The impact of oropharyngeal dysphagia and dysphonia on health-related quality of life in Parkinson's disease

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Preface

Waar is de sleutel.

De sleutel voor de bevrijding van opgesloten woorden?

Deze tekst is geschreven door Jan van Bergen op initiatief en met begeleiding van Eveline Helder, Logopediste.

Groeningen, Maart 2023

Hallo? Ja Hallo!
Wij kennen elkaar.

Hallo mijn dierbaar familielid/hallo mijn beste vriend/hallo mijn goede kennis.

Jij kent mij, ik ken jou.

Parkinson heeft zich genesteld in mijn lijf en heeft een kille schaduw geworpen over mijn leven.

Ik ben daar erg van geschrokken, vreselijk. Ik wilde het niet weten, nee echt niet. Ik ben boos, verdrietig, opstandig geweest, heel erg.

Ik wil niet bibberen in de kilte van de schaduw. Ik wil zonnestralen zoeken, ik wil leven in de warmte van de zon, in de warmte van liefde en vriendschap. Ik wil van het leven blijven genieten.

En jij? Ben je ook geschrokken? Zie je mij zitten in de kille schaduw van mijn ziekte? Niet doen! Zie je mij de hoofdrol dansen in het ballet van de stervende zwaan? Niet doen! Luister naar ‘Le Carnaval des Animaux’, de mooie muziek die Camille Saint-Saëns componeerde bij het vrolijke leven van Carnaval. Daarin luister je naar een cellosolo van La Mort du Cygne. Luister naar de muziek van het leven. Luister!

Ik nodig je uit om naar mij te luisteren. Luister naar mij, luister ook als ik de woorden moet zoeken of de woorden fluister. Luister!

Ik daag je uit om met mij het gesprek aan te gaan, om met mij van gedachten te wisselen. Ik daag je uit om je niet af te wenden als mijn woorden niet meer bij je overkomen. Ik daag je uit mij te zeggen als je me niet kunt verstaan. Dan zal ik diep ademhalen en opnieuw de woorden zoeken.

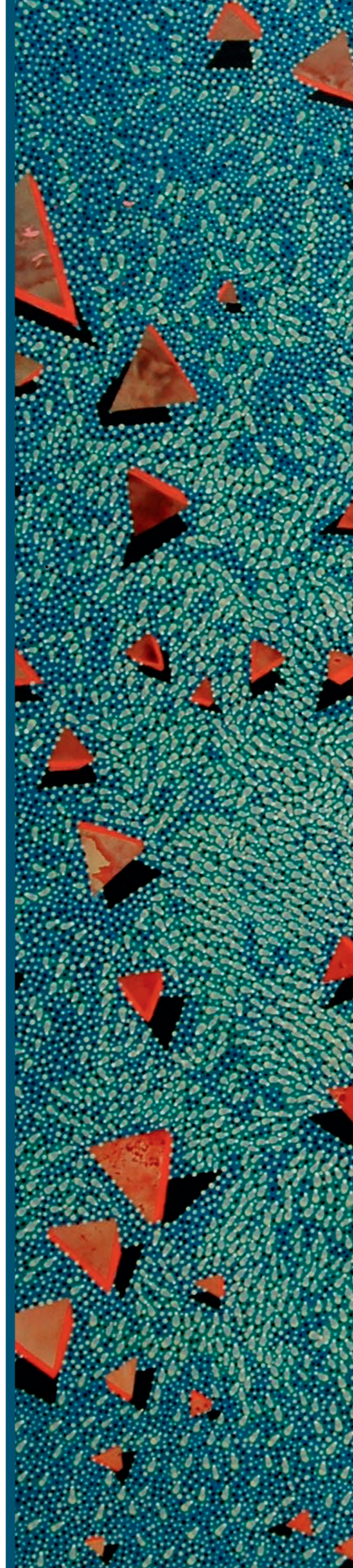
Ja Hallo? Ja Hallo!

Ik ken jou. Jij kent mij. Wij blijven luisteren naar elkaar en in gesprek.

Dankjewel!

1

General introduction



General introduction

Parkinson's disease

Idiopathic Parkinson's disease (IPD) is a chronic progressive neurodegenerative disorder, characterized by several distinct symptoms. It is one of the hypokinetic movement disorders. The diagnosis is based on the clinical criteria of having bradykinesia and at least one other motor symptom (rest tremor, rigidity, and postural disturbances) without a known cause. [1-3] The global prevalence of IPD is about 40 per 100.000 in 40-49 year old patients to approximately 1.900 per 100.000 in patients older than 80 years. [4] IPD affects 1% of the world population over the age of 60. [5] Male sex and Caucasian race are associated with a higher prevalence and incidence of IPD. [6, 7]

The pathophysiology of IPD is still not fully understood. It is thought that motor symptoms such as bradykinesia and rest tremor are due to a lack of dopamine in the basal ganglia. To control involuntary muscle contractions, a constant inhibition of muscle contractions by the basal ganglia is needed. If this inhibition is inadequate due to a loss of dopamine in the substantia nigra and globus pallidus pars interna, involuntary muscle contraction can occur, leading to e.g., rest tremor. Another consequence of an inadequate inhibition of muscle contractions is that voluntary movements tend to be more uncoordinated. During voluntary movements a decreased inhibition of selected muscles is needed to allow muscle contractions in a particular movement pattern. If this inhibition is impaired, co-contractions of other muscles can occur or one is not able to stop a movement immediately. Additionally, a reduced concentration of dopamine in the striatum leads to excessive inhibition of movement patterns leading to bradykinesia. [3]

Now we know that dopamine loss is where James William Keys Parkinson was probably aiming at in his 'essay on the Shaking Palsy' in 1817. [8] He described the first cases of the disease with the following definition:

"Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forwards, and to pass from a walking to a running pace; the senses and intellects being uninjured."

