

MANAGEMENT OF DYSPHAGIA IN HUNTINGTON'S DISEASE: A DESCRIPTIVE REVIEW

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ABSTRACT

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 dysphagia and aspiration pneumonia is the leading cause of death. However, little is known about dysphagia management in HD.

A revision of the literature was conducted to depict the state-of-art on the assessment and treatment of dysphagia in HD. Literature search of the last 10 years was performed using PubMed and EMBASE. Twenty-four 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.

Based on the studies retrieved, dysphagia should be assessed from the early stage of the disease, especially when specific clinical markers occurs. Timing for dysphagia re-assessment should be based on the recommendation of the swallowing experts on the individual case. Instrumental assessment of swallowing by videofluoroscopy or videoendoscopy is feasible 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 dysphagia 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 dysphagia in HD remains poorly studied compared to its clinical relevance.

Key Words: Huntington's Disease - Deglutition - Deglutition disorders - Dysphagia - Diagnosis - Treatment

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 dysphagia [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. Dysphagia contributes to increase caregiver's burden and to reduce QOL [9]. Despite its clinical relevance, little is known about dysphagia in HD. In 2011, Heemskerk and Roos published a literature review on dysphagia 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 dysphagia in HD showing that abnormalities of swallowing in HD are found in both the preparatory, oral and pharyngeal phases of ingestion [4,5]. Moreover, the retrieved studies provided preliminary evidence on the applicability of the videofluoroscopic study of swallowing (VFSS) and the efficacy of mealtimes interventions in this population. As 10 years have passed since the literature search, this review aims to provide an update on current knowledge about dysphagia in HD. In particular, the review aims to identify and summarize the existing evidence on 3 clinical questions related to the management of dysphagia in this population: 1) When should dysphagia be assessed in patients with HD?;

2) How should dysphagia be assessed in patients with HD?; 3) Can pharmacological and rehabilitative treatments influence dysphagia in HD?

METHODS

Literature searches were performed using PubMed and EMBASE. A resident otorhinolaryngologist and a speech and language therapist (SLT) conducted the literature revision. 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)). Filters of language was applied. Records needed to be published in English, Italian, French, German or Spanish. Literature searches were executed on June 15th, 2019.

Papers have been selected based on their titles and abstracts, and afterward on full-text, when available. Exclusion criteria were: studies on HD not linked to dysphagia or not answering to the 3 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; narrative reviews and letters to the editor; studies already included in the review by Heemskerk and Roos [10]. In order to give an extensive overview of current knowledge on dysphagia 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.

All selected studies were later summarized in tables and based on the clinical question they provided an answer. For each study, design, aim, number and characteristics of participants, methods, and key findings were reported in order to highlight their main features systematically. Studies were included in more than one table if they responded to two or more clinical questions.

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 published between 2009 and 2018 were included in the review. 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 dysphagia assessment timing. Table 2 synthesized 13 studies (11 cross-sectional studies and 2 case reports) on dysphagia 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.

Table 1: Swallowing assessment timing

Authors, year [study design]	Purpose of the Study	Participants	Examinations	Main Results
Dello Monaco <i>et al</i> , 2014 [13] [cross-sectional, abstract]	To investigate swallowing function in HD and provide appropriate management	N=38 HD patients	<ul style="list-style-type: none"> Swallowing evaluation (<i>nfd</i>) Clinical neurological assessment (UHDRS) Classification according to disease stage: early, middle, late stage 	<ul style="list-style-type: none"> Early stage: 11% had swallowing difficulties; required compensatory strategies and diet restrictions Middle stage: 11% had swallowing difficulties Late stage: 26% had severe dysphagia
Mariscal <i>et al</i> , 2014 [9] [cross-sectional, abstract]	To determine the prevalence of dysphagia in HD	N=224 HD patients	<ul style="list-style-type: none"> 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 	<ul style="list-style-type: none"> 88% of sample completed EAT-10: 37% of them complained of dysphagia symptoms (equal frequency between women and men) Patients with dysphagia: <ul style="list-style-type: none"> were older had higher UHDRS motor score had lower cognitive scores and lower level of education had lower TFC score
Schradt <i>et al</i> , 2014 [14] [cross-sectional, abstract]	To determine dysphagic symptoms by FEES according to HD-stage	N=29 HD patients	<ul style="list-style-type: none"> 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 	<ul style="list-style-type: none"> No statistical difference in spillage between HD stages Significant difference between HD-stages in: residuals, penetration, aspiration, and Percutaneous Endoscopic Gastrostomy recommendation Dysarthria, dysphonia, gag reflex and voluntary cough distinguished dysphagic from non-dysphagic patients in FEES
de Tommaso <i>et al</i> , 2015 [15] [cross-sectional]	To evaluate dysphagia in HD in view of motor, cognitive and functional decline	N ₁ =37 HD patients N ₂ =39 controls	<ul style="list-style-type: none"> 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 (<i>nfd</i>*) Dysphagia Outcome and Severity Scale (DOSS) on clinical evaluation by SLTs 	<ul style="list-style-type: none"> 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 <i>et al</i> , 2016 [16] [cross-sectional, abstract]	To correlate swallowing parameters with cognitive assessment and CAG repeats	N=19 patients (13 with HD and 6 controls)	<ul style="list-style-type: none"> • HD patients underwent to: <ul style="list-style-type: none"> - 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 <i>et al</i> , 2016 [6] [cross-sectional, abstract]	To collect data of dysphagia features in HD To identify risk factors for severity of dysphagia in HD	N=86 HD patients (61 investigated retrospectively and 25 prospectively)	<ul style="list-style-type: none"> • Clinical swallowing examination • FEES • Swallowing-Quality of Life (SWAL-QOL) questionnaire 	<ul style="list-style-type: none"> • Subclinical dysphagia found at all stages of the disease • Dysarthria and dysphonia were identified as predictors for the risk of aspiration
Manor <i>et al</i> , 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	<ul style="list-style-type: none"> • UHDRS • Montreal Cognitive Assessment • Swallowing Disturbances Questionnaire (SDQ) • Swallowing-Quality of Life (SWAL-QOL) questionnaire • FEES 	Significant correlations were found between: <ul style="list-style-type: none"> - 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 <i>et al</i> , 2018 [17] [case series, abstract]	To study predictors of dysphagia in HD	N = 73 HD patients	<ul style="list-style-type: none"> • 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%.

Authors, year [study design]	Purpose of the Study	Participants	Examinations	Main Results
Schumann et al, 2018 [47] [cross-sectional, abstract]	To define clinical risk factors for HD-associated dysphagia	N = 21 HD patients	<ul style="list-style-type: none"> • UHDRS • Clinical swallowing examination • FEES 	<ul style="list-style-type: none"> • FEES showed penetration or aspiration in 80%. • No significant correlations were found between dysphagia severity and any of the clinical markers (motor score, cognition, functional assessment, age, CAG).

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

Table 2: Tools for swallowing assessment in HD

Authors, year [study design]	Purpose of the Study	Participants	Examinations	Main Results
SELF-ASSESSMENT				
Heemskerk <i>et al</i> , 2014 [33] [cross-sectional]	To develop and validate a self-assessment questionnaire for dysphagia in HD	N= 55 HD patients from three clinical stages	<ul style="list-style-type: none"> Huntington's Disease Dysphagia Scale (HDDS) Swallowing Disturbance Questionnaire (SDQ) 	<ul style="list-style-type: none"> 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 <i>et al</i> , 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	<ul style="list-style-type: none"> 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 <i>et al</i> , 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	<ul style="list-style-type: none"> 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)

Authors, year [study design]	Purpose of the Study	Participants	Examinations	Main Results
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	<ul style="list-style-type: none"> 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 <i>et al</i> , 2014 [14] [cross-sectional, abstract]	To investigate clinical assessment diagnostic accuracy compared to FEES in HD	N=29 HD patients	<ul style="list-style-type: none"> 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 dysphagia in HD
de Tommaso <i>et al</i> , 2015 [15] [cross-sectional]	To evaluate dysphagia in HD in view of motor, cognitive and functional decline	N=37 HD patients	<ul style="list-style-type: none"> 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 (<i>nfd</i>*) Dysphagia Outcome and Severity Scale (DOSS) on clinical evaluation by SLTs* 	According to BSAS: 35.1% had relevant/serious swallowing difficulties
INSTRUMENTAL ASSESSMENT				

Authors, year [study design]	Purpose of the Study	Participants	Examinations	Main Results
Vogel <i>et al.</i> , 2011 [49] [retrospective cross-sectional, abstract]	To describe frequency and nature of swallowing deficits in HD using VFSS	N=45 HD patients, different stages, all symptomatic	<ul style="list-style-type: none"> 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 	<ul style="list-style-type: none"> 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 <i>et al.</i> , 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) - <i>standard protocol</i> , catheter from hypopharynx to stomach; 5-min assessment of basal sphincter pressure; 10 x 5 mL saline swallows + 10 x 5 mL viscous swallows - <i>modified protocol</i> , catheter pulled back by 10 cm to assess the whole pharynx: same sessions as standard method + vocalizing “kakakaka” (to locate velopharyngeal swallowing pressure)	HRIM: - <i>standard protocol</i> : incomplete relaxation of lower esophageal sphincter; spastic esophageal motility; normal upper esophageal sphincter relaxation, normal peristaltic pharyngeal pressure - <i>modified protocol</i> : irregular and simultaneous contractions between velopharyngeal- and meso-hypopharyngeal zone; impaired bolus transit
Süssmuth <i>et al.</i> , 2012 [50] [cross-sectional, abstract]	To evaluate dysphagia in HD by FEES	N=23 HD patients, different disease stages	FEES testing puree, liquid and solid boluses	<ul style="list-style-type: none"> 19/23 patients: disturbances of the pre-oral, oral, and pharyngeal stage of swallowing 10/19 patients: pharyngeal dysphagia with aspiration or risk of aspiration

Authors, year [study design]	Purpose of the Study	Participants	Examinations	Main Results
Heemskerk <i>et al.</i> , 2015 [12] [cross-sectional]	To identify specific dysphagia features in HD using VFSS	N=45 HD patients from three clinical stages	<ul style="list-style-type: none"> • VFSS analyzed by two raters • VFSS protocol: <ul style="list-style-type: none"> - thin liquid: 3mL (x1) and 10 mL (x1) - thick liquid: 5 mL (x1) - a piece of barium bread • VFSS features that were analyzed: <ul style="list-style-type: none"> - tongue protrusion - head hyperextension - mastication - spilling before and during swallow - penetration and aspiration (PAS scale) - residues in valleculae and pyriform sinuses duration times	<ul style="list-style-type: none"> • 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 <i>et al.</i> , 2016 [51] [case report]	To describe swallowing endoscopic findings of the pharyngeal phase in HD	N=2 HD patients from the same family	<ul style="list-style-type: none"> • 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 	<ul style="list-style-type: none"> • Clinical assessment: difficulties in labial sealing, oral incoordination, compensatory head movements, impaired oral transit • FEES: <ul style="list-style-type: none"> - Posterior oral spillage (for liquid and nectar bolus) - Pharyngeal residue in small quantities • Absence of penetration and/or aspiration
Schindler <i>et al.</i> , 2017 [19] [cross-sectional, abstract]	To analyze applicability of FEES for evaluation of dysphagia in patients with HD	N=14 HD patients	<ul style="list-style-type: none"> • Assessments included BMI and FEES (with ingestion of thin liquid, semisolid and solid) • Quantitative analysis of dysphagia through FEES: <ul style="list-style-type: none"> - Penetration-Aspiration Scale (PAS) - Yale Pharyngeal Residue Severity Rating Scale (YPRSRS) - Dysphagia Outcome and Severity Scale (DOSS) 	<ul style="list-style-type: none"> • VFSS was never required to improve diagnostic accuracy of dysphagia • FEES can be easily applied in everyday clinical practice for swallowing assessment in HD patients

Authors, year [study design]	Purpose of the Study	Participants	Examinations	Main Results
Manor <i>et al</i> , 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	<ul style="list-style-type: none"> • UHDRS • Montreal Cognitive Assessment • FEES • Swallowing Disturbances Questionnaire (SDQ) • Swallowing Related Quality Of Life (SWAL-QOL) questionnaire 	<ul style="list-style-type: none"> • 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

* not validated measures for the swallowing assessment method used in the study

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 dysphagia onset as an adverse effect of TBZ therapy
Shen <i>et al.</i> , 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 dysphagia onset as an adverse effect of TBZ therapy
de Tommaso <i>et al.</i> , 2015 [15] [cross-sectional]	To investigate the effect of neuroleptics on swallowing function	N _i =37 HD patients (10 patient treated with neuroleptics)	Use of neuroleptics (nfd)	<ul style="list-style-type: none"> • 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					

Authors, year [study design]	Purpose of the study	Participants	Treatment	Outcome Measures	Main Results
Reyes <i>et al</i> , 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): - <i>Control group</i> : fixed resistance of 9 cm H ₂ O - <i>Experimental group</i> : 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 <i>et al</i> , 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	<ul style="list-style-type: none"> • Feasibility (technical issues, time) • Patient feedback 	<ul style="list-style-type: none"> • 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
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	<ul style="list-style-type: none"> • Patient reported outcome • VFSS in 1 patient 	<ul style="list-style-type: none"> • Most patients could perform at least one swallowing maneuver • Most patients reported that they benefit from the treatment
Schradt <i>et al</i> , 2018 [17] [case series, abstract]	To study efficacy of compensatory Strategies for dysphagia in HD	N =73 HD patients	Chin tuck posture and diet adaptation	<ul style="list-style-type: none"> • 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

DISCUSSION

The present review provides an updated overview of the current knowledge on the assessment and treatment of dysphagia 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 dysphagia 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 dysphagia in this population [10]. Since 2009, the number of studies investigating dysphagia 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 dysphagia in HD, but the topic is still poorly explored compared to its clinical relevance in this population.

When to assess swallowing in HD

In the studies retrieved by Heemskerk and Ross, no data on dysphagia in different stages of the disease were available. Based on the results of the studies included in this review, dysphagia was found in all stages of the disease [6, 12]. 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 dysphagia in the early stage of the disease. Data on the prevalence of dysphagia in the different stages of the disease based on instrumental assessment are lacking or currently not accessible (abstracts from conference proceedings). In the same study by Dello Monaco and colleagues [13], the prevalence of dysphagia was found to be stable between the early and the middle stage of the disease, while it increased only in the advanced stage. Conversely, other studies reported a progression in the severity of the signs of dysphagia with significant differences also between the early and the moderate stage [12,14].

Different authors tried to identify clinical predictors of dysphagia, 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 dysphagia 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 dysphagia or worsening of severe dysphagia that could become life-threatening.

Thus, although different studies led to contrasting results, dysphagia should be assessed since the early stage of the disease, in particular in case of the presence of the above-mentioned clinical markers. Re-assessment of dysphagia 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 dysphagia in HD

Different techniques are used to assess dysphagia, 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 dysphagia. The two methods for instrumental assessment have been demonstrated to yield comparable sensitivity and specificity to signs of dysphagia 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 dysphagia 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 dysphagia in patients with HD. No study has compared FEES and VFSS in this population, nor investigated the effects of choreic movements on the accuracy of the instrumental examination. Therefore, analogously to other population at risk of dysphagia, 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 HRIM over FEES and VFSS is that it provides an objective assessment of swallowing biomechanics, potentially enhancing the understanding of dysphagia 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 dysphagia 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 [27]. 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 dysphagia 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 dysphagia [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 represent essential tools to understand patient's perception of swallowing function as well as the impact of dysphagia on QOL, however can not replace the instrumental assessment of swallowing for the diagnosis of dysphagia in this population. Indeed, none of the questionnaires have been validated against instrumental procedures. Additionally, anosognosia for dysphagia was previously reported [4] uncovering the issue of unreliable self-reporting of symptoms. This finding was more recently investigated by Carozzi and colleagues, who identified specific cognitive scores that dramatically reduce the reliability of the PRO swallowing outcomes, as assessed through the HDQLIFE Swallowing tool [11].

Finally, assessing dysphagia 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].

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 dysphagia 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 dysphagia 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 dysphagia 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 dysphagia have appeared [38-39]. It is difficult to establish whether dysphagia 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 dysphagia 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 dysphagia 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 dysphagia, 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]. Varying-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 dysphagia 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). 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 descriptive review, the risk of bias of the included studies was not assessed, and results were not weighted accordingly; as stated, it was beyond the aims of the review. 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 dysphagia 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 dysphagia in this population. Relevant gaps in literature have been identified.

Based on the studies retrieved, dysphagia should be assessed from the early stage of the disease, especially when specific clinical markers occurs. Timing for dysphagia re-assessment should be based on the recommendation of the swallowing experts on the individual case. Instrumental assessment of swallowing by VFSS or FEES is feasible and recommended to diagnose dysphagia 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 dysphagia 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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