g., patient's desire to eat). However, participation, defined as 'involvement in a life situation' or as "the lived experience" of people in the actual context in which they live'[18], was not included in the MAS. Indeed, assessing patients in their everyday context is frequently not possible in clinical practice, while the MAS aims to be a tool that can be extensively applied in a wide range of settings. Thus, participation is not directly assessed. Nevertheless, swallowing performance during mealtime may better predict the psychosocial impact of swallowing disorders than safety and efficacy of a limited number of swallowing acts tested during the clinical and instrumental assessment.

The items of the subscales *structures, functions and activities influencing meal* and *environmental factors influencing meal* are not summed together because of their clear multidimensionality. Moreover, a sum-score for these subscales would be a little informative. Indeed, the MAS was developed with the aim to assess swallowing safety and efficacy during the meal and therefore the items included in the above-mentioned subscales do not assess these aspects directly. However, the analysis of their scores can be helpful to the clinician in order to understand in which condition the patient can or cannot consume the meal safely and efficiently and subsequently identify those aspects, other than solely swallowing ability, to focus on during swallowing therapy (e.g., environmental modifications, bolus modifications, counseling to the patient and/or caregivers). Therefore, practical information can be gained from the MAS for the management of the patient with dysphagia. However, no Rasch analysis has been currently performed for testing whether or not items from the subscales *swallowing safety during the meal* and *swallowing efficacy during the meal* measure an unidimensional construct, which is necessary for summation of ordinal scores[55]. Moreover, Rasch analysis may be useful to investigate whether the reliability of the tool could be increased

by modifying the number of scoring categories, to achieve the greatest homogeneity within the same category and the most significant distance among different categories. Therefore, it should be conducted in a further study. Moreover, a factor analysis should be performed as well to confirm the assignation of items into subscales.
A strong point of the MAS is its feasibility. Firstly, after meal observation, it can be quickly filled in, taking around 5-10 minutes. Secondly, its administration is not intrusive and, except for the presence of an observer, it preserves the ecologicity of the situation. Moreover, the need of patient's collaboration is limited to the consumption of at least part of a meal (minimum a quarter of a course), and it can be therefore applied to all individuals who consume a meal orally, despite of cognitive impairment, aphasia or behavioral issues. Furthermore, no specific equipment is required. The working group was made up of professionals daily involved in the evaluation and treatment of individuals with swallowing impairments. Thanks to the different background and working facilities of the group members, high regard to the applicability of the scale to different settings and populations was held during item generation and revision.

Limitations and Future perspectives
The variability of each meal situation represents a limit of meal assessment. Indeed, as stated in the introduction, several personal and environmental factors may interfere with swallowing safety and efficacy during a meal, and they changes every lunch and dinner. Being aware of this intrinsic limit, it is, therefore, essential to conduct the meal observation using typical food and amounts (e.g., consistencies, number of courses, quantity of food for each course) usually consumed during meals in daily living and, if possible, to observe the patient in its typical meal setting (e.g., posture, utensils, dining companion, eventual source of distraction). Ecological validity of meal assessment using MAS in a clinical setting should be assessed in future studies.
In the present study comprehensiveness of the scale was judged by the working group which generated items. However, it would be more appropriate that a group of experts, not involved in item development and, preferably, made up of members from different professions, assess comprehensiveness and, in general, face validity of the MAS. It may be therefore addressed for the purposes of a future study aiming to further contribute to MAS development. Another limit of the study is the small sample size included, notably, concerning inter-rater agreement. The present study did not aim to validate the scale but only to undergo a pilot testing to highlight items that should be revised or removed. Certainly, a bigger sample size should be included in further steps of MAS development and validation. Lastly, in case the MAS would be demonstrated to be a valid and reliable tool, its ability to predict dysphagia's complications on QOL, pulmonary function and nutritional status, which was addressed among potential clinical applications, should be investigated.

CONCLUSION

The MAS was developed to assess the safety and efficacy of swallowing during the meal. Further development steps, including Rasch analysis, factor analysis, content validity analysis by an external group of experts, and expanding sample size, as well as a validation process should be conducted. In case its validity and reliability would be demonstrated, it may represent a valuable tool to be used both in clinical practice and research.

4.2 THE MEALTIME ASSESSMENT SCALE (MAS): II. PRELIMINARY PSYCHOMETRIC ANALYSIS

Abstract

Background. The Mealtime Assessment Scale (MAS) was developed to assess swallowing safety and efficacy during the meal.
Objective. The study aims to undergo a preliminary validation of MAS by investigating internal consistency, inter-rater agreement, concurrent and known-group validity, and responsiveness.
Methods. MAS was tested on 100 persons without dysphagia (Group 1) and 100 persons with dysphagia (Group 2). Fifty subjects were simultaneously evaluated at mealtime using MAS by two independent clinicians to test inter-rater agreement. For concurrent validity, MAS was correlated with the Mann Assessment of Swallowing Ability (MASA). MAS scores of Groups 1 and 2 were compared for known-group validity. Responsiveness was tested re-assessing 36 patients from Group 2 after diet improvement.
Results. Internal consistency was α=0.615 for the safety score and α=0.858 for the efficacy score. Inter-rater agreement was good with an average deviation index<0.66 was found for all items. MAS showed significant correlations with MASA (r=-0.75 with the safety score and r=-0.81 with the efficacy score). A statistical significant different in MAS scores was found between Groups 1 and 2. For responsiveness analysis, a statistical significant different was found in patients after diet improvement only for the efficacy score (p=0.001).
Conclusion. Preliminary evidence of the validity and reliability of MAS was established. Future studies should be focused on improving internal consistency of the safety scale and to complete the psychometric validation of the MAS.

INTRODUCTION

Complications of oropharyngeal dysphagia (OD) comprise reduction of patients and caregivers' quality of life (QOL)[1-2], aspiration pneumonia, malnutrition, and dehydration[3]. Pulmonary complications are the result of the impaired safety of swallowing leading to tracheobronchial aspiration; malnutrition and dehydration are secondary to the impaired efficacy of swallowing reducing oral intake of nutrients and liquids[4-6]. Currently, OD assessment mainly focuses on the quantification of the safety and efficacy of swallowing through the observation of a limited number of swallowing acts. However, when consuming a meal or drinking a beverage in everyday living, personal and environmental factors, such as food, appetite, fatigue, may impact swallowing safety and efficacy[7-9]. Hence, a specific assessment of swallowing safety and efficacy while consuming a meal should be conducted along with instrumental and clinical swallowing assessment in the management of individuals with OD.

In a companion article, our working group developed a scale to assess swallowing safety and efficacy during the meal, named Mealtime Assessment Scale (MAS), to be applied to all the patients who consume a meal orally regardless of the diagnosis and the setting[10]. Potential applications of the scale in clinical practice and research, to be used in association with other swallowing measures, are: 1) appraising the risk of pulmonary and nutritional complications, 2) measuring changes in over time; 3) assessing swallowing treatments' efficacy in terms of impact on the activities of daily living; 4) comparing swallowing safety and efficacy during meal among different populations. The MAS was developed based on the International Classification of Functioning, Disability and Health (ICF) framework[11] and a pilot study for item selection and revision was conducted.

Consequently, this study aims to undergo a preliminary psychometric testing of the MAS including reliability and validity analysis. Our hypothesis are that: i) the item selection and revision conducted in the previous part of the study related to scale development have improved MAS reliability reaching adequate levels for both clinical and research application; ii) the MAS may represent a valid measure of meal safety and efficacy being able to discriminate individuals with different performances in meal consumption, to detect clinically relevant changes over time and to moderately correlate with other swallowing outcome measures.

METHODS

The present study was carried out according to the Declaration of Helsinki. Each patient included in the study gave written informed consent. The study consisted of: i) reliability analysis; ii) validity analysis.

Mealtime assessment scale

The MAS is a scale for the assessment of the safety and the efficacy of swallowing during meal. It comprises an initial section to record demographic information and medical history of the patient. The scale is, then, divided into four subscales: 1) *structures, functions, and activities influencing the meal*, 2) *environmental factors influencing the meal*, 3) *swallowing safety during the meal*, 4) *swallowing efficacy during the meal*. Overall, 26 items are included in the MAS. The MAS ends with a section for the scoring and an optional

section concerning eventual compensations and indications to give to the patient or to the caregiver during the post-assessment counseling. A 4-point Likert scale, ranging from 0 (normal) to 3 (severely deviant), was used to score each item. A safety score (0-12) and an efficacy score (0-18) can be computed by summing the items' scores of the subscales *swallowing safety during the meal* and *swallowing efficacy during the meal*, respectively. Moreover, in order to nullify the difference in the number of items, for both the safety and the efficacy sections a percentage can be calculated to quantify the level of impairment in each aspect. The higher the score or the percentage, the less safe or efficacious is the swallowing during the meal. The time the patient needed to end the meal must be recorded.

Patients

Patients were recruited in a rehabilitation center and an acute-care hospital.

Three groups of patients were included: group 1) 100 patients without OD; group 2) 100 patients with OD of different etiology and tolerating a complete or partial oral diet; group 3) 36 patients with OD from the group 2 evolving from a more restricted diet to a less restricted diet during the hospitalization period. The sample size of 100 subjects was determined as Hansen et al. set this number as the cut-off for an excellent sample size [12]. Inclusion criteria were: *group 1*) hospitalized or non- hospitalized, Mann Assessment of Swallowing Ability (MASA) score[13] ≥178, aged over 18; *group 2*) hospitalized, OD of any origin, MASA score <178, aged over 18; *group 3*) hospitalized, OD of any origin, MASA score at the first assessment <178, diet restriction improvement during the hospitalization period. Patient's characteristics for the three groups are reported in Table 1. None of the patients were lost or had withdrawn.

Procedure

All patients from Groups 1 and 2 were evaluated with the MASA protocol[13] by a SLT. All the patients were then observed during mealtime by a different SLT blinded to the results of the previous evaluation within 7 days (in the rehabilitation center) or within 24 hours (in the acute-care hospital) from the assessment with MASA, in order to use of the MAS protocol. For 50 patients from the Group 2, the meal observation was simultaneously conducted by two independent SLTs, blinded to the results of the clinical assessment, who observed the same meal and independently filled in the MAS protocol at the end of the meal. Overall, 5 SLTs with over five years of experience in dysphagia assessment and management were involved in patients' assessment. Each rater read MAS' instruction manual and could ask the working group of the MAS for explanations during a dedicated meeting.

The MASA is a standardized and validated clinical bedside assessment tool for the evaluation of oropharyngeal dysphagia, composed of 24 items scored on a 10-point scale. The total score ranging from 38 to 200 is obtained by summing up items scores; the lower the score, the higher the swallowing impairment. A MASA score of 178 is considered to be the cutoff for the absence of dysphagia, and a MASA score of 170 is considered to be the cutoff for the absence of aspiration risk. Inter-rater reliability for the MASA had been established with values of k=0.85 for dysphagia and k=0.74 for aspiration[14].

Table 1: Demographic and clinical characteristics of the sample

		Group 1 (n = 100)	*Group 2 (n = 100)*	*Group 3 (n = 36)*
Age		58 (18-91)	81 (37-96)	78.5 (51-92)
Gender				
	M	30/100 (30%)	56/100 (56%)	23/36 (63.9%)
	F	70/100 (70%)	44/100 (44%)	13/36 (36.1%)
Diet type				
	C1	0/100 (0%)	80/100 (80%)	36/36 (100%)
	C2	0/100 (0%)	16/100 (16%)	0/36 (0%)
	C3	0/100 (0%)	3/100 (3%)	0/36 (0%)
	C4	100/100 (100%)	1/100 (1%)	0/36 (0%)
Etiology				
	Ischemic stroke	-	50/100 (50%)	19/36 (52.8%)
	Hemorrhagic stroke	-	20/100 (20%)	10/36 (27.7%)
	PD	-	11/100 (11%)	4/36 (11.1%)
	Vasculopathy	-	5/100 (5%)	0/36 (0%)
	Encephalopathy	-	2/100 (2%)	0/36 (0%)
	Encephalitis	-	1/100 (1%)	0/36 (0%)
	Severe acquired injury	-	3/100 (3%)	1/36 (2.8%)
	NHL	-	1/100 (1%)	0/36 (0%)
	AD	-	1/100 (1%)	0/36 (0%)
	Lower motor neuron disease	-	1/100 (1%)	1/36 (2.8%)
	Glossectomy	-	1/100 (1%)	0/36 (0%)
	Cranial nerve palsy	-	1/100 (1%)	1/36 (2.8%)
	Dysphagia of unspecified etiology	-	3/100 (3%)	0/36 (0%)

Note: Values are median (range), n/N (%), or as otherwise indicated.
C1 = homogenous puree consistency diet; C2 = soft food diet; C3 = normal diet except for dual consistencies, friable and filamentous foods; C4 = normal diet; PD = Parkinson's disease; NHL = Non-Hodgkin lymphoma; AD = Alzheimer's disease

The setting of the meal observation was not established to allow the observation of each patient in the setting most similar to daily living. Out-patients were assessed in the therapy room, hospitalized patients were evaluated in their room or in the ward's dining room. Patients in Group 1 were observed in the setting where they usually consume the meal (home, workplace canteen, ward dining room). In case the patients needed assistance during the meal, the usual helper gave it. During meal, the rater could talk with the patient, encourage him to complete the meal or ask for specific tasks required to complete the MAS (e.g., open the mouth to assess post-swallow residue in the oral cavity), but no additional request nor alimentary instruction could be given, unless necessary for patient's safety. Patients were not asked to assume any particular position. Each patient was allowed to choose the food to eat, respecting eventual consistencies restrictions indicated by previous swallowing evaluations. The whole meal was observed for all the patient, and the MAS was filled in only once meal consumption was ended.

In Group 3, a fiberoptic endoscopic evaluation of swallowing (FEES) was performed before diet modification by a phoniatrician who verified that patients could tolerate a less restricted oral diet; SLT's observation of the patients during mealtime and MAS' compilation was conducted twice: first during the more restricted diet, secondly after less restricted diet, before the patient's discharge.

Data analysis

Results are reported as median and range. Statistical analysis was performed using IBM Statistics SPSS® for Windows software (SPSS Inc, Chicago, IL). A Shapiro-Wilk test showed that the normality assumption was violated for all variables in all groups ($p<0.05$).

Reliability analysis. Reliability is the degree to which the measurement is free from measurement error[15]. Among the different types of reliability, internal consistency is the degree of the interrelatedness among the items, while inter-rater reliability represents the extent to which scores for patients who have not changed are the same when assessed by different persons on the same occasion[15]. Cronbach's alpha was used to calculate internal consistency of both the *swallowing safety during the meal* and the *swallowing efficacy during the meal* subscales using Group 1 and Group 2 scores. A Cronbach's alpha >0.70 was regarded as "good" internal consistency[16]. The average deviation index (AD index) was used to test the inter-rater agreement. A good inter-rater agreement was considered for AD index below 0.66[17].

Validity analysis. Validity is the degree to which a tool measures the construct it aims to measure[16]. It includes concurrent validity, namely the degree a test correlates with a known indicator of the behavior being measured[18]. As a gold standard for meal assessment does not exist and no other validated tools assessing meal consumption are available in Italian, the MAS scores were correlated with MASA. Non-parametric Spearman correlation test was used to analyze the correlations between MAS total and subscale's scores and the score obtained on the MASA protocol in Group 1 and 2. The correlations were considered strong for values >0.6, moderate for values ranging between 0.4 and 0.6, and weak for values <0.4[19].

Another type of validity is the known-group validity. It addresses the ability of a tool to reflect in its score a difference between two or more groups that are known to have or that logically should have different levels of the construct to be measured[20]. For the known-group validity analysis, MAS scores in Group 1 and Group 2 were compared. Subjects were divided into four age groups: young (18-39 years), adult (40-64), old (65-74), very old (over 75). Based on this age division, Group 1 and Group 2 patients were distributed as follows: 24/100 (24%) and 1/100 (1%) young, 35/100 (35%) and 9/100 (9%) adults, 14/100 (14%) and 17/100 (17%) old, 27/100 (27%) and 73/100 (73%) very old respectively. Non-parametric Mann-Whitney U test was used to compare MAS scores of Group 1 and Group 2 for the age groups of adults, old and very old. Kruskal-Wallis non-parametric test with Dunn post-hoc test and Bonferroni correction was used to compare MAS scores between different age groups within Group 1, as a slow deterioration of meal safety and efficacy may be observed with the aging process even in individuals without swallowing alterations. A p <0.05 was considered statistically significant.

An assessment tool should be able to detect variations in the construct to be measured over time, a property known as responsiveness[15]. The responsiveness of the scale was tested re-assessing patients with the MAS after the modification of diet recommendation. Non-parametric Wilcoxon test was used to compare the first and the second SLT's assessment in Group 3's patients. A p <0.05 was considered statistically significant.

RESULTS

Reliability analysis

Cronbach' alpha was α=-0.615 for the safety scale and α=0.858 for the efficacy scale. Results of the inter-rater agreement are reported in Table 2. An AD index<0.66 was found for all the items.

Table 2: MAS' inter-rater agreement

	AD index
STRUCTURES, FUNCTIONS, AND ACTIVITIES INFLUENCING THE MEAL	
Linguistic comprehension	0.04
Attention	0.07
Short-term memory	0.10
Patient's compliance with alimentary instructions	0.17
Patient's desire to eat	0.07
Head-to-trunk control	0.06
Independence in eating	0.02
Ability to take food to mouth	0.04
Control of drooling	0.02
Teeth	0.01
Voluntary cough	0.05
Voice quality	0.05
ENVIRONMENTAL FACTORS INFLUENCING THE MEAL	
Food consistency	0.03
Bolus size	0.02
Liquids consistency	0.02
Possibility to rely on caregiver	0.01
SWALLOWING SAFETY DURING THE MEAL	
Oral control of the bolus	0.09
Residue in the oral cavity after swallowing	0.06
Presence of cough or throat cleaning	0.01
Voice quality post-swallow	0.09
SWALLOWING EFFICACY DURING THE MEAL	
Control of food leakage while chewing	0.09
Oral preparation	0.08
Ability to complete the meal without exhortations	0.11
Fatigue	0.14
Percentage of the meal eaten	0.05
Amount of food eaten	0.07

Validity analysis

Concurrent validity. Correlations between MAS scores and MASA scores were used to analyze concurrent validity. Median MASA score was 188.5 (range 107-200). The correlation with MASA scores showed Spearman's coefficient of r=-0.75 ($p<0.01$) for safety score and of r=-0.81 ($p<0.01$) for the efficacy score.

Known-group validity. Comparison of the MAS scores obtained by Group 1 and Group 2 are reported in Table 3. A statistically significant difference, with Group 1 patients scoring higher than Group 2 patients, was found for both the safety score and the efficacy score for all age groups. The time needed to complete the meal was significantly lower in individuals without dysphagia (median 25 minutes, range 15-40) than in individuals with dysphagia (median 30 minutes, range 10-60) for the >75 years age group ($p=0.024$), while no statistically significant difference was found for the other age groups. In the 40-64 years age group, no statistically significant difference was found for 5/12 items of the scale *structures, functions and activities influencing meal*, for the item "Possibility to rely on caregiver" of the scale *environmental factors influencing meal*, for the item "Oral control of the bolus" of the safety scale and 5/6 items of the efficacy scale. Concerning the 65-74 years age groups, no statistically significant difference was found for the items "Head-to-trunk control," "Control of drooling" and all except 1 item of the safety scale. Subjects without dysphagia scored significantly higher than subjects with dysphagia in all items in the >75 years age group.

Results of the Kruskal-Wallis test comparing different age groups within Group 1 are reported in Table 4. All subjects scored ≤3 on both the safety and efficacy score. All subjects scored 0 in all the items of the *environmental factors influencing meal* scale. Time needed to end the meal was shorter than or equal to 40 minutes in all age groups. A statistically significant difference between age groups was found for the safety score ($p=0.041$), for the efficacy scale ($p<0.001$) and for the following 4 items: "Teeth" ($p=0.048$), "Control of food leakage while chewing" ($p=0.041$), "Oral preparation" ($p=0.014$), "Amount of food" ($p=0.041$). In particular, 18-39 years old patients scored higher than >75 years old patients in the item "Oral preparation" ($p=0.028$), the safety score ($p<0.001$), the preliminary assessment scale ($p=0.028$), the signs of dysphagia scale ($p=0.050$), and the efficacy scale ($p=0.001$). Moreover, patients in the 40-64 age group scored higher than patients in the >75 years old age group in the efficacy scale ($p=0.004$).

Responsiveness. The MAS responsiveness was analyzed in Group 3; Table 5 shows the results. All patients evolved from a C1 diet, corresponding to homogenous puree consistency diet, to a C2 diet, corresponding to a soft food diet. A statistically significant improvement was found in the efficacy score but not in the safety score. The time needed to finish the meal did not change significantly ($p=0.056$). Five out of 12 items of the *structures, functions, and activities influencing the meal* subscale scored significantly higher at the second assessment; they were mostly related to patient's independence and postural and oral cavity control. A statistically significant difference was found for all the items of the *environmental factors influencing the meal* subscale, except for the item "Consistency modification of liquids" ($p=0.088$). Finally, a significant difference was recorded in only 3/6 items of the efficacy scale, in particular "Ability to continue the meal without solicitations" ($p=0.003$), "Percentage of meal eaten" ($p=0.001$) and "Amount of food eaten" ($p=0.002$), while none of the items of the safety scale.

Table 3: Comparison of the MAS scores between subjects without dysphagia (group 1) and subjects with dysphagia (group 2) in each age group

	40-64 years			65-74 years			>75 years		
	Group 1	**Group 2**	**p**	**Group 1**	**Group 2**	**p**	**Group 1**	**Group 2**	**p**
STRUCTURES, FUNCTIONS, AND ACTIVITIES									
Linguistic comprehension	0 (0-0)	2 (0-3)	0.010*	0 (0-0)	1 (0-3)	<0.001*	0 (0-0)	2 (0-3)	<0.001*
Attention	0 (0-0)	1 (0-2)	0.010*	0 (0-0)	1 (0-3)	<0.001*	0 (0-1)	1 (0-3)	<0.001*
Short-term memory	0 (0-0)	1 (0-3)	0.010*	0 (0-1)	1 (0-3)	<0.001*	0 (0-1)	2 (0-3)	<0.001*
Patient's compliance with alimentary instructions	0 (0-1)	1 (0-3)	<0.001*	0 (0-0)	1 (0-3)	<0.001*	0 (0-0)	1 (0-3)	<0.001*
Patient's desire to eat	0 (0-0)	0 (0-2)	0.627	0 (0-1)	1 (0-3)	0.026*	0 (0-1)	1 (0-3)	<0.001*
Head-to-trunk control	0 (0-0)	0 (0-1)	0.627	0 (0-0)	0 (0-1)	0.053	0 (0-0)	1 (0-3)	<0.001*
Independence in eating	0 (0-0)	2 (0-3)	<0.001*	0 (0-0)	3 (0-3)	<0.001*	0 (0-0)	3 (0-3)	<0.001*
Ability to take food to mouth	0 (0-1)	1 (0-3)	0.010*	0 (0-1)	1 (0-3)	<0.001*	0 (0-1)	2 (0-3)	<0.001*
Control of drooling	0 (0-0)	0 (0-3)	0.314	0 (0-0)	0 (0-3)	0.597	0 (0-0)	0 (0-3)	0.005*
Teeth	0 (0-0)	0 (0-1)	0.132	0 (0-1)	1 (0-3)	0.023*	0 (0-1)	1 (0-3)	<0.001*
Voluntary cough	0 (0-0)	2 (0-3)	<0.001*	0 (0-0)	1 (0-3)	<0.001*	0 (0-0)	1 (0-3)	<0.001*
Voice quality	0 (0-1)	0 (0-3)	0.373	0 (0-1)	1 (0-3)	<0.001*	0 (0-1)	1 (0-3)	<0.001*
ENVIRONMENTAL FACTORS									
Food consistency	0 (0-0)	3 (1-3)	<0.001*	0 (0-0)	3 (1-3)	<0.001*	0 (0-0)	3 (0-3)	<0.001*
Bolus size	0 (0-0)	1 (0-3)	0.010*	0 (0-0)	2 (0-3)	<0.001*	0 (0-0)	2 (0-3)	<0.001*
Liquids consistency	0 (0-0)	3 (0-3)	<0.001*	0 (0-0)	3 (0-3)	<0.001*	0 (0-0)	3 (0-3)	<0.001*
Possibility to rely on caregiver	0 (0-0)	0 (0-3)	0.132	0 (0-0)	3 (0-3)	<0.001*	0 (0-0)	3 (0-3)	<0.001*
SWALLOWING SAFETY DURING THE MEAL	0 (0-2)	3 (1-7)	<0.001*	0 (0-3)	1 (0-6)	<0.032*	0 (0-3)	3 (0-6)	<0.001*
Oral control of the bolus	0 (0-1)	0 (0-1)	0.165	0 (0-2)	0 (0-1)	0.860	0 (0-1)	0 (0-2)	0.013*
Residue in the oral cavity after swallowing	0 (0-2)	1 (0-1)	0.018*	0 (0-1)	0 (0-2)	0.215	0 (0-1)	1 (0-3)	<0.001*
Presence of cough or throat cleaning	0 (0-1)	1 (0-3)	0.005*	0 (0-1)	0 (0-2)	0.215	0 (0-1)	1 (0-3)	0.011*
Voice quality post-swallow	0 (0-1)	2 (0-3)	0.002*	0 (0-1)	0 (0-3)	0.173	0 (0-1)	1 (0-3)	<0.001*
SWALLOWING EFFICACY DURING THE MEAL	0 (0-1)	1.5 (0-6)	0.001*	0 (0-2)	6 (0-11)	<0.001*	0 (0-3)	7 (0-14)	<0.001*
Control of food leakage while chewing	0 (0-0)	0 (0-2)	0.314	0 (0-0)	0 (0-2)	0.100	0 (0-1)	1 (0-3)	<0.001*
Oral preparation	0 (0-1)	1 (0-1)	0.021*	0 (0-1)	1 (0-2)	0.006*	0 (0-1)	1 (0-3)	<0.001*
Ability to complete the meal without exhortations	0 (0-0)	0 (0-2)	0.314	0 (0-0)	0 (0-2)	0.026*	0 (0-0)	1 (0-3)	<0.001*
Fatigue	0 (0-0)	0 (0-1)	0.132	0 (0-0)	1 (0-3)	<0.001*	0 (0-1)	1 (0-3)	<0.001*
Percentage of the meal eaten	0 (0-1)	0 (0-1)	0.710	0 (0-1)	1 (0-3)	0.015*	0 (0-2)	2 (0-3)	<0.001*
Amount of food eaten	0 (0-0)	0 (0-0)	1	0 (0-0)	1 (0-3)	0.012*	0 (0-1)	1 (0-3)	<0.001*
TIME (minutes)	20 (15-30)	25 (15-40)	0.249	25 (15-40)	30 (15-60)	0.084	25 (15-40)	30 (10-60)	0.024*

* $p<.05$ **Notes:** Results are reported as median (range)

Table 4: Results of Kruskal-Wallis test across age groups within Groups 1

	18-39 (n= 24)	40-64 (n= 35)	65-74 (n= 14)	>75 (n= 27)	p
STRUCTURES, FUNCTIONS, AND ACTIVITIES INFLUENCING THE MEAL					
Linguistic comprehension	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	1
Attention	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-1)	0.440
Short-term memory	0 (0-0)	0 (0-0)	0 (0-1)	0 (0-1)	0.326
Patient's compliance with alimentary instructions	0 (0-0)	0 (0-1)	0 (0-0)	0 (0-0)	0.603
Patient's desire to eat	0 (0-0)	0 (0-0)	0 (0-1)	0 (0-1)	0.326
Head-to-trunk control	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	1
Independence in eating	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	1
Ability to take food to mouth	0 (0-0)	0 (0-0)	0 (0-1)	0 (0-1)	0.326
Control of drooling	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	1
Teeth	0 (0-0)	0 (0-0)	0 (0-1)	0 (0-1)	0.048*
Voluntary cough	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	1
Voice quality	0 (0-0)	0 (0-1)	0 (0-1)	0 (0-1)	0.659
ENVIRONMENTAL FACTORS INFLUENCING THE MEAL					
Food consistency	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	1
Bolus size	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	1
Liquids consistency	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	1
Possibility to rely on caregiver	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	1
SWALLOWING SAFETY DURING THE MEAL	0 (0-1)	0 (0-2)	0 (0-3)	0 (0-3)	0.041*
Oral control of the bolus	0 (0-0)	0 (0-1)	0 (0-2)	0 (0-1)	0.285
Residue in the oral cavity after swallowing	0 (0-0)	0 (0-2)	0 (0-1)	0 (0-1)	0.055
Presence of cough or throat cleaning	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-1)	0.106
Voice quality post-swallow	0 (0-0)	0 (0-1)	0 (0-1)	0 (0-1)	0.518
SWALLOWING EFFICACY DURING THE MEAL	0 (0-0)	0 (0-1)	0 (0-2)	0 (0-3)	<0.001*
Control of food leakage while chewing	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-1)	0.041*
Oral preparation	0 (0-0)	0 (0-1)	0 (0-1)	0 (0-1)	0.014*
Ability to complete the meal without exhorations	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	1
Fatigue	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-1)	0.141
Percentage of the meal eaten	0 (0-0)	0 (0-1)	0 (0-1)	0 (0-2)	0.168
Amount of food eaten	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-1)	0.041*
TIME (minutes)	20 (15-30)	20 (15-30)	25 (15-40)	25 (15-40)	0.191

*$p<.05$

NOTE: Data are reported as median and range

Table 5: Comparison of the MAS scores obtained by group 3 (n = 36) at the first assessment and at the second assessment

	1st assessment		2nd assessment		p
	median	range	median	range	
STRUCTURES, FUNCTIONS, AND ACTIVITIES INFLUENCING THE MEAL					
Linguistic comprehension	1	0-3	1.5	0-3	0.822
Attention	1	0-2	1	0-3	0.334
Short-term memory	1	0-3	1	0-3	0.210
Patient's compliance with alimentary instructions	1	0-3	1	0-3	0.384
Patient's desire to eat	0	0-3	0	0-2	0.053
Head-to-trunk control	0	0-1	0	0-1	0.034*
Independence in eating	3	0-3	2	0-3	0.002*
Ability to take food to mouth	1.5	0-3	1	0-2	<0.001*
Control of drooling	0	0-3	0	0-2	0.031*
Teeth	1	0-3	0	0-3	0.005*
Voluntary cough	1	0-3	1	0-3	0.199
Voice quality	1	0-3	1	0-3	0.088
ENVIRONMENTAL FACTORS INFLUENCING THE MEAL					
Food consistency	3	2-3	2	2-2	<0.001*
Bolus size	3	0-3	0.5	0-3	<0.001*
Liquids consistency	3	3-3	3	0-3	0.083
Possibility to rely on caregiver	3	0-3	3	0-3	0.005*
SWALLOWING SAFETY DURING THE MEAL	3	0-6	3	0-7	0.916
Oral control of the bolus	0	0-2	1	0-2	0.149
Residue in the oral cavity after swallowing	1	0-3	1	0-3	0.503
Presence of cough or throat cleaning	1	0-3	0	0-2	0.056
Voice quality post-swallow	0	0-3	0	0-2	0.317
SWALLOWING EFFICACY DURING THE MEAL	5	0-11	3	0-7	0.001*
Control of food leakage while chewing	0	0-3	0.5	0-2	0.617
Oral preparation	1	0-2	1	0-2	0.373
Ability to complete the meal without exhortations	0.5	0-3	0	0-2	0.003*
Fatigue	1	0-2	1	0-2	0.059
Percentage of the meal eaten	1	0-3	0	0-2	0.001*
Amount of food eaten	1	0-3	0	0-2	0.002*
TIME (minutes)	35	10-60	40	20-50	0.056

*$p<.05$

DISCUSSION

The preliminary psychometric analysis of the MAS, a scale for the assessment of swallowing safety and efficacy during the meal, has been conducted. The results suggest preliminary evidence of MAS validity and reliability, except for the internal consistency of the safety subscale. An adequate inter-rater agreement was found for all the items. A strong correlation was found with swallowing clinical assessment. The MAS seems to distinguish among different levels of performance in consuming a meal as well as to register improvements over time.

One hundred patients with dysphagia were involved in the validation process of the MAS. Swallowing disorders had different etiologies in the patients' group. It allowed testing the MAS on patients showing different type and different severity of swallowing impairment. Moreover, patients were recruited in two different clinical settings, a University acute-care hospital and a rehabilitation center. The heterogeneity of the population and the setting is of primary importance for the application of the MAS in several clinical settings and in patients with different pathologies[12,21].

A Cronbach's alpha >0.70 was regarded as "good" internal consistency, at least in the early stage of research and for scales with fewer than 7 items[16,22-23]. The Cronbach's alpha of the efficacy scale reached the recommended limit, with a value of α=0.858, while it was slightly below it for the safety scale, with an α=0.615. Therefore, subsequent revision of the MAS should focus on improvement of the safety scale's internal consistency. Cronbach's alpha is a measure of the correlation among the items of a scale. However, Cronbach's alpha is not only dependent on the magnitude of the items' correlation, but also on the number of items that are included in the scale[25]. The safety subscale includes only 4 items, compared to the 6 items of the efficacy subscale. Hence, a revision of the safety scale should focus on increasing the number of items. It may be achieved by 1) investigating comprehensiveness of the scale by a working group of experts; 2) performing a Rasch analysis to identify the level of difficulties that newly developed items should cover. Finally, as the value of Cronbach's alpha also depends on the sample size, the MAS should be tested on a higher number of patients.

A good inter-rater agreement is necessary for the clinical use of the assessment tool as it allows to compare the results obtained by different clinicians and for the research use in order to compare results of different studies[24]. All items showed a desirable inter-rater agreement, suggesting that the MAS may be applied to both clinical and research practice.

Since no "gold standard" evaluation for assessing meal exists, criterion validity could not be investigated. Other scales aiming to assess patients while consuming a meal exist and were considered during the development study of the MAS[10], even though exhibit some limits when aiming to assess both safety and efficacy of meals. However, the only validated assessment tool for the meal, the McGill Ingestive Skills Assessment[21,25] has not been translated and validated in Italian and, therefore, could not be used in the present study. Therefore, the relationship between the MAS and constructs with a known relationship to eating and drinking was investigated for testing concurrent validity. In particular, MASA protocol was used, being a currently adopted and validated tool for clinical evaluation of swallowing. The statistical analysis showed a strong correlation

between MAS scales and MASA, slightly higher for the efficacy scale than for the safety scale. In the MASA, the efficacy of swallowing is not directly assessed, as a limited number of trial for each consistency is performed, while great attention is given to the prerequisites of swallowing, such as alertness, cooperation, respiration, lip seal, tongue strength, and coordination. It can be speculated that these aspects play an important role on the ability of a person in completing a whole meal and can account for the strong correlation among the efficacy scale of the MAS and the MASA. For example, Namasivayam and colleagues have shown a statistically significant correlation between tongue strength, meal duration and food intake, with lower tongue strength associated with longer meal duration and lower food intake[26]. Moreover, although not directly assessing efficacy, it is intuitive that some of the items assessed in the MASA (e.g., "lip seal" or "oral preparation/transit") have an influence on those of the efficacy scale of the MAS (e.g., respectively "control of food leakage while chewing" and "oral preparation").

An essential property of an assessment tool is the ability to distinguish between different health states. A significant difference between subjects with OD and subjects without OD was found for the safety and the efficacy scales in all age groups; therefore, the MAS seems to differentiate between individuals with and without OD adequately. Differences between age groups were found for single items. The number of items showing significant differences between patients with and without OD increased with the increasing of age. Moreover, a significant difference concerning the time the patient needed to end the meal was found only for the >75 years old group. Concerning signs of OD, control of drooling, voice, fatigue and time needed to end the meal, we can suppose that the pathological mechanisms leading to dysphagia may have a higher impact on swallowing function in older patients than in younger patients, involving muscles already reduced in strength, stability and endurance because of the aging process. Indeed, the aging process contributes to a shift in muscle composition from faster to slower contracting muscle fibers' type[27]. As a result, swallowing speed decreases[27]. Pathological mechanisms associated with the onset of a disease (e.g., stroke) may further contribute to muscle wasting, impacting on strength and endurance. For instance, muscle atrophy and disuse generally affects slow contracting muscle fibers[28]. Longer meal duration is associated with a deterioration of swallowing safety and an increase in the sense of effort in older adults[29]. However, in the interpretation of the present data, it should be taken into account that the sample size of patients and control groups differ in each age group, which is a limit of the study. Significant differences were found for the items "Percentage of the meal eaten," "Amount of food eaten," "Patients desire to eat" in the 65-74 years old group and in the >75 years old group, but not in the 40-64 years old group. This is in accordance with the study of Serra-Prat et al., who investigated the risk of malnutrition in a cohort of persons aged 70 years and over; they reported a significantly higher incidence of malnutrition because of poor oral intake in elderly with OD than in elderly without OD[30]. Moreover, the reduction in patient's appetite and oral intake may be correlated with the results of the item "Teeth." Indeed, as for the items mentioned above, a significant difference between patients and control groups were found for the item "Teeth" in the 65-74 years old group and in the >75 years old group, but not in the 40-64 years old group. Ortega et al. studied oral health in

subjects aged over 70 and found that subjects with OD showed a significantly higher prevalence of edentulism than subjects without OD[31]. Concerns on the inclusion criteria used to recruit subjects without OD may be raised. Indeed, as both hospitalized or non-hospitalized subjects were included in Group 1, it comprises both healthy individuals and patients with diseases not interfering with swallowing. Diagnosis of the patients, as well as physicians and nursing reports on mealtime, were accurately analyzed to avoid the risk of enrolling patients with possible swallowing impairment. The choice of including hospitalized patients without dysphagia in Group 1 lies in the need to assess whether the MAS should be able to reflect the presence of a swallowing impairment regardless to other medical conditions with a possible influence on other factors related to eating. Based on the results of known-group validity, showing a statistically significant difference in nearly all the items, as well as a ceiling effect in patients of Group 1 in most of the remaining items, we are confident in excluding any risk of bias introduced by having recruited hospitalized patients in Group 1.

Changes in MAS scores across different age groups within healthy subjects were investigated. It is currently accepted that aging process reduces swallowing efficacy[32-34]; therefore, a decrease of meal safety and efficacy can be supposed as age progression as well. A statistically significant difference was found between different age groups for the items "Control of food leakage while chewing" and "Oral preparation." Hiramatsu et al. compared the effort required for swallowing during the meal in healthy old and young adults[35]. They found that tongue pressure and motor function of the lips are reduced by aging, in particular after meal consumption because of fatigue. Decreased tongue pressure may impact on the ability to form a bolus, thus increasing the time needed for oral preparation; reduced lip closure may lead to anterior spillage. A significant difference was also found for the items "Teeth" and "Amount of food." Tooth loss and poor oral intake are common problems in the elderly[36-37]. Moreover, it has been demonstrated that poor oral status increases difficulties in eating and decreases eating pleasure, thus leading to an increased risk of malnutrition[36]. Therefore, our findings are in accordance with data reported in the literature.

An assessment tool should be able to measure clinically significant variations in patient's performance over time, a property known as responsiveness. In the present study, this property was tested re-assessing patients with the MAS after the modification of diet recommendation. All patients in Group 3 evolved from a pureed diet to a soft food diet. The MAS was found to be able to register patient's improvement as the efficacy score significantly increased. Improvements of the efficacy score may be directly related to the type of diet. Soft foods are usually more palatable than homogenous pureed foods. Studies have shown that both the pleasure of eating and the amount of food intake significantly decrease also in healthy subjects when a meal is served pureed compared to standard texture[38-39]. Thus, changes in the scores of the items "Ability to complete the meal without exhortations," "Percentage of the meal eaten," and "Amount of food eaten" may reflect these findings. Moreover, a significant increase was also found for those items of the *structures, functions, and activities influencing the meal* scale related to patients' independence in eating. Hence, the improvement of swallowing efficacy may also reflect the improvement of patients general conditions, leading for instance to an improvement of upper limbs' movement which allows the patient to feed himself

independently. A study by Lin et al. have found that moderate dependency triples the likelihood of low food intake compared to independence in feeding[40]. Furthermore, a significant improvement in the item "Teeth" was observed as more patients wore dentures at the time of the second meal observation. The use of dentures significantly affects the efficacy of the oral phase of swallowing[41]. As expected the safety score and the total time needed to complete the meal did not significantly change; this seems to be reasonable assuming, as it was done in the present study, that the diet recommendation was decided on the basis of an accurate swallowing instrumental evaluation. Indeed, although the patients' swallowing function and general conditions were improved, the management of a soft food diet requires a more efficient swallowing mechanism for its preparation and deglutition compared to a pureed diet. Thus, no differences were found in those items as diet evolution followed patient evolution. A possible interpretation is that patients maintained a safe oral feeding, even if they extended the range of consistencies taken orally. Finally, no significant variations were found for the consistency of liquids' scores. The majority of the patients continued to drink thickened liquids even after diet modification. It is not surprising as it is well known that the safety in the management and swallowing of solid foods do not overlap the safety in the management and swallowing of liquids.

Limitations and Future directions

Limits of the present study are the lack of data on the intra-rater agreement and a control of effect sizes, leading to a nonhomogeneous distribution of subjects with and without swallowing disorders in different age groups. Furthermore, data on the inter-rater agreement were gained only for the patients with OD, but not for the healthy group. Moreover, even though swallowing disorders had different etiologies in the patients group, a large part of the participant sample was skewed towards stroke, whereas other etiologies were only little represented. Therefore, MAS validation is still an ongoing process, and further studies should be conducted in order to overcome these limitations, as well as to describe MAS scores in different populations of patients (e.g. , frail elderly patients, head and neck cancer patients). The study on the MAS responsiveness may also be expanded to the study of the tool ability to measure modification of meal safety and efficacy in patients with dysphagia on free oral diet before and after swallowing assessment and diet restriction. Moreover, the correlation between MAS and nutritional status' indexes, and between MAS and general and swallowing-related QOL should be investigated. Concurrent validity was tested against MASA, a tool for clinical assessment. Clinical assessment typically includes an evaluation of non-swallowing factors, such as cognitive or motor functions, because of the potential impact on both a single swallowing act and the swallowing performance during meal. The MASA was initially developed and validated for patients with stroke, but it was more recently tested in patients with OD of mixed etiology[42-45]. Instrumental assessment of swallowing through videofluoroscopy (VFS) or fiberoptic endoscopic evaluation of swallowing (FEES) represent the "gold standard" for the evaluation of swallowing safety and efficacy[46]. Hence, it would be interesting to study the correlation between MAS scores and findings from instrumental assessment during meal consumption. However, ethical issues related to x-ray exposition in VFS and discomfort due to the flexible endoscope in

FEES make it not feasable. Lastly, the concurrent validity of the MAS against the McGill Ingestive Skills Assessment, another assessment tool for meal validated in English and Dutch, may be investigated after an adequate translation process and validation in Italian.

CONCLUSION

This study showed preliminary evidence of validity and reliability of the MAS for the assessment of swallowing safety and efficacy during the meal in patients with swallowing disorders of different etiology and severity. Its application in clinical and research practice may be beneficial to measure outcomes of swallowing treatments, to detect changes over time, to compare different populations, and to estimate the risk of swallowing complications.

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THE MEALTIME ASSESSMENT SCALE (MAS): II. PRELIMINARY PSYCHOMETRIC ANALYSIS

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CHAPTER 5

Dysphagia in neurodegenerative diseases: Association with risk of malnutrition

PhD candidate's role: Conceptualization, study design, project administration, supervision, formal analysis, data interpretation, visualization, paper writing

Abstract
Background: Malnutrition is common among patients with neurodegenerative diseases and is of multifactorial origin. Oropharyngeal dysphagia (OD) is generally recognized to increase the risk of malnutrition. However, OD contribution to malnutrition risk in patients with neurodegenerative disease has still to be determined.
Objective: The cross-sectional study aimed to investigate the impact of oropharyngeal dysphagia (OD) on nutritional risk in patients with neurodegenerative diseases.
Methods: Patients with oral nutrition and diagnosis of Huntington's disease (HD), Parkinson's disease (PD), or Amyotrophic Lateral Sclerosis (ALS) were recruited. The type of oral intake was rated using the Functional Oral Intake Scale (FOIS). The swallowing assessment included a fiberoptic endoscopic evaluation of swallowing, an oral phase assessment using the Test of Masticating and Swallowing Solids (TOMASS), and a meal observation scored with the Mealtime Assessment Scale (MAS). Nutritional status comprised the Mini Nutritional Assessment (MNA®) and anthropometric and biochemical measures. Patients with an MNA® <24 were considered at risk of malnutrition. Univariate and multivariate regression analysis was performed to assess the impact of OD on malnutrition risk.
Results: Overall, 162 patients were recruited (66 HD, 34 PD, and 62 ALS). One-hundred (61.7%) patients were considered at risk of malnutrition. Age, type of oral intake (FOIS), residue in the valleculae with semisolids, penetration with liquids, meal safety (MAS), number of masticatory cycles and time at TOMASS were found to be significantly associated with risk of malnutrition at the univariate analysis. At the multivariate analysis, age (OR 1.08, CI95% 1.03-1.12, p=0.001) and MAS safety (OR 1.39, CI95% 1.04-1.86, p=0.033) were found to be significantly associated with the risk of malnutrition.
Conclusion. Dysphagia is associated with the risk of malnutrition in three neurodegenerative diseases.

INTRODUCTION

Oropharyngeal dysphagia (OD) is an alteration of bolus transport from the mouth to the stomach[1] and represents an important issue in patients with neurodegenerative diseases. Most patients with neurodegenerative disease suffer from OD at a certain point of disease progression, reaching, for instance, a prevalence of 85% in Amyotrophic Lateral Sclerosis (ALS)[2] and of 95% in advanced-stage Parkinson's disease (PD)[3]. Often, OD is characterized by an initial alteration of the oral phase of swallowing, with a later onset of pharyngeal signs of OD (f.i. penetration and aspiration) in these populations[4-5]. Thus, different stages of the swallowing process are disrupted by the disease[6], although pharyngeal alterations are commonly more investigated in the studies[7]. Moreover, along with OD, other signs of the diseases may impact on eating. For instance, involuntary movements to the neck and trunk, limb involvement, cognitive impairment, and fatiguability are some of the typical features of ALS, PD, or Huntington's disease (HD) that can additionally compromise swallowing safety and efficacy during meals.

In ALS, alterations of the oral phase (i.e. reduced/disorganized tongue movements, increased oral preparatory and transit time) are frequent, ranging from 22% to 89% of the patients[8-12], and have been detected also in patients with no clinically detected bulbar symptoms[13-15]. Concerning pharyngeal signs of OD, post-swallow pharyngeal residue prevails over penetration and aspiration, being reported in 22-100%[,9-12,16-19], 39-61%[9,12,17-18], and 7-44%[8-9,11,17-18] of the patients, respectively. The type and the frequency of swallowing alterations in this population seems to be mainly related to the presence of bulbar symptoms and the time since their onset[13,15]. Swallowing alterations have been extensively investigated also in patients with PD. Patients in the early stage of PD can exhibit significant swallowing deficits[20]. Instrumental swallowing assessment can reveal pharyngeal residue and/or silent penetration in a certain percentage of patients with PD and no subjective symptoms of swallowing impairment[21-22]. Analogously to ALS, the occurrence of post-swallow pharyngeal residue (30-93%[22-24]) is higher than the occurrence of penetration and aspiration (5-69%[23-27]). Oral phase of swallowing is often disrupted earlier than the pharyngeal phase in the disease progression[5,25-28]. During mastication, electromyographic muscle activity is higher in patients with PD than in healthy controls, suggesting a reduction of chewing efficiency[29]. Regarding HD, literature in OD is poor, but it confirms the pattern of a combined oral and pharyngeal phases' involvement[30-31] documented in the other neurodegenerative diseases.

OD may lead to pulmonary, nutritional, and psychosocial consequences. Aspiration pneumonia is the leading cause of death in HD and PD[32-34]. The negative impact of OD on quality of life, mental well-being, and caregivers burden have been reported in HD, PD, and ALS[35-38]. Malnutrition is a common finding in several neurodegenerative diseases and is associated with a poor prognosis. A lower BMI has been related to a faster rate of disease progression in HD and PD[39-40]. Unintentional weight loss has been associated with an increased risk of institutionalization, morbidity, and mortality in patients with HD[41]. In ALS, malnutrition was reported to increase the risk of death by 7.7 times[42].

Malnutrition is of multifactorial origin in neurodegenerative diseases. Along with OD, intrinsic hypermetabolic state is common among different diseases and increased energy expenditure has been reported in literature, for instance, related to choreic movements

in HD, fasciculations and increased respiratory in ASL, and tremor and hypertonia in PD[43-48]. Cognitive impairment, depression, taste, and olfactory alterations can additionally reduce oral intake[49]. Although it is clear that malnutrition is a multifactorial process in neurodegenerative diseases, how much OD contributes to malnutrition and unintentional weight loss in patients with neurodegenerative disease and which swallowing alterations (f.i. reduction of swallowing safety, chewing rate, oral phase duration) are more importantly impacting on nutritional status have still to be determined. Early weight loss was found to be mainly associated with the presence of OD (clinically assessed by the neurologist) in ALS, but a subgroup of spinal onset patients without OD at diagnosis still exhibited a severe early weight loss, similarly to bulbar patients[50]. The only study investigating the relation between OD and nutritional status in HD found that patient-reported swallowing difficulties were not associated with Body Mass Index (BMI)[51]. In PD, the evidence is contrasting. Sheard and colleagues showed that swallowing difficulties (patient-reported) were significantly related to malnutrition[52], but other authors reported that OD was not independently associated with nutritional risk or weight changes[53-54]. However, outcomes used to assess nutritional status were highly heterogeneous among the studies and OD presence was only recorded based on patient-reported symptoms or clinical judgment by the neurologist, which may be biased by the poor awareness of swallowing difficulties and sensory impairment leading to silent aspiration. Thus, to the best of our knowledge, no study has been conducted to investigate this association in neurodegenerative diseases using instrumental assessment of swallowing nor measures of the efficiency of the oral phase. The primary aim of the study was to investigate the impact of OD on nutritional risk in three neurodegenerative diseases (HD, PD, ALS). The hypothesis was that oral phase alterations and meal performance would be more associated with risk of malnutrition than pharyngeal phase alterations. The secondary aim of the study was to compare swallowing profile with regard to pharyngeal phase, oral phase, and performance during meal among these populations.

METHODS

The cross-sectional study was carried out according to the Declaration of Helsinki and was previously approved by the Institutional Review Board of the Luigi Sacco Hospital (n.2016/ST/262) and from the Ethics Committee of the Istituti Clinici Scientifici Maugeri IRCCS and the IRCCS Istituto Auxologico Italiano. All participants provided written informed consent. The study was reported according to STROBE guidelines (see Appendix 1).

Subjects

Patients were recruited among inpatients and outpatients of three neurological centers between January 2017 and June 2019 during the first or the follow-up visit. Three groups were recruited as follows:

- **Group HD** patients with a diagnosis of HD (genetically confirmed, CAG ≥39)
- **Group PD** patients with a diagnosis of PD[55]
- **Group ALS** patients with a diagnosis of ALS[56]

Other inclusion criteria were full oral nutrition and age 18-90 years. Exclusion criteria were a history of head and neck cancer, known gastrointestinal diseases, or other concomitant neurological diseases.
Age, gender, disease duration, history of aspiration pneumonia, use of nutritional supplements, and typical oral intake were collected. The Italian version of the Functional Oral Intake Scale (FOIS), a 7-point ordinal scale, was used to record the typical oral intake[57].
Disease severity was assessed by a neurologist using the following disease-specific clinical scales:

- **HD)** Unified Huntington's Disease Rating Scale (UHDRS)[58]: divided into 6 subscales, Part I and Part VI were considered in the present study. UHDRS Part I provides a rating on total motor function in HD, ranging from 0 (no abnormalities) to 124 (severe impairment). Based on UHDRS Part VI (Functional Capacity), patients were divided into early (score 13-7; Shoulson-Fahn stage 1-2), moderate (score 6-4; Shoulson-Fahn stage 3), and advanced-stage HD (score 3-0; Shoulson-Fahn stage 4-5)[59-60]
- **PD)** Hoehn & Yahr (H&Y)[61] scale: a clinical rating scale capturing typical patterns of motor function in PD. Seven stages are used to describe symptoms progression; the higher the stage, the greatest the motor impairment
- **ALS)** ALS Functional Rating Scale-Revised (ALSFRS-R)[62]: a functional rating system of independence in activities of daily living for patients with ALS. The scale is divided into 4 domains (bulbar, upper limb, lower limb, and respiratory functions). The total score ranges from 0 to 48, while the bulbar score from 0 to 12; a lower score indicates a more severe loss of function.

Swallowing assessment
The swallowing assessment included a fiberoptic endoscopic examination of swallowing (FEES), an assessment of the oral phase efficiency, a meal observation, and a measurement of maximum tongue pressure (MTP).
Fiberoptic endoscopic evaluation of swallowing
FEES was conducted with liquids (3 trials x 5-10-20 cc), semisolids (3 trials x 5-10-20 cc), and solids (2 trials x half cracker). The protocol was reduced in case a consistency or a volume was not considered safe to be administered.
FEES recording were de-identified and independently assessed by 2 speech and language therapists (SLTs) using validated ordinal scales. In case a difference >1 level at each FEES rating scale occurred between the 2 raters, a 3rd SLT with >5 years experience on FEES assessed the videos and decided on the rating. The following scales were used:

- *Penetration-aspiration scale (PAS)*[63], an ordinal scale ranging from 1 to 8, to assess penetration and aspiration events. The higher the score, the more severe the lower airways invasion. The worst score for each consistency was recorded.
- *Yale Pharyngeal Residue Severity Rating Scale (YPRSRS)*[64], an ordinal scale ranging from 1 to 5, to assess the amount of post-swallow residue in two sites (valleculae and pyriform sinus). The higher the score, the greater the amount of residue. The worst score for each consistency was recorded.

Oral phase efficiency assessment

The *Test of Masticating and Swallowing Solids (TOMASS)*[65] was used to quantitatively assess the efficiency of oral phase function and solid bolus ingestion. During the test, the patient is asked to eat half GranPavesi™. The number of bites, masticatory cycles, and swallows are counted and the time required to complete the task is measured. The test was not performed for patients with restrictions on solid food for safety reasons.
TOMASS was video-recorded, de-identified, and assessed by 2 independent SLTs.

Meal observation

Observation of a typical meal was conducted by a SLT and was scored using the *Mealtime Assessment Scale (MAS)*[66]. The MAS is a scale for the assessment of the safety and the efficacy of swallowing during the meal. A safety score (0-12) and an efficacy score (0-18) are obtained. The higher the score, the less safe or efficient is the swallowing function during the meal. The time the patient needed to end the meal is recorded.

Nutritional assessment

Presence of malnutrition and risk of malnutrition were assessed using the *Mini Nutritional Assessment (MNA®)*[67] by a clinician that was not involved in swallowing assessment. The MNA® is a validated clinical tool made up of a screening and an assessment of nutritional status. Patients scoring <17 are considered malnourished, patients scoring 17-23.5 are considered at risk of malnutrition.
Moreover, nutritional assessment comprised calculation of the BMI (undernourishment <18.5 kg/m^2) and the following biochemical nutritional markers: albumin (undernourishment <3.5g/dL), total protein (<6.5 g/dL), cholesterol (<120mg/dL), hemoglobin (<11.9 g/dL), creatinine (<0.4 mg/dL).

Statistical analysis

Data is reported as absolute (relative) frequency and mean ± sd or median (IQR), according to the variable's distribution. Statistical analysis was performed with the IBM SPSS Statistics 25.0® package for Windows (SPSS Inc, Chicago, IL) and MedCalc Version 19.1.3.
Inter-rater agreement for FEES outcomes between the two independent raters was calculated using the linear weighted kappa coefficient. The weighted kappa values was considered poor (0), slight (0.00–0.20), fair (0.21–0.40), moderate (0.41–0.60), substantial (0.61–0.80), and almost perfect agreement (0.81–1)[68]. TOMASS' inter-rater agreement was assessed using the Intraclass Correlation Coefficient (ICC) one-way random model with measures of absolute agreement. Inter-rater agreement was interpreted as poor for ICC values <0.5, moderate for ICC values between 0.5 and 0.75, good for ICC values between 0.75 and 0.9, and excellent for ICC values >0.90[69].
The normality assumption of the continuous variables was verified with the Kolmogorov-Smirnov test. Measures of swallowing function and nutritional status were compared among the three groups of patients using the one-way ANOVA with post-hoc Tukey test for multiple comparisons or the Kruskal-Wallis non-parametric test with Dunn post-hoc test and Bonferroni correction, according to the distribution of the

variable. Univariate logistic regression was performed to estimate the degree of association between swallowing variables and nutritional status. Nutritional status was the dependent variable. Patients were divided into two groups: patients at risk of malnutrition (MNA®<24) and patients with normal nutritional status (MNA®≥24). Swallowing variables were used as independent variables. TOMASS measures and MAS scores were used as continuous variables. Residue (YPRSRS >2), penetration (PAS >2), and aspiration (PAS >5) were used as categorical variables. Other independent variables were age, gender, diagnosis, and type of oral intake (FOIS). Measures of association were presented as odds ratios (OR) with 95% confidence intervals. Statistically significant variables at univariate analysis were included in the multivariate logistic regression using backward elimination method of variable selection. Significance was set at $p<0.05$. Missing values were excluded pairwise.

RESULTS

Subjects

Overall, 162 patients with a diagnosis of neurodegenerative diseases were recruited, 66 had HD, 34 had PD, and 62 had ALS. Demographic and clinical characteristics of the groups are reported in Table 1.

Patients with PD had a higher mean age and longer mean disease duration. Patients with ALS had the shorter mean disease duration, while patients with HD had the younger mean age. Type of oral intake, as recorded by FOIS, was comparable among the 3 diseases (Kruskal-Wallis test, $H(2)=3.064$, $p=0.216$).

Inter-rater agreement

Inter-rater agreement for FEES outcomes ranged from moderate to substantial (0.51-0.76). Values of weighted kappa are shown in Table 2.

Concerning TOMASS, inter-rater agreement was excellent for time (ICC 0.95; CI95% 0.93-0.97) and bites (ICC 0.97; CI95% 0.95-0.98), good for masticatory cycles (ICC 0.81; CI95% 0.71-0.87), and moderate for swallows (ICC 0.70; CI95% 0.57-0.80).

Table 1. Demographic and clinical characteristics of study participants (n = 162)

Variable	Overall n = 162	HD n=66	PD n=34	ALS n=62
Demographic characteristics				
Age in years	64.2±13.1 [19-86]	56.7±13.3 [19-79]	72.1±10.7 [45-84]	67.8±9.7 [38-86]
Gender				
Male	88 (54.3%)	30 (45.5%)	26 (76.5%)	32 (51.6%)
Female	74 (45.7%)	36 (54.5%)	8 (23.5%)	30 (48.4%)
Clinical characteristics				
Disease duration in years	6.3±5.6 [0.5-28]	7.5±4.2 [0.5-20]	8.9±6.7 [0.6-28]	3.9±5.3 [0.3-15]
History of apiration pneumonia	5 (3.1%)	2 (3%)	2 (5.9%)	1 (16.1%)
Oral nutritional supplements	31 (19.1%)	16 (24.2%)	1 (2.9%)	14 (22.6%)
Disease severity				
HD UHDRS Part I (total motor score)		48.2±23.5 [7-106]		
HD stage				
Early		28 (42.4%)		
Moderate		20 (30.3%)		
Advanced		18 (27.3%)		
ALS ALSFRS-R total score			27±9 [8-41]	
ALSFRS-R bulbar score			9±2 [4-12]	
PD H&Y stage				
1.5				4 (11.8%)
2				6 (17.6%)
2.5				8 (23.5%)
3				8 (23.5%)
4				7 (20.6%)
5				1 (2.9%)
Type of oral intake				
FOIS 7	52 (32.1%)	27 (40.9%)	8 (23.5%)	17 (27.4%)
FOIS 6	44 (27.2%)	8 (12.1%)	19 (55.9%)	17 (27.4%)
FOIS 5	41 (25.3%)	23 (34.8%)	4 (11.8%)	14 (22.6%)
FOIS 4	25 (15.4%)	8 (12.1%)	3 (8.8%)	14 (22.6%)

NOTE: Values are presented as *n* (%) or as mean±sd [range].

FOIS = Functional oral intake scale. FOIS 7 = total oral intake with no restrictions; FOIS 6 = total oral intake with restriction to specific foods or liquid items; FOIS 5 = total oral intake of multiple consistencies requiring special preparation; FOIS 4 = total oral intake with homogeneous pureed diet

Table 2. Inter-rater agreement for FEES outcomes: weighted kappa

Consistency	PAS	YPRSRS valleculae	YPRSRS pyriform sinus
Liquids	0.76 (0.04)	0.51 (0.06)	0.51 (0.04)
Semisolids	0.57 (0.06)	0.55 (0.05)	0.59 (0.05)
Solids	0.56 (0.09)	0.68 (0.05)	0.52 (0.07)

Weighted kappa is reported as kappa value (SEM).

Swallowing function: comparison among the diseases

Based on the Kolmogorov-Smirnov normality test, the normality assumption was violated for all swallowing variables. Thus, non-parametric Kruskal-Wallis test with Dunn post-hoc test and Bonferroni correction was performed to compare swallowing function among the three neurodegenerative diseases. Results are shown in Table 3.

Fiberoptic endoscopic evaluation of swallowing

Fifteen patients were not tested with solids during FEES for safety reasons.

Overall, residue in the valleculae and penetration were the main FEES findings. Residue in the valleculae (YPRSRS >2) occurred in 108 (66.7%) patients: in 73 (45.1%) patients with liquids, in 86 (53.1%) with semisolids, and in 70 (43.2%) with solids. Residue in pyriform sinus (YPRSRS >2) was found in 88 (54.3%) patients: in 57 (32.5%) with liquids, in 60 (37%) with semisolids, and in 34 (21%) with solids. Penetration (PAS >2) was observed in 108 (66.7%) patients, in particular, in 105 (64.8%) patients with liquids, in 56 (34.6%) with semisolids, and in 13 (8%) with solids. Aspiration (PAS >5) occurred in 38 (23.5%) patients and always with liquids; moreover, 4 (2.5%) and 3 (1.9%) of the patients aspirating with liquids had aspiration also with semisolids and solids, respectively. Aspiration (PAS=8) was silent in 21 (13%) patients.

Patients with HD showed a significantly lower severity of signs of OD during FEES compared to patients with PD and ALS. In particular, patients with HD had lower residue (YPRSRS) both in the valleculae (all comparisons $p<0.001$) and the pyriform sinus (liquids $p<0.001$, semisolids $p=0.002$ vs ALS, solids $p=0.013$ vs PD) compared to the other populations, except for the YPRSRS in the valleculae with solids. Moreover, PAS scores were significantly lower in patients with HD than in patients with ALS despite the consistency of the bolus tested (liquids $p<0.001$, semisolids $p=0.002$, solids $p=0.004$).

Oral phase efficiency

Eighteen patients were not tested with the TOMASS for safety reasons.

The number of masticatory cycles was comparable among the three diseases. Patients with HD showed a significantly higher number of bites ($p=0.007$) and swallows ($p<0.001$) compared to patients with PD. Patients with HD and ALS showed a significantly longer time to complete the task ($p<0.001$ and $p=0.037$, respectively).

Performance during meal

Meal duration and meal safety during the meal (MAS) were comparable among the three diseases. Patients with PD showed significantly better performance during the meal in the MAS efficacy scale than patients with HD ($p=0.001$) and with ALS ($p=0.012$).

Table 3. Swallowing function: comparison among the three diseases

Variable	HD n=66	PD n=34	ALS n=62	p
FEES findings				
YPRSRS valleculae				
Liquids	**1 [1-2][a,b]**	**3 [3-3]**	**3 [3-3]**	<0.001*
Semisolids	**2 [2-3][a,b]**	**3 [2-4]**	**3 [2-4]**	<0.001*
Solids	2 [2-4]	3 [1-3.8]	3 [1-3]	0.657
YPRSRS pyriform sinus				
Liquids	**1 [1-1.3] [a,b]**	**3 [2-3]**	**3 [2-3]**	<0.001*
Semisolids	**2 [2-2]**	3 [2-3]	**2 [2-4]**	0.002*
Solids	**2 [1-3]**	**1 [1-2]**	1 [1-2]	0.007*
PAS				
Liquids	**2.5 [1-5]**	3 [2.3-5]	**4 [3-7]**	<0.001*
Semisolids	**1 [1-1]**	2.5 [1-1.8]	**2 [1-2]**	0.002*
Solids	**1 [1-1]**	1 [1-1.8]	**1 [1-2]**	0.005*
Oral phase efficiency				
TOMASS bites	**3 [2-4.3]**	**2.5 [1-4]**	3 [1-4]	0.011*
TOMASS masticatory cycles	37 [29.3-51]	49 [32.5-67.3]	45 [35-54]	<0.390
TOMASS swallows	**2 [2-3]**	**1 [1-2.8]**	2 [1-3]	<0.001*
TOMASS time, *s*	**59.5 [39.8-93.5]**	**42 [32.3-65][a,c]**	**50 [41-72]**	<0.001*
Meal observation				
MAS safety	2 [1-4]	1 [0-4]	2 [1-3]	0.232
MAS efficacy	**3 [1-4.3]**	**1 [0-2][a,c]**	**2 [1-4]**	0.001*
Meal duration, *min*	20 [15-25]	20 [15-25]	15 [15-23]	0.302

NOTE: Values are presented as median [interquartile range].

HD, Huntington's disease; PD, Parkinson's disease; ALS, Amyotrophic lateral sclerosis; YPRSRS, Yale pharyngeal residue severity rating scale; PAS, penetration-aspiration scale; TOMASS, Test of masticating and swallowing solids; MAS, mealtime assessment scale.

*p<0.05. P-values refers to Kruskal-Wallis non-parametric test. Statistically significant comparisons at the post-hoc analysis are reported in bold.

[a]HD vs PD p<0.05

[b]HD vs ALS p<0.05

[c]PD vs ALS p<0.05

Impact of dysphagia on nutritional status

Based on the Kolmogorov-Smirnov normality test, all nutritional variables were normally distributed. Descriptive statistics are reported in Table 4. Based on the MNA®, 70 (43.2%) patients were at risk of malnutrition, while 30 (18.5%) patients were malnourished. Nineteen (11.7%) patients had a BMI <18.5. Biochemical values suggestive of undernourishment were found only in 16 (9.9%) patients for albumin, 41 (25.3%) for total protein, 2 (1.2%) for cholesterol, 6 (3.7%) for creatinine, and 19 (11.7%) for hemoglobin. Patients with ALS exhibited the worst nutritional status.

Table 4. Nutritional status among the three diseases

Variable	Overall n = 162	HD n=66	PD n=34	ALS n=62
Continuous				
MNA	20.9±4.3 [9-28]	22.1±3.9 [11-28]	21.8±3.7 [9-27]	19.3±4.5 [11-27.5]
BMI	23.5±3.7 [14.7-33.1]	22.8±3.1 [17.6-31.3]	25.3±4 [16.5-32.7]	23.2±3.9 [14.7-33.1]
Albumin	4±0.7 [2.6-9.7]	4.2±0.4 [2.7-4.7]	3.8±1 [3-5]	3.9±0.9 [2.6-5.5]
Total protein	6.7±0.5 [5.2-8.1]	7±0.4 [6.1-8.1]	6.6±0.6 [5.6-7.6]	6.5±0.5 [5.2-7.5]
Cholesterol	191.4±40.7 [105-298]	205±41.6 [133-298]	162.4±26.8 [105-210]	189.3±38.9 [117-283]
Hemoglobin	13.4±1.5 [8.9-18.7]	13.7±1.2 [10.7-16.1]	12.5±1.8 [8.9-16.2]	13.5±1.6 [10.4-18.7]
Creatinine	0.8±0.6 [0.2-5.5]	1.1±1 [0.4-5.5]	1±0.3 [0.4-1.6]	0.6±0.2 [0.2-1]
Categorical				
MNA				
Risk of malnutrition (17-23.5)	70 (43.2%)	26 (39.4%)	20 (58.8%)	24 (38.7%)
Malnutrition (<17)	30 (18.5%)	6 (9.1%)	2 (5.9%)	22 (35.5%)
BMI <18.5 kg/m^2	19 (11.7%)	7 (10.6%)	3 (8.8%)	9 (14.5%)
Albumin <3.5 g/dL	16 (9.9%)	3 (4.5%)	2 (5.9%)	11 (17.7%)
Total protein (<6.5 g/dL)	41 (25.3%)	3 (4.5%)	9 (26.5%)	29 (46.8%)
Cholesterol (<120 mg/dL)	2 (1.2%)	0	2 (5.9%)	0
Hemoglobin (<11.9 g/dL)	19 (11.7%)	5 (7.6%)	8 (23.5%)	6 (9.7%)
Creatinine (<0.4 mg/dL)	6 (3.7%)	0	0	6 (9.7%)

NOTE: Values are presented as *n* (%) or as mean±sd [range].

HD, Huntington's disease; PD, Parkinson's disease; ALS, Amyotrophic lateral sclerosis; MNA, Mini Nutritional Assessment; BMI, body mass index

For the univariate analysis, 62 (38.3%) patients were in the normal nutritional status group and 100 (61.7%) patients were in the malnutrition risk group. Results of the univariate analysis are reported in Table 5. Age, type of oral intake (FOIS), residue in the valleculae with semisolids, penetration with liquids, meal safety (MAS), number of masticatory cycles and time at TOMASS were found to be significantly associated with risk of malnutrition and were, therefore, included in the multivariate analysis. Eighteen patients were excluded from the model because of missing values on the TOMASS (not performed for safety reasons). The model accounted for 28.9% of the variability in the outcome (Nagelkerke R^2) and correctly classified 75% of the patients. Age (OR 1.08, CI95% 1.03-1.12, p=0.001) and MAS safety (OR 1.39, CI95% 1.04-1.86, p=0.033) were found to be significantly associated with the risk of malnutrition at the multivariate analysis.

Table 5. Associated between demographic, clinical, and swallowing factors with malnutrition risk based on univariate logistic regression analysis

Factors	Univariate analysis	
Demographic and clinical factors	OR (95% CI)	p
Age	1.04 (1.01 – 1.07)	**0.003**
Gender (F vs M)	1.53 (0.76 – 3.07)	0.236
Diagnosis		
HD vs PD/ALS	0.47 (0.21 – 1.05)	0.066
PD vs HD/ALS	0.65 (0.26 – 1.65)	0.652
FOIS	0.43 (0.29 – 0.65)	**0.001**
FEES findings (present vs absent)		
Residue valleculae liquids	1.90 (0.91 – 3.98)	0.088
Residue valleculae semisolids	2.46 (1.17 – 5.18)	**0.018**
Residue valleculae solids	1.30 (0.61 – 2.78)	0.503
Residue pyriform sinus liquids	1.80 (0.83 – 3.90)	0.134
Residue pyriform sinus semisolids	1.96 (0.91 – 4.24)	0.086
Residue pyriform sinus solids	1.36 (0.56 – 3.32)	0.503
Penetration liquids	2.23 (1.02 – 4.85)	**0.022**
Penetration semisolids	1.24 (0.58 – 2.67)	0.579
Penetration solids	1.29 (0.31 – 5.26)	0.727
Aspiration liquids	1.71 (0.70 – 4.17)	0.236
Aspiration semisolids	0.89 (0.79 – 10.1)	0.926
Aspiration solids	1.02 (0.75 – 1.86)	0.754
Oral phase efficiency		
TOMASS bites	1.26 (0.99 – 1.60)	0.052
TOMASS masticatory cycles	1.03 (1.01 – 1.06)	**0.011**
TOMASS swallows	1.25 (0.94 – 1.67)	0.131
TOMASS time	1.02 (1.01 – 1.04)	**0.012**
Meal observation		
MAS safety	1.38 (1.08 – 1.78)	**0.011**
MAS efficacy	1.09 (0.92 – 1.30)	0.325
Meal duration	1.01 (0.96 – 1.05)	0.786

OR, odds ratio; CI, confidence interval; F, female; M, male; HD, Huntington's disease; PD, Parkinson's disease; ALS, Amyotrophic lateral sclerosis; FOIS, Functional oral intake scale; TOMASS, Test of masticating and swallowing solids; MAS, mealtime assessment scale.

Significant p values are reported in bold. For categorical variables, an OR >1 means a higher probability of the reference group than the control group(s) to be at risk of malnutrition. For continuous variables, an OR >1 means that an increase of 1 point in the value of the variable increases the probability of malnutrition risk.

DISCUSSION

OD and malnutrition are common findings in neurodegenerative diseases. OD does not solely refer to the presence of pharyngeal signs, such as residue, penetration, and aspiration, but also may involve a reduced oral phase efficiency and poor swallowing performance during the meal. The association between OD and nutritional status has been extensively investigated in other populations, i.e. elderly[70-72], stroke[73-74], but only few and contrasting findings are available from the literature on neurodegenerative diseases, mainly based on patient-reported symptoms[50-54]. The study reports the first data on the difference among swallowing profiles and their impact on nutritional risks in three populations of patients with neurodegenerative disorders, namely HD, PD, and ALS.

Patients with HD exhibited the lowest severity of signs of OD in FEES, whereas patients with PD had the best swallowing efficacy during the meal. Swallowing was mostly compromised in patients with ALS, who also exhibited the highest risk of malnutrition. Age, type of oral intake, residue in the valleculae with semisolids, penetration with liquids, swallowing safety during meal, number of masticatory cycles and oral phase duration were significantly associated with risk of malnutrition, but only age and swallowing safety during the meal showed an independent association.

Patients in the three groups had a comparable type of oral intake, as measured by the FOIS. Nevertheless, swallowing profiles were significantly different among diseases. Based on FEES findings, patients with HD had the least severe OD. In particular, they showed a lower amount of residue than patients with PD and ALS and less severity of penetration and aspiration's events than ALS. Interestingly, an opposite pattern was observed in the oral phase assessment. Indeed, patients with HD had a significantly higher number of bites and swallows than PD and than normal values previously reported in the literature[75]. A common characteristic among the three diseases was a generally longer duration of the oral phase, tested with the TOMASS, compared to normal values[73], with an even more prolonged duration in patients with HD and ALS. The findings from the FEES and the oral phase assessment confirmed that both oral and pharyngeal phases of swallowing are impaired by neurodegenerative diseases[4-6]. The present study additionally quantified the impairment of both phases of swallowing, highlighting a different degree of involvement of the two phases in different diseases.

A novel finding of the study was the discrepancy between FEES findings and swallowing performance during the meal in these populations. Indeed, the differences in swallowing safety (PAS) recorded during FEES among the diseases were not found in the safety profile during the meal (MAS safety). Patients with HD not only did not differ from the other groups, but also had on average slightly worse scores in the MAS safety. Swallowing performance during the meal is not only related to swallowing function. Other environmental and disease-related factors can impact on swallowing during meal and eating activity. In particular, in HD choreic movements to the head and trunk, tachyphagia, large bolus volumes secondary to difficulties in self-feeding and poor swallowing-breathing coordination resulted in a detrimental effect on swallowing safety. Concerning the efficacy, MAS efficacy scores seem to reflect the performance in the oral phase assessment, with patients with PD having a better performance than patients with HD and ALS.

Concerning nutritional status, only 11.7% of the patients were malnourished based on the criteria of having a BMI <18.5 kg/m^2[76], ranging from 8.8% in PD to 14.5% in ALS. Similar percentages have been reported in previous publications on these populations[51-53,77]. Nevertheless, 61.7% of the patients were at risk of malnutrition, based on a combination of anthropometric measures and data on weight loss, food intake, independence in daily living, and medications. Importantly, the guidelines of the European Society for Clinical Nutrition and Metabolism (ESPEN) states that "risk of malnutrition […] is in itself a condition related to increased morbidity and mortality"[78] and should be targeted to prevent the evolution to a state of malnutrition. Therefore, it was chosen as the dependent variable for regression analysis.

Type of oral intake, residue in the valleculae with semisolids, penetration with liquids, number of masticatory cycles, and oral phase duration was significantly associated with the risk of malnutrition at the univariate analysis but not at the multivariate analysis. Concerning the type of oral intake, texture modified diets were reported to provide lower energy and protein content than normal diets[79] and to be associated with weight loss in PD[80]. However, because of the lack of significance at the multivariate analysis, the univariate association with the type of oral intake (FOIS) seems to reflect an association with the degree of OD severity, thus requiring a more or less restricted diet, more than with a reduced oral and nutrients intake directly related to the type of diet. With regard to pharyngeal signs of OD, signs of reduced safety (penetration) and efficacy (residue) showed the highest association with malnutrition risk at the univariate analysis (OR 2.23 and 2.46, respectively). The association between signs of reduced safety and efficacy and malnutrition risk has been little investigated in literature also in other populations because few studies investigated the presence of OD based on instrumental assessment. In a study by Oliveira and colleagues, residue but not aspiration was associated with a BMI <18.5 kg/m^2 in patients referred for videofluoroscopic swallowing study (VFSS)[81]. Saito et al found that penetration and aspiration were not associated with BMI and serum albumin but were associated with the risk of malnutrition, assessed by a nutritional screening tool, in patients with OD of different etiologies[82]. Differences in findings among the studies can be ascribed to the differences in nutritional outcomes, bolus consistencies and volumes, and populations investigated. Finally, the association, although not independent, between a prolonged oral phase and malnutrition risk is not surprising but novel. Indeed, the role of oral phase efficiency on nutritional status has never been previously quantified. Chewing difficulties, reduced masticatory rate, prolonged duration of oral preparation are typical characteristics of neurodegenerative diseases and deserve a specific assessment for their relation with nutritional outcome.

Multivariate regression model accounted correctly identified 75% of the patients but accounted only for the 28.9% of the variance. It confirms that OD is only one of the factors contributing to malnutrition risk in HD, PD, and ALS. Age and swallowing safety during the meal were the only two independent factors associated with malnutrition risk. Increased age is known to be a risk factor for malnutrition. Older adults are more prone to have nutritional deficiencies and reduced BMI because of a combination of cognitive and physical decline, reduce muscle mass, depressive symptoms, poor oral health, and socioeconomic changes[83]. Based on multivariate analysis, every year of age the risk of malnutrition increases by 8% in patients with neurodegenerative diseases. Concerning swallowing safety during the meal, an increase of 1 point of the MAS safety score is associated with an increase of malnutrition risk by 39% in the investigated populations. As stated earlier in the discussion, swallowing safety during meal depends not only on swallowing safety assessed by instrumental assessment but also on other cognitive, motor, and behavioral aspects that can either impact on swallowing safety during meals. For instance, during meals, the patient is required to consume a greater amount of food than during swallowing trials and to convey attentional resources on eating activity for a longer period and often in presence of distracting factors. Thus, in the event of fatiguability or cognitive impairments swallowing safety may be reduced when compared to the findings of the instrumental assessment. Therefore, the impact of other

factors on swallowing performance may be more relevant than swallowing function per se in appraising the risk of nutritional complications in patients with neurodegenerative diseases.

Implications for clinical practice

Instrumental assessment is the gold standard for diagnosis of OD and is essential to identify patients with silent penetration and aspiration as well as to guide OD treatment[84]. Very often the main goal is to prevent aspiration and pulmonary complication. Nevertheless, results from the present study support the need of a multidimensional assessment of swallowing in patients with neurodegenerative diseases, including also an oral phase assessment and a meal observation, to: (i) outline a comprehensive swallowing profile of the patient; (ii) provide tailored recommendation on diet and meal management, taking into account both the findings from instrumental assessment and the swallowing performance in a more ecological situation; and (iii) identify the presence of swallowing impairments exposing the patient at a higher risk of malnutrition and requiring prompt referral to the nutritional team.

Limitations and future perspectives

Neurodegenerative diseases are a broad category of diseases characterized by a different average age of disease onset and disease duration. Therefore, patients with HD, PD, and ALS included in the study differed for age and disease duration. Moreover, only three neurodegenerative diseases were included in the study and, therefore, results may not be generalizable to other diagnoses, such as Steinert myotonic dystrophy or Alzheimer's disease, which should be included in future.

Patients that could not be assessed with TOMASS because swallowing of solids was not considered safe were excluded from the multivariate analysis due to missing data. However, excluded patients had more severe OD than included patients. Analogously, the inclusion criteria of full per oral nutrition, essential to study nutritional outcomes, probably resulted in the exclusion of patients with severe OD. Therefore, the impact of dysphagia on nutritional status may have been underestimated.

Instrumental assessment of swallowing was performed using FEES. FEES has the advantage over VFSS to allow the test of a higher number of boluses. Conversely, the oral phase can not be visualized during FEES. Although oral phase efficiency was investigated using TOMASS in the current study, some patients could not perform TOMASS due to the safety risk with solid food. Therefore, future studies using VFSS may provide a better insight on the impact of oral phase efficiency even in patients with more severe OD.

Subjectivity is a potential cause of bias. Indeed, both FEES interpretation and TOMASS measures requires to control for subjectivity. Inter-rater agreement was satisfactory for TOMASS, but often moderate for FEES. The use of a 3rd rater to resolve disagreements on FEES should have limited the risk of bias in the outcome assessment.

Age, gender, diagnosis, type of oral intake and swallowing variables were included in the model for regression analysis. Variables of disease severity were not included because were assessed with different neurological scales based on the diagnosis. Data from single neurological scales show that included patients represented a wide range of

disease severity, except for the more severe stages because of the exclusion of patients with enteral nutrition. Future studies should include non-disease measures of motor and cognitive function into the model.
Considerations on the use of MNA should be taken in account. Firstly, it is important to address that the MNA provides a screening of malnutrition, but does not diagnose malnutrition. Previous studies have shown that MNA yields high sensitivity, but moderate specificity[85]. Therefore, the frequency of malnutrition risk may have overestimated the actual prevalence of malnutrition in neurodegenerative diseases. Thus, a complete assessment of nutritional status is advisable in future studies. Secondly, MNA was developed for and mainly applied in elderly patients (aged ≥65)[67,86]. MNA was used to assess risk of malnutrition because of the predominance of elderly patients with neurodegenerative diseases and, in particular, in the study cohort (63%). Although MNA may not be the most appropriate tools for patients <65, previous studies have applied MNA in young adults and reported good sensitivity[87] and predictive ability of mortality in hospitalized patients[88] and adequate validity and reliability in patients with PD[89].
Finally, studies should expand the investigation by objectively quantify oral intake and analyze the association between OD and hydration status in neurodegenerative disease.

CONCLUSIONS

Age, type of oral intake, residue in the valleculae with semisolids, penetration with liquids, swallowing safety during meal, number of masticatory cycles and oral phase duration were significantly associated with risk of malnutrition in three neurodegenerative diseases (HD, PD, and ALS), but only age and swallowing safety during the meal were independent predictors of malnutrition risk. A multidimensional assessment of swallowing, including instrumental assessment, oral phase assessment, and meal observation, is advocated in patients with neurodegenerative diseases to appraise the risk of malnutrition secondary to OD.

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CHAPTER 6

Summary and Future Perspectives

This doctoral dissertation provides novel findings to the knowledge on oropharyngeal dysphagia (OD) in neurodegenerative disease, in particular in HD and ALS. Moreover, a new tool to assess swallowing performance during meal was developed to fill the lack of clinical tools in the area. Finally, the dissertation reports the first data on the association between OD and risk of malnutrition in patients with neurodegenerative diseases, including a comprehensive evaluation of swallowing, not only focused on pharyngeal signs of dysphagia but also on oral efficiency and performance during meal. Main findings, implication for clinical practice, and future research perspectives are summarized in this chapter.

6.1 Dysphagia in Huntington's disease

Fourty-three patients with a diagnosis of HD and oral nutrition were recruited and underwent a fiberoptic endoscopic evaluation of swallowing. Patients were divided based on the disease severity: 20 patients in the early stage, 10 patients in the moderate stage, 13 patients in the advanced stage.

For the first time, frequency of OD in different stages of the disease was reported based on an instrumental evaluation of swallowing. In particular, 30% of the patients in the early stage exhibited OD and 10% had silent aspiration. Frequency of OD and severity of penetration and aspiration significantly increased with disease progression, while severity of pharyngeal residue remained generally stable.

Significant correlations between OD severity and disease severity were found. Among the neurological clinical scales, the Total Motor Score of the Unified Huntington's Disease Rating Scale showed satisfactory accuracy in identifying patients with OD with a cut-off of 37.

Implication for clinical practice

- A swallowing assessment is recommended in patients with HD already in the early stage
- A Total Motor Score ≥37 can be used by the neurologists as a clinical cut-off for referral to the swallowing team.

Future research

- Longitudinal studies on the evolution of OD in HD
- Interventional studies to assess the impact of an early assessment and management of OD on health and psychosocial consequences in patients with HD and their caregivers.

6.2 Dysphagia in Amyotrophic Lateral Sclerosis

The association between Maximum Tongue Pressure (MTP) and signs of OD was studied in 55 patients with a diagnosis of ALS and oral nutrition. The swallowing protocol included 5-10-20ml liquid, 5-10-20ml semisolid, and solid.

Patients with residue in the pyriform sinus had significantly lower MTP than patients without residue with 10ml and 20ml of semisolid. A trend toward a lower MTP was found also in patients with residue in the pyriform sinus with solids, although not reaching the statistical significant, possibly due to the impossibility to test 1/5 of the patients with this consistency for safety reasons.

Implication for clinical practice

- Including a MTP measures during swallowing assessment may provide additional information on swallowing function
- In patients with reduced MTP, smaller volumes and less viscous consistencies may be preferable, if swallowing safety is preserved.

Future research

- Observational studies to verify the potential role of MTP as a marker of eating-related fatigue
- Interventional studies on the feasibility and efficacy of a low-load tongue resistance training in patients with ALS

6.3 The Mealtime Assessment Scale

The Mealtime Assessment Scale (MAS) was developed to assess swallowing performance during meal based on the International Classification of Functioning, Disability and Health framework. The scale separately assesses the safety of swallowing and the efficacy of swallowing during meal. Non-swallowing factors possibly influencing swallowing performance during meal can be systematically described.

A first validation process was performed. Internal consistency was good for the efficacy scale and moderate for the safety scale. An adequate inter-rater agreement was found for all the items. A significant correlation with clinical assessment and swallowing outcome scales was found. The MAS was able to distinguish among different levels of swallowing performance and to register swallowing improvements over time.

Implication for clinical practice

- The MAS provides a quali-quantitative assessment of swallowing performance during meal using a standard terminology and rating method, which allows to record changes over time and facilitates communication among health professionals
- The descriptors of non-swallowing factors with potential influence on the performance can be useful to identify modifiable factors that may be targeted to improve swallowing safety and efficacy during meal, along with a specific swallowing treatment.

Future research

- Validation study to expand the psychometric testing of the MAS
- Longitudinal studies to investigate the predictive value of the MAS in appraising the risk of dysphagia-related complications.

6.4 Dysphagia and nutritional risk in neurodegenerative diseases

One hundred sixty-two patients with neurodegenerative diseases (66 with HD, 34 with PD, 62 with ALS) and oral nutrition were studied for swallowing and nutritional outcomes.

Residue in the valleculae, penetration with liquids, and prolonged oral phase duration were the most common findings. Based on the disease, different swallowing profiles were identified. Patients with HD had the lowest severity of signs of OD during instrumental examination, but oral phase efficiency was generally impaired and swallowing safety was more compromised during meal. Patients with PD often exhibited alteration of both oral and pharyngeal phases, but swallowing efficacy during meal was better than in HD and ALS. Finally, swallowing was mostly compromised in patients with ALS in all the investigated swallowing tasks.

Based on a Mini Nutritional Assessment® score <24, 62% of the patients were at risk of malnutrition. Age, type of oral intake, penetration with liquids, residue in the valleculae with semisolids, number of masticatory cycles and duration of oral phase were significantly associated with risk of malnutrition at the univariate analysis. Swallowing safety during meal and age were independent significant predictor ($p<0.05$ at the univariate and multivariate analysis).

Implication for clinical practice

- A multidimensional assessment of swallowing, including an instrumental evaluation, a test of oral phase efficiency, and a meal observation is recommended for patients with neurodegenerative diseases as both oral and pharyngeal stages may be impaired and other disease-related factors may influence swallowing performance in daily living
- Patients with impaired safety of swallowing during meal, but also penetration with liquids, residue in the valleculae with semisolids, prolonged oral phase duration, and increased number of masticatory cycles are at higher risk of malnutrition and should therefore be carefully monitored for nutritional status.

Future research

- Observational studies to expand the investigation to other neurodegenerative diseases and to provide quantitative measures of oral intake
- Observational studies on the association between OD and hydration status
- Interventional studies to investigate the efficacy of rehabilitation strategies targeted on the signs of OD significantly associated with malnutrition on swallowing and nutritional outcomes.

6.5 General conclusion

Neurodegenerative diseases are complex disorders in which symptoms may influence and exacerbate each other. Swallowing function may be impaired by the disease itself, but swallowing performance in daily living may be additionally influenced by cognitive, behavioural, and other motor symptoms. OD is a serious but often underestimated problem. Avoidance of pulmonary complications is very often the primary target of OD management as aspiration pneumonia is the leading cause of death in many diseases. Nevertheless, malnutrition is a multifactorial condition that is known to influence survival and prognosis. OD is associated to an increased risk of malnutrition in neurodegenerative diseases. In these populations, OD is progressive and, currently, no strong evidence of treatments to slow down its progression exists. However, early recognition of OD may reduce health and psychosocial consequences on the patients and their caregivers. Firstly, when OD is suspected, instrumental assessment of swallowing should be performed. In patients with HD, a Total Motor Score of the UHDRS ≥37 is an accurate clinical marker for referral to the swallowing team. Secondly, based on the results of the present dissertation, a multidimensional assessment of swallowing can help in identifying not only patients at a higher risk of pulmonary complications, but also those at a higher risk of malnutrition. Meal assessment is recommended in patients with neurodegenerative disease to evaluate the influence of other disease-related and environmental factors on swallowing. The MAS may be a useful tool to assess swallowing performance during meal and guide the identification of strategies to improve meal management. Other measures, such as maximum tongue pressure, may provide additional information on swallowing function, being, for example, associated with reduced swallowing efficacy in patients with ALS.

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Appendix 1
Reporting Checklists

Chapter 2 - Study 2.1 Management of dysphagia in Huntington's disease: A scoping review

Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review.	15
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	15
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	16
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	16, lines 34-39
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	17, line 7
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	17, lines 12-19
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	16, line 41 + 17, lines 7-8
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	16, lines 41-43 + 17, lines 1-7
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	17, lines 9-12 + 17, lines 19-20
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	17, lines 21-22
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	17, lines 22-24
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	NA
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	17, lines 24-26

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	17, lines 30-32 + 18, Figure 1
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	17, lines 33-42
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	NA
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	19-20, Table 1 + 22-24, Table 2 + 27-28 Table 3
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	19-20, Table 1 + 22-24, Table 2 + 27-28 Table 3
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	18-30 (excluded tables)
Limitations	20	Discuss the limitations of the scoping review process.	30
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	30-31
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	31

NA = not applicable

From: Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMAScR): Checklist and Explanation. Ann Intern Med 2018;169:467–473.

Chapter 2 - Study 2.2 Dysphagia in early to advanced stage Huntington's disease

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	32, line 11
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	32
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	33
Objectives	3	State specific objectives, including any prespecified hypotheses	33, lines 31-35
Methods			
Study design	4	Present key elements of study design early in the paper	33, lines 39-40
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	34, lines 1-2 + lines 8-9 + lines 30-31
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	34
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	34-35
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	34-35
Bias	9	Describe any efforts to address potential sources of bias	34, lines 36-39
Study size	10	Explain how the study size was arrived at	34, lines 1-2 (consecutive sample)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	35, line 33 + lines 39-40
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	35
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	No missing
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	NA

Results			
Participants	13	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	35-36 (n. patients screened for eligibility is not available)
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	35-36
		(b) Indicate number of participants with missing data for each variable of interest	No missing data
Outcome data	15	Report numbers of outcome events or summary measures	37-39
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	37-41
		(*b*) Report category boundaries when continuous variables were categorized	37-41
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	41, lines 11-15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	42
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	41
Generalisability	21	Discuss the generalisability (external validity) of the study results	42
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	43

NA = not applicable

From: von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet 2007;370:1453-1457.

Chapter 3. Association between maximum tongue pressure and swallowing safety and efficacy in Amyotrophic Lateral Sclerosis

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	49, line 5
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	49
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	50
Objectives	3	State specific objectives, including any prespecified hypotheses	50, lines 26-32
Methods			
Study design	4	Present key elements of study design early in the paper	50, line 35
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	51, lines 2-4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	51, lines 2-9
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	51-52
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	51-52
Bias	9	Describe any efforts to address potential sources of bias	51, lines 29-35 + 52, lines 6-7, 12, 14-19
Study size	10	Explain how the study size was arrived at	Consecutive sample
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	52, lines 23-29, 30-31, 39-40
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	53
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	No missing (excluded)
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	NA

Results			
Participants	13	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	53 (n. patients screened for eligibility is not available)
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	53
		(b) Indicate number of participants with missing data for each variable of interest	53
Outcome data	15	Report numbers of outcome events or summary measures	54-55
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	55-56
		(*b*) Report category boundaries when continuous variables were categorized	54, 56
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	55-56
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	59
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	57-58
Generalisability	21	Discuss the generalisability (external validity) of the study results	59, lines 21-28
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	60

NA = not applicable

From: von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet 2007;370:1453-1457.

Chapter 5. Dysphagia in neurodegenerative diseases: Association with risk of malnutrition

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	103, line 6
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	103
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	104-105
Objectives	3	State specific objectives, including any prespecified hypotheses	105
Methods			
Study design	4	Present key elements of study design early in the paper	105, line 31
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	103, lines 39-40
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	105-106
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	106-107
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	106-107
Bias	9	Describe any efforts to address potential sources of bias	106, lines 34-36 + 107, lines 7+18-19
Study size	10	Explain how the study size was arrived at	Consecutive
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	107-108
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	107-108
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	108, line 12
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	NA

Results			
Participants	13	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	108
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	109
		(b) Indicate number of participants with missing data for each variable of interest	110
Outcome data	15	Report numbers of outcome events or summary measures	110-112
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	111-113
		(*b*) Report category boundaries when continuous variables were categorized	110-111
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	113-114
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	116-117
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	114-116
Generalisability	21	Discuss the generalisability (external validity) of the study results	116
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	117

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Appendix 2
DOSS Translation into Italian and Adaptation to FEES

DOSS' adaptation to FEES after backtranslation process

The Italian version of the scale is reported in *Italics*.
Authorization to translation and adaptation has been provided by original authors of the scale (on April 2nd, 2017).

ENTIRELY ORAL NUTRITION: NORMAL DIET

Level 7: normal in all situations
- Normal diet
- Non necessity of any strategy or additional time

Level 6: within the functional limits/changes in the independence
- Normal diet, functional swallow
- The patient should present a slight delay in the oral and pharyngeal phase of swallowing, residue or traces of undercoating at epiglottic level, but autonomously and spontaneously cleansed
- May need additional time for meal
- Absent aspiration or penetration, with all the consistencies

ENTIRELY ORAL NUTRITION: MODIFIED DIET AND/OR INDEPENDENCE

Level 5: mild dysphagia: distant supervision, the restriction of a diet consistency may be needed
It can show one of more of the following signs:
- Aspiration only with liquids, but with a strong reflexive cough, able to clean in a complete way
- Penetration in the airways over the vocal cords with one or more consistencies or up to the vocal cords with one consistency which, however, cleans spontaneously.
- Residue in pharynx spontaneously cleansed
- Prolonged times of oral preparation

Level 4: mild-moderate dysphagia: intermittent supervision/indications, restriction to one or two consistencies
It can show one or more of the following signs:
- Residue in pharynx cleansed with cue
- Aspiration with one consistency, with a weak reflexive cough or absent or airways penetration up to the vocal cords level with cough with two consistencies, or airways penetration up to the vocal cords level without cough with one only consistency.

Level 3 moderate dysphagia: total assistance and/or supervision and/or continuous use of strategies, restriction of one or two consistencies
It can show one or more of the following signs:
- Moderate residue in pharynx cleansed with cue
- Penetration up to the vocal cords level without cough with one or more consistencies, or aspiration in two consistencies with weak reflexive cough or absent, or aspiration with one consistency without reflexive cough and in airways penetration up to the vocal cords with one consistency, without cough

NECESSARY NON-ORAL NUTRITION

Level 2: moderately severe dysphagia: maximum assistance and use of strategies with just partial oral nutrition (it tolerates at least one consistency safely with a total use of strategies)
It can show one of the following signs:
- Severe residue in pharynx, which the patient is not able to cleanse or not able to cleanse himself after multiple cues
- Aspiration with two or more consistencies without reflexive cough and with weak voluntary cough or aspiration with one or more consistencies without cough and penetration in the airways up to the vocal cords with one or more consistencies without cough

Level 1: severe dysphagia: NPO: unable to tolerate any oral nutrition safely
It can show one or more of the following signs:
- Severe residue in pharynx which the patient is not able to cleanse
- Silent aspiration with two or more consistencies non efficient voluntary cough
- Patient not able to swallow

NUTRIZIONE INTERAMENTE ORALE: DIETA NORMALE

Livello 7: normale in tutte le situazioni
- Dieta normale
- Non necessita di alcuna strategia né di tempo aggiuntivo

Livello 6: entro i limiti funzionali/modifiche nell'autonomia
- Dieta normale, deglutizione funzionale
- Il paziente potrebbe presentare lieve ritardo nella fase orale e faringea della deglutizione, ristagno o tracce di verniciatura a livello epiglottico ma deterso in maniera autonoma e spontanea
- Potrebbe necessitare di tempo aggiuntivo al pasto
- Assenti aspirazione o penetrazione con tutte le consistenze

NUTRIZIONE INTERAMENTE ORALE: DIETA E/O AUTONOMIA MODIFICATA

Livello 5: disfagia lieve: supervisione a distanza, può essere necessaria la restrizione di una consistenza dietetica
Può mostrare uno o più dei seguenti segni:
- Aspirazione solo con liquidi ma con tosse riflessa forte in grado di ripulire completamente
- Penetrazione nelle vie aeree sopra le corde vocali con una o più consistenze o fino alle corde vocali con una consistenza ma che si ripulisce spontaneamente
- Ristagno in faringe deterso spontaneamente
- Tempi di preparazione orale prolungati

Livello 4: disfagia lieve-moderata: supervisione/indicazioni intermittenti, restrizioni di una o due consistenze
Può mostrare uno o più dei seguenti segni:
- Ristagni in faringe detersi su suggerimento
- Aspirazione con una consistenza con tosse riflessa debole o assente oppure penetrazione nelle vie aeree fino al livello delle corde vocali con tosse con due consistenze oppure penetrazione nelle vie aeree fino al livello delle corde vocali senza tosse con una sola consistenza

Livello 3: disfagia moderata: assistenza e/o supervisione totale e/o uso continuo di strategie, restrizione di due o più consistenze
Può mostrare uno o più dei seguenti segni:
- Ristagni moderati in faringe detersi su suggerimento
- Penetrazione fino al livello delle corde vocali senza tosse con due o più consistenze oppure aspirazione con due consistenze con tosse riflessa debole o assente oppure aspirazione con una consistenza senza tosse riflessa e penetrazione nelle vie aeree fino alle corde vocali con una consistenza senza tosse

NECESSARIA NUTRIZIONE NON ORALE

Livello 2: disfagia moderatamente grave: massima assistenza o uso di strategie con solo parziale nutrizione orale (tollera almeno una consistenza in sicurezza con un uso totale di strategie)
Può mostrare uno o più dei seguenti segni:
- Gravi ristagni in faringe che il paziente non è in grado di detergere o detersi dopo numerosi suggerimenti
- Aspirazione con due o più consistenze senza tosse riflessa e con tosse volontaria debole oppure aspirazione con una o più consistenze senza tosse e penetrazione nelle vie aeree fino alle corde vocali con una o più consistenze senza tosse

Livello 1: disfagia grave: NPO: incapace di tollerare qualsiasi alimentazione orale in sicurezza
Può mostrare uno o più dei seguenti segni:
- Gravi ristagni in faringe che il paziente non è in grado di detergere
- Aspirazione silente con due o più consistenze, tosse volontaria non efficace
- Paziente non in grado di deglutire