Although it has been 200 years, most of the definition he created is still valid. The only major modification of the definition made in the past decades is that the senses and intellect may be affected by IPD as well. These impairments are not only due to the dopamine loss in the basal ganglia but also due to loss of other neurotransmitters or neurons outside the basal ganglia such as in the locus ceruleus, raphe nuclei, nucleus basalis of Meyert, and dorsal motor nuclei. [9, 10] Moreover, the development of alpha-synuclein-containing inclusion bodies in the form of Lewy bodies is not only present in the basal ganglia but also in the cerebral cortex and brainstem, and even in the enteric

nervous system. [11, 12] This formation of Lewy bodies and loss of other neurotransmitters or neurons may lead to so-called non-motor symptoms which may include hyposmia, sleep behavior disorders, neuropsychiatric disorders, constipation, urinary disturbances, and upper aerodigestive tract symptoms such as dysphagia, dysphonia, and dysarthria. [13-15] In fact, these non-motor symptoms may sometimes be present even before motor symptoms occur. One theory is that the first symptoms of IPD are as a matter of fact not the motor symptoms such as bradykinesia or rest tremor, but are non-motor symptoms like for example hyposmia and constipation. Nowadays it is referred to as prodromal Parkinson's disease. [16, 17] One reason for the fact that non-motor symptoms may precede the motor symptoms is that there seems to be a threshold of dopaminergic cell loss in the substantia nigra and striatum before the first motor symptoms occur. This motor symptom threshold is estimated between 40-70% dopaminergic cell loss. Age-related physiological cell loss in the substantia nigra is on the order of 4-5% per decade. In IPD however, an exponential increase in cell loss occurs. Especially in the first decade it is estimated at 45%. Therefore, it may take more than 10 years before motor symptoms occur. [16, 18]

Oropharyngeal dysphagia

More than 80% of patients with IPD will develop oropharyngeal dysphagia (OD) during the course of disease. [4, 19] OD can occur in any stage of IPD. Although severe OD is rare in the earliest stages of the disease, mild or asymptomatic dysphagia can occur. Complaints vary from a prolonged mealtime due to impaired lingual movements and mastication or choking due to aspiration, to no complaints at all. [20] Common findings during flexible endoscopic evaluation of swallowing (FEES) or videofluoroscopic swallowing study (VFSS) are premature anterior and posterior oral spillage of the bolus, pooling of liquids or solids in the pyriform sinus and/or vallecula, and penetration or aspiration of the bolus into the respiratory tract. [4, 21] Pflug et al. found that 95% of patients with IPD showed swallowing abnormalities during FEES, although only 27% reported subjective swallowing complaints. [22] This reduced awareness of the presence and severity of OD is common in IPD, with silent aspiration due to decreased cough reflexes being the most well-known phenomenon. [23] This makes the identification of patients with IPD and OD challenging. Screening tools such as OD-specific screening questionnaires or a water swallowing test are less reliable in IPD, mainly because the water swallowing test depends on signs of coughing and choking. [21, 24, 25] OD-specific screening questionnaires designed solely for IPD such as the Munich Dysphagia test-Parkinson's disease (MDT-PD) or Radboud Oral Motor Inventory (ROMP) seem promising, although sensitivity and specificity remain modest. [25-27] For a disease with such a high prevalence as IPD and a high prevalence of OD, it makes sense to conduct further research into disease-specific screening tools for OD.

The pathophysiology of OD in IPD is poorly understood. Most likely, the lack of dopamine in the basal ganglia contributes to OD, since drugs that replace dopamine and deep

brain stimulation (DBS) restoring dopamine levels in the basal ganglia have shown to improve swallowing function in some patients with IPD. [3, 4, 28] However, besides the basal ganglia other sites in the nervous system are affected as well in IPD. Reduced cortical activation in the supplementary motor area, receiving input from the putamen in the basal ganglia and responsible for motor programming, initiation, and movement execution, is seen in dysphagic patients with IPD. [29] Moreover, Lewy body deposits are found in the dorsal nuclei of the glossopharyngeal and vagal nerve and in the sensory and motor nerves of the pharyngeal wall. [12, 30, 31] Interestingly, not all patients with IPD with pathology in before mentioned structures have swallowing deficits seen during FEES or VFSS. [29] A possible explanation for this finding is that especially during the earliest stages of disease, compensatory mechanisms may occur which prevent patients with IPD from having OD or at least delay the onset of OD symptoms. During magneto-encephalography (MEG) a shift from the affected supplementary motor area to more activation in the lateral motor, premotor, and inferolateral parietal cortices is seen in patients with IPD (mean Hoehn and Yahr scale 2.2) without clinical signs of OD. [29] These 'compensatory' cortices mainly receive information from the less affected brain areas in IPD such as the caudate nucleus in the basal ganglia and cerebellum. Patients with IPD and clinical signs of OD do not show this shift on MEG. [29]

Eating consists of two major dimensions. First, it is a functional activity performed to acquire the sufficient amount of nutrients to maintain one's bodily functions. Second, it has a strong social and cultural dimension. Eating and drinking form an important part of social interaction. Eating with others makes people feel connected to each other, feel happier, more satisfied with their lives, and enables them to have interactions that provide social and emotional support. [32] Traditionally the main focus of clinicians is to diagnose and treat the somatic aspect of swallowing impairment. As a result, the diagnostic workup mainly consists of instrumental assessments such as e.g. FEES, VFSS, or high-resolution manometry (HRM). From an anatomical point of view, swallowing can be divided into four stages and these stages include the oral preparatory, oral, pharyngeal, and esophageal stage. Impairments can occur in each one of these stages in IPD. [33] During FEES and VFSS, boluses of various volumes and consistencies can be administered to the patient while the safety and efficiency of swallowing are observed with a flexible transnasal endoscope or dynamic X-ray respectively. [34] The pharyngeal and part of the oral stage can be visualized using FEES, and the oral preparatory, oral, pharyngeal, and esophageal stage can be observed using VFSS. [34, 35] An advantage of FEES over VFSS is that it directly visualizes the laryngopharynx. This makes it superior in detecting coincidental neoplastic lesions, impaired saliva swallowing, and vocal fold mobility disorders. Furthermore, depending on the type of endoscope used, FEES can be accompanied by transnasal esophagoscopy or stroboscopy to detect esophageal abnormalities or to evaluate vocal fold disfunction when a patient has concomitant voice complaints. The downside of FEES is that for a short period (0.5 to 0.6 seconds) during the pharyngeal stage of swallowing direct visualization is impossible during the

'whiteout'. The pharyngeal air space is obliterated by tissue contacting other tissue during bolus transit. At this moment the light from the distal end of the endoscope is reflected back into the endoscope, resulting in the so-called 'whiteout'. VFSS is slightly superior over FEES in detecting aspiration. [35] Both FEES and VFSS are considered as gold standard to diagnose OD, but should be used with previously mentioned differences kept in mind. [34, 35] Additionally HRM can be used to detect pharyngoesophageal dysphagia. [4] With HRM, circumferential pressure transducers are inserted in the esophagus, and in some cases in the pharynx, in order to measure a location-specific intraluminal pressure during resting stage and swallowing. The intraluminal pressure differs during swallowing. This gives useful information about whether the relaxation, contraction, and resting state of the muscles in that specific location is normal, increased or decreased. [35]

Lately, the increasing interest in the impact of OD on the social and emotional dimensions of well-being, led to the development and increased use of quality of life questionnaires on OD. [36-39] This trend is not only seen in OD assessment. With the development of improved treatment strategies in every aspect of medicine, former deadly diseases become chronic. This evolution led to decreased mortality but also to an aging population suffering from chronic disease. In 2002 the World Health Organization (WHO) described the concept of 'active aging'. This concept encompasses, amongst others, that health policies and health programs should not only improve physical health status, but improve mental and social health status as well. People should be able to participate in society throughout their lives according to their needs, desires, and capacities. [40] This concept is not new since in 1948 the WHO defined 'health' as a state of physical, mental, and social well-being and not merely the absence of disease. However tools to measure social and emotional dimensions of well-being were lacking. In that light, quality of life became more and more important over the past decades. Quality of life is described by the WHO as 'an individual's perception of their position in life in the context of the culture an value systems in which they live, and in relation to their goals, expectations, standards and concerns.' [41-43] To evaluate the individual's perception of their health, patient-reported outcome measures (PROMs) can be helpful tools. PROMs are any status report of a patient's health coming directly from the patient. For OD, the most commonly used PROMs focus on health-related quality of life (HR-QoL), functional health status (FHS), or a combination of both. HR-QoL is a person's quality of life in relation to functions, impairments, and symptoms, whereas FHS focusses on the loss of function due to the disease. [24, 44] For patients with IPD commonly used OD-specific PROMs are the swallowing quality of life questionnaire (SWAL-QOL)[45], the MD Anderson dysphagia inventory (MDADI)[46], and the eating assessment tool (EAT-10)[47]. The items of the SWAL-QOL and MDADI are mainly related to HR-QoL and the items of the EAT-10 mainly related to FHS. To get as close as possible to elaborating the health status of the patient with IPD and OD, it is recommended to use one or more PROMs next to a comprehensive history taking and standardized dynamic swallowing imaging using

FEES and/or VFSS. Considering the different dimensions of 'health' during the diagnostic workup of OD will enable the development of a person-focused treatment strategy.

The treatment of OD in IPD remains challenging as well. The 'one and only' optimal treatment approach for OD in IPD does not exist (yet). Usually, regardless of OD, patients with IPD start with dopaminergic drugs, with mixed effects on OD. [48] OD treatment strategies e.g., bolus modification, postural compensation techniques such as chin-down, or behavioral treatment such as expiratory muscle strength training (EMST)[49] have been successful in some patients with IPD. The choice of treatment can differ per patient and should wherever possible be based on FEES and/or VFSS to assess which treatment or combination of treatment modalities could benefit or not. [48, 50, 51] Moreover, patients with IPD may develop cognitive impairments when IPD progresses. This makes it more challenging to instruct and educate patients and to self-implement learned swallowing strategies in daily life. Other treatment strategies such as video assisted swallowing training (VAST), surface electrical stimulation (SES), thermal tactile stimulation, or the Lee Silverman Voice treatment (LSVT) have a limited body of evidence of their effectiveness. [48, 52] In the past decades DBS has been performed in IPD. [53, 54] Most studies focus on subthalamic nucleus or globus pallidus interna stimulation. It remains unclear whether or not and to what extent DBS has a beneficial effect on swallowing impairment. Some patients seem to improve, others do not or even experience a decline in swallowing function. [28, 55] Site of stimulation and high or low-frequency stimulation may influence the outcomes of DBS on swallowing function. [53, 54] More well-designed studies regarding the effects of DBS on OD in IPD are needed to clarify this matter.

Dysphonia

Up to 90% of patients with IPD present with voice and speech impairment during the course of disease. [56] Reduced loudness, breathy voice, restricted pitch variability, dysregulated speed and pauses, and impaired articulation are some of many different complaints patients may present with. [57, 58] These complaints often result in communication problems, as they may reduce the speech intelligibility. [59] In this thesis we will only focus on voice impairment in IPD.

IPD-related voice complaints can be seen in the earliest stages of the disease. [36] The exact pathophysiology of dysphonia in IPD is still not clear. Similar as for OD, inadequate muscle control seems to play an important role in voice impairment. A decreased closure of the vocal folds due to vocal fold bowing and abnormal vocal fold adduction leads to a more breathy or hoarse voice. [60] This may lead to reduced subglottic air pressure resulting in decreased vocal loudness. [60] There are several brain areas involved in producing a 'normal' voice. The periaqueductal grey matter in the mesencephalon plays an important role in regulating the synchronous activity of respiration and vocal fold tension during phonation. [61, 62] The periaqueductal grey matter receives input from the limbic system, and therefore the voice is also subjected to emotions. [61] Other

areas of the central nervous system involved in voice are the neocortical motor and supplementary motor area, cerebellum, and the thalamo-cortical circuitry including the basal ganglia. These areas are mainly involved in the voluntary control of phonation based on among others auditory feedback. [61] A reduced activation of the supplementary motor area and putamen is seen in patients with IPD and dysphonia compared to healthy controls using functional magnetic resonance imaging (fMRI). [63, 64] Also, a reduction in connectivity of the thalamo-cortical and cortical audio-vocal pathways is seen. [64] In dysphonic patients with IPD, an increased connectivity is seen between the periaqueductal grey matter and the putamen compared to healthy controls. [62] This increased connectivity may be due to spontaneous neural compensation or due to treatment. [62] The exact reason for this increased connectivity has not yet been studied.

Besides inadequate muscular control, impaired sensory perception and sensorimotor integration problems may affect voice production as well. [65] Many patients with IPD have a decreased loudness of voice. When asked to speak louder, some are able to produce a 'normal' loudness of voice. [66] However, when asked, patients with IPD feel that they are speaking too loud. [65, 67] Besides that, when patients with IPD receive instantaneous auditory feedback of their own speech at an artificial louder volume or when they are exposed to an increased back-ground noise, the majority of patients with IPD fail to reduce or increase their loudness of voice accordingly. [66] In healthy controls, auditory feedback mechanisms result in an involuntary and automatic increase or decrease of volume and pitch. They are able to adapt their voice based on the circumstances. The involuntary and automatic adjustment of speech audibility, such as altered loudness, pitch, vowel duration, and speaking rate based on auditory input is called the Lombard effect. [68] The areas in the brain involved in this audio-vocal integration are not fully understood, but may include several areas in the brainstem, such as the superior olivary complex, the periolivary region, and the pontine reticular formation. [69] Possibly these areas are affected in dysphonic patients with IPD as well.

Assessing the voice can be challenging. Mainly because it is hard to define what a normal voice exactly is. 'The normal voice' is dependent on age, gender, culture, and the language spoken and can also easily be influenced by emotions, stress, or fatigue. There are individual preferences of what one considers as a normal or even a beautiful voice. Nonetheless for many diagnostic methods of voice assessment there are normative values, although some with a wide range. [34, 70-72] Voice assessment can be done in several ways. We can distinguish instrumental assessment, perceptual assessment, and PROMs. The most commonly used instrumental assessment tools are videolaryngostroboscopy, aerodynamic measurements, and acoustic analysis. Videolaryngostroboscopy can be used to assess vocal fold vibration patterns and anatomical abnormalities of the larynx. The stroboscopic light source emits light of a certain frequency based on the frequency of vocal fold vibration, 1 or 2 Hz out of phase, usually determined with a microphone. In this way the observer can assess cycle symmetry, lateral and vertical displacement

(amplitude and periodicity respectively), and closure of the vocal folds. If the patient is not able to maintain the frequency or has irregularities in the frequency, the image might be visible as a flutter and videostroboscopic imaging of vocal fold vibration becomes impossible. Aerodynamic measurements such as subglottic air pressure during phonation and mean airflow during phonation can be carried out using a spirometer of pneumotachograph, although the simplest and most frequently used aerodynamic measurement being the maximum phonation time (MPT) only needs a stopwatch. The MPT is the duration to produce a sustained vowel /a:/ at a comfortable pitch and loudness for as long as possible after maximum inspiration. [70, 73] Acoustic analysis is carried out using a microphone linked to voice recording software to analyze the acoustic aspects of the voice such as frequency, loudness and perturbation. [73-75] Audioperceptual assessment of the voice consists of parameters rated by a clinician. The most well-known audioperceptual parameters are the consensus auditory-perceptual evaluation of voice (CAPE-V) or the grade-roughness-breathiness-asthenic-strained (GRBAS) scale. [34, 35, 74] Other parameters of the perceptual assessment are less quantifiable. Musculoskeletal signs such as muscle tension of e.g., the sternocleidomastoid muscle or the infrahyoid muscles, but also ones basic posture may influence vocal physiology at that given time. Also neuropsychological signs can be observed, such as impaired coordination of movements, anxiety or introvert personality-related behavior, which can give vital information of the emotional and neurological status. [34, 35]

Another important dimension of the diagnostic workup for voice impairment are PROMs. There is no consensus on what 'a normal voice' is. One can consider breathiness as an abnormal voice, but some may find that beautiful. Breathiness may be part of one's singing style, but it can determine the first impression that others may have of you. Someone's voice is part of his/her identity. An alteration of that voice may therefore have a major impact on someone's confidence and well-being. [76, 77] Voice-specific PROMs can help to identify dysphonia-specific abnormalities in functional, emotional, and psychological well-being. There are several validated PROMs for voice. Some for a specific disease or subpopulation such as the voice handicap index (VHI) for singers or the Quality of Life in Recurrent Respiratory Papillomatosis questionnaire. Commonly used PROM questionnaires in daily clinical practice are the VHI, Voice-related quality of life (V-RQOL), and Voice symptom Scale (VoiSS). [34, 77]

The scientific evidence of the effectiveness of various therapeutic options for dysphonia in IPD is scarce. Dopaminergic drugs do not seem to affect voice outcomes. In a meta-analysis by Pinho et al. vocal intensity did not significantly differ using dopaminergic drugs. [78] F0 and jitter changed in some studies after dopaminergic drug use. However, the sample sizes of the included studies are small and results should be interpreted with caution. [78] Voice therapy is the treatment of choice for dysphonia in IPD. [71] Standard voice therapy is usually based on the patient's individual needs and may include a broad range of strategies and exercises such as voice or respiratory exercises. A recent meta-analysis

by Xu et al. regarding voice therapy showed a significant improvement of the sound pressure level (SPL) six months after treatment. Moreover the VHI improved after three months with a mean difference of minus ten points. Most of the studies in this meta-analysis used the Lee Silverman voice treatment (LSVT LOUD) program.[79] LSVT LOUD is an intensive training of sixteen individual clinical sessions of one hour in four weeks and exercises to practice at home for 10-15 minutes daily. The aim of LSVT is to improve vocal loudness by focusing on attaining, monitoring, and maintaining a loud voice in different exercises. [80] Other treatment strategies such as Pitch Limiting Voice Treatment (PLVT) or Speak out! Voice program are based on similar intensive 'bootcamp' treatment principles. [81, 82] As mentioned before, standard voice therapy usually includes a broad range of strategies and exercises such as voice or respiratory exercises. Currently, there is no evidence that one particular strategy or exercise regimen is significantly better than the other. A pilot three-armed randomized controlled trial comparing LSVT LOUD versus standard voice therapy versus controls showed a significant improvement of both the LSVT LOUD and the standard voice therapy group compared to the control group. No significant differences were found between the two treatment arms, however the sample size is small. [83, 84]

Few studies are available regarding surgical treatment of dysphonia. Correction of glottal insufficiency from a variety of causes, can be carried out using a thyroplasty type 1 or vocal fold injection augmentation in selected patients with IPD. [85] These are surgical procedures in which one or both of the vocal folds is/are medialized/augmented by placing an implant into the vocal fold. The effect of DBS on dysphonia is still under debate in the literature. [86] There is no evidence of the efficacy of DBS on voice parameters. A study by Morello et al. showed that depending on the high- or low frequency stimulation some parameters may improve. Interestingly high-frequency subthalamic nucleus DBS improves some voice parameters, in particular the GRBAS. However, this type of stimulation has an adverse effect on speech control. So, in an attempt to improve one part of the communication problem, another problem arises. [87]

Outline of this thesis

Part I - PROMs of swallowing and voice function in Parkinson's disease
Chapter 2 describes the validation of the MDADI for patients with OD of a neurogenic etiology.

Chapter 3 presents the exploratory, prospective clinical study regarding whether changes in swallowing- and voice related quality of life are associated with progression of IPD. Furthermore the relationship between a patient's perception of both voice and swallowing complaints in IPD is examined using VHI, MDADI, and two visual analogue scales (VAS).

Chapter 4 elaborates on the relationship between patient and investigator reported outcome measures (PROMs versus IROMs) of OD in patients with IPD using neural network analysis. To explore possible disagreements between PROMs and IROMs two-step cluster analysis was used to find a reason for these disagreements.

Part II - An update on the treatment of OD and dysphonia in IPD
Chapter 5 provides a systematic review of the literature on treatment effects for OD in IPD.

Chapter 6 presents a new treatment strategy for dysphonia in IPD: surface electrical stimulation (SES) of the neck adjacent to intensive voice therapy. In other diseases some promising results in voice outcome were seen by using SES to the neck. In chapter 6 we evaluated this treatment strategy for patients with IPD.

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PART I

Patient reported outcome measures of swallowing and voice function in Parkinson's disease

2

Validation of the Dutch version of the MD Anderson Dysphagia Inventory (MDADI) for neurogenic patients

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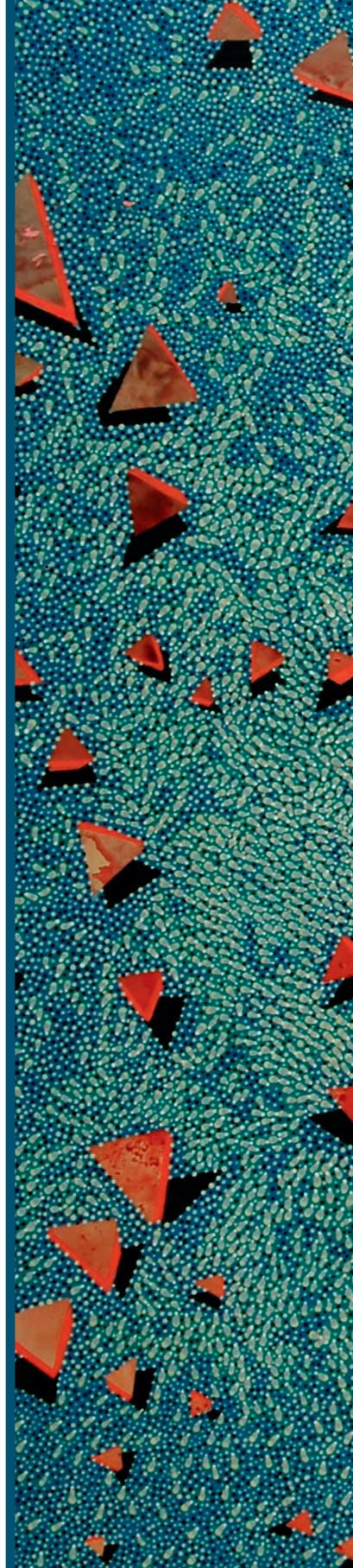


Abstract

Background/aim
The aim of this study was to validate the Dutch-language version of the M.D. Anderson Dysphagia Inventory (MDADI) for patients with neurogenic oropharyngeal dysphagia (OD).

Methods
One hundred and seventy-eight patients with neurogenic OD and 92 healthy control subjects completed the MDADI and the Dutch version of the Swallowing Quality-of-Life Questionnaire (SWAL-QOL-NL). Exclusion criteria were: suffering from a concurrent head-and-neck oncological disease, scoring below 23 on a Mini Mental State Examination, being older than 85 years, and being illiterate or blind. None of the patients was in a palliative state of disease. Floor and ceiling effects, known-groups validity, internal consistency, construct validity, and criterion validity were assessed.

Results
The MDADI total score showed no floor or ceiling effects for the patient group. Known-groups validity was confirmed by group differences in score distributions between patients and healthy control subjects. The internal consistency showed Cronbach's α-values ranging from 0.77 to 0.92. Correlations between the MDADI subscales and SWAL-QOL-NL domains were moderate to strong: 0.71, 0.70, and 0.62 (convergent construct validity). Correlations between the MDADI scores and the SWAL-QOL-NL domains general burden, food selection, eating duration, communication, mental health, social functioning, and frequency of symptoms were moderate to strong, ranging from 0.41 to 0.75. Weak correlations (<0.4) were found between the MDADI scores and the SWAL-QOL-NL domains eating desire, sleep, and fatigue.

Conclusion
The results of this study show that the Dutch translation of the MDADI is a psychometrically validated and suitable dysphagia-specific quality-of-life questionnaire for patients with neurogenic OD.

Introduction

Oropharyngeal dysphagia (OD) is a common finding in patients suffering from neurogenic disorders. Swallowing impairment can be acute or chronic in nature. Acute OD is observed in patients after a stroke, head injury, neurosurgical intervention, or in patients with Guillain- Barré syndrome, for instance. Patients who do not recover after stroke can develop chronic OD. Degenerative OD is seen in patients with progressive neurological diseases such as Parkinson's disease, amyotrophic lateral sclerosis, myasthenia gravis, Huntington's disease, myotonic dystrophy type 1, and multiple sclerosis.[1] All 4 stages of the swallowing process can be affected: the preparatory, the oral, the pharyngeal, and the esophageal stage. Gener- ally speaking, as neurological disease severity increases, so does OD.[1] The prevalence of OD in neurogenic patients ranges from 3 to 50% in stroke patients [2,3] and to almost 100% in patients suffering from Huntington's disease.[4] OD can cause weight loss, malnutrition, social isolation, aspiration pneumonia, and decreased health- related quality of life (QoL).[5]

A study performed in 5 European countries showed that swallowing disorders have a major impact on the health-related QoL of dysphagic patients.[6] Some studies reported that dysphagia-specific QoL was poorly correlated with, among other things, the severity of OD as measured using fiberoptic endoscopic evaluation of swallowing (FEES) and videofluoroscopy of swallowing (VFFS).[7–9] Therefore, used alongside these instrumental assessments, dysphagia-specific QoL questionnaires add value by providing insight into patients' perception of OD, which can be taken into account in the treatment plan.

Nowadays several validated dysphagia-specific QoL questionnaires are available in the Dutch language: the Swallowing Quality-of-Life Questionnaire (SWAL-QOL, 44 items) [10-12], the Deglutition Handicap Index (30 items) [13,14], the Dysphagia Handicap Index (25 items) [15,16], and the M.D. Anderson Dysphagia Inventory (MDADI, 20 items).[14,17] The multidisciplinary dysphagia clinics in the Netherlands are mainly visited by patients with OD of head-and-neck oncological or neurological origin.[18] A smaller proportion of patients have a heterogeneous etiology of OD: cervical osteophyte formation, frail elderly age, Zenker diverticulum, cervical hernia surgery, congenital mental impairment, syndromic diseases, and so on. As such, these dysphagia clinics of- fer a suitable setting for deploying a questionnaire that could be applied to all OD patients irrespective of the underlying etiology. Among all questionnaires available in the Dutch language, the MDADI seemed the most suit- able choice, because it allows global judgment of the dysphagia-specific QoL and it is easy to implement in a busy daily otorhinolaryngological outpatient clinic for OD. Other questionnaires such as the SWAL-QOL-NL and the Deglutition Handicap Index are longer than the MDADI and take more time to complete. The aim of this study was to validate the Dutch version of the MDADI for patients with neurogenic OD.

Methods

Subjects

Patients with neurogenic disorders and OD were recruited from an otorhinolaryngological outpatient clinic for OD at a tertiary university referral hospital between January 2009 and October 2016. Data were also collected from healthy control subjects in the local community who had no swallowing complaints and whose overall health was good. Exclusion criteria were: a Mini Mental State Examination score below 23 points [19], blindness, illiteracy, a history of head and neck cancer (HNC), and age below 18 or above 85 years. Informed consent was obtained from all patients for clinical purposes, and the study protocol was approved by the medical Ethics Committee according to the non-WMO obligatory Medical Research Involving Human Subjects Act.

M.D. Anderson Dysphagia Index

The MDADI is a self-administered, psychometrically validated dysphagia-specific questionnaire for HNC patients that is de- signed to assess the impact of OD on health-related QoL.[17] Like the original English version, the validated Dutch translation of the MDADI consists of 20 items pooled in 4 subscales: the global scale (1 item); the functional scale (5 items); the physical scale (8 items); and the emotional scale (6 items).[14] The global assessment question (MDADI-G) evaluates the effect of swallowing disability on overall QoL. The functional scale (MDADI-F) illustrates the im- pact of OD on daily activities. The physical scale (MDADI-P) measures the patient's self-perception of the physical impact of OD. The emotional scale (MDADI-E) represents the patient's affective response to the swallowing disorder in terms of embarrassment, self-esteem, and self-consciousness. All items are scored on a 5-point scale (1–5), where "1" corresponds to "total agreement" and "5" to "total disagreement." In the original version of the MDADI, all but 2 items were scored such that higher scores indicated higher functioning.[17] In the Dutch translation, it was decided to use a uniform scoring method. [14] Thus, by adjusting the scoring of these 2 items, low scores came to indicate low functioning and high scores high functioning. Responses on all domains were summed to calculate the total score (MDADI-T). The maximum score is 100, indicating high functioning, and the minimum score is 20, indicating poor functioning.

Dutch Version of the SWAL-QOL

The SWAL-QOL questionnaire was designed to evaluate the impact of OD on health-related QoL in dysphagic patients. It consists of 44 items divided among 11 domains: general burden (2 items); food selection (2 items); eating duration (2 items); eating desire (3 items); fear of eating (4 items); sleep (2 items); fatigue (3 items); communication (2 items); mental health (5 items); social functioning (5 items); and frequency of symptoms (14 items). Each item is scored on a 5-point scale: the higher the score, the better the OD-specific QoL. Completion of the questionnaire takes 15–30 min. The Dutch version

of the SWAL-QOL (SWAL-QOL- NL) is considered the gold standard for determining dysphagia- specific QoL in patients with OD. [11, 12, 14, 16, 20, 21]

Two studies translated the SWAL-QOL questionnaire into the Dutch language and validated it for a mixed population of dysphag- ic patients: SWAL-QOL-NL and DSWAL-QOL.[11,12]. In the current study, the SWAL-QOL-NL was used as a gold standard for the validation of the MDADI. In the validation study of the SWAL-QOL- NL, 2 domains – "eating desire" and "communication" – did not reach sufficient internal validity (Cronbach's $\alpha = 0.67$ and 0.6, respec- tively) and were removed from the final questionnaire. As the internal consistency is greatly dependent on the underlying population under scrutiny, it was decided to use the 44 items of the SWAL-QOL version, which was used to validate the original SWAL-QOL-NL, in the present study too in order to establish and present the psychometric properties of the questionnaire for the current target sample.

Statistical Analysis

Floor and ceiling effects of the MDADI-T and subscales were defined as evident effects when 15% or more of the patients obtained the lowest or highest possible scores and were recorded as proportions (%) of the extreme scores (20–100).[22] Given the skewness of the data, the 2 groups (patients and healthy control subjects) were compared for known-groups validity using the Mann-Whitney U test. The internal consistency of the MDADI and the SWAL-QOL-NL was determined using Cronbach's α-value. The lowest acceptable level of internal consistency was set at $\alpha < 0.70$.[22] Convergent construct and criterion validities were assessed using Spearman's correlation, as were all validities. Correlations between 0.00 and 0.19 were considered very weak, be- tween 0.20 and 0.39 weak, between 0.40 and 0.59 moderate, between 0.60 and 0.79 strong, and between 0.80 and 1.0 very strong.[23] Regarding convergent construct validity, it was hypothesized that the MDADI-F would show a strong correlation with the SWAL-QOL-NL domain "social functioning," the MDADI-P with the SWAL-QOL-NL domain "frequency of symptoms," and the MDADI-E with the SWAL-QOL-NL domain "mental health." Regarding discriminant construct validity, it was hypothesized that the SWAL-QOL-NL domains "sleep" and "fatigue" would show a weak correlation with all MDADI subscales. Statistical analysis was performed using SPSS 24 (IBM, SPSS Inc., Chicago, IL, USA). Given the multitude of statistical tests conducted, type I error inflation was controlled for via step-down Bonferroni (Holm) correction. A statistical effect was determined if the p value was <0.05 following adjustment for multiple testing. Table 1 provides the reader with a short definition of some of the statistical terms used here.

Table 1. Definition of statistical terms

Term	*Definition*
Floor and ceiling effect	The number of respondents that achieved the lowest or highest possible score
Known-groups validity	The extent to which it is possible to discriminate between two known groups
Internal consistency	The extent to which items in a (sub)test measure the same concept
Construct validity	The extent to which scores of a questionnaire correlate with other measurements concerning the hypotheses put forward
Convergent construct validity	The extent of correlation between scores on two different questionnaires that aim to measure the same concept (the closer to 1 the higher the correlation)
Discriminant construct validity	The extent of correlation between scores on two different questionnaires that do not aim to measure the same concept (the closer to 0 the higher the correlation)
Criterion validity	The extent to which scores of a questionnaire correlate with the gold standard measurement
Cronbach's alpha	An index of internal consistency of items
Correlation coefficient	The extent of correlation between two independent variables expressed as a value between -1 and 1. 1 meaning perfect relationship, 0 no relationship and -1 a negative relationship

Results

Characteristics of the Population

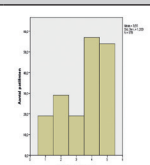
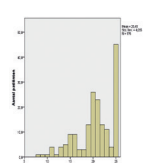
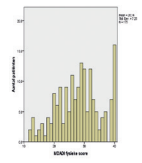
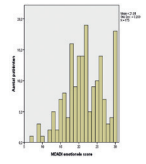
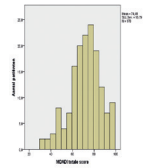
The patient group comprised 178 persons (n = 113 men, 64%) with a mean age of 59 years, ranging from 21 to 82 (SD 15). Their diagnoses were Parkinson's disease (n = 94, 52.8%), myotonic dystrophy type 1 (n = 60, 33.7%), and other neurogenic diseases such as stroke, multiple sclerosis, and amyotrophic lateral sclerosis (n = 24, 13.5%). All included patients completed the Dutch version of the MDADI and the SWAL-QOL-NL. Ninety-two healthy control subjects (45 men) were recruited from the local community, and their mean age was 47 years, ranging from 20 to 82 (SD 15). Fifty-five healthy subjects completed the MDADI and 37 completed the SWAL-QOL- NL. All subjects were native speakers of Dutch.

Floor and Ceiling Effects

Tables 2 and 3 present the descriptive statistics for the healthy control subjects and the patient group. No floor effect was detected for any of the MDADI subscales in the

patient group. However, a ceiling effect was found for the MDADI-G and the MDADI-F subscales. In the healthy control group, a ceiling effect was found for all MDADI subscales and the MDADI-T.

Table 2. Group differences in MDADI scores

MDADI subscales	Healthy control group (N = 55)	Patient group (N = 178)			p-value
	Median (25^{th}; 75^{th})	Median (25^{th}; 75^{th})	ceiling effect (%)	frequency distribution	
Global	5 (5-5)	4 (2-5)	30.3		<.001
Functional	25 (25-25)	21 (19-35)	25.3		<.001
Physical	40 (40-40)	29 (23-25)	9.0		<.001
Emotional	30 (29-30)	22 (18-25)	10.1		<.001
Total	100 (99-100)	75 (65-85)	8.4		<.001

MDADI, M.D. Anderson Dypshagia Inventory; p value assessed by the Mann-Whitney U test

Known-Groups Validity

The median MDADI scores (total and subscales) were significantly lower for the patient group than for the healthy control group (Table 2). The median (25th–75th percentiles) of the MDADI-T scores for patients was 75 (65–85); for the healthy control group it was 100 (99–100; $p < 0.001$). As such, the MDADI questionnaire was able to distinguish between those with and those without OD, as evidenced by statistically significant group differences for all MDADI subscales and MDADI-T (Table 2).

Internal Consistency

Cronbach's α ranged from 0.77 to 0.92, showing a good internal consistency; that is, the items on each subscale of the MDADI questionnaire measure the same general construct (Table 4). The internal consistency of the domains of the SWAL-QOL-NL appeared to be good too, with values ranging from $\alpha = 0.76$ to 0.90. Only the domain "frequency of symptoms" showed a weaker correlation between the items ($\alpha = 0.62$).

Table 3. Median and percentiles of SWAL-QOL-NL scores for the healthy control and patient groups

SWAL-QOL-NL domains	Healthy control group (*n* = 37), median (25th–75th percentiles)	Patient group (*n* = 178), median (25th–75th percentiles)
General burden	100 (100–100)	63 (38–88)
Food selection	100 (100–100)	75 (63–100)
Eating duration	100 (100–100)	50 (25–89)
Eating desire	100 (92–100)	75 (48–100)
Fear of eating	100 (100–100)	91 (75–100)
Sleep	88 (75–100)	75 (38–88)
Fatigue	92 (79–100)	58 (33–75)
Communication	100 (100–100)	63 (38–75)
Mental health	100 (100–100)	80 (60–95)
Social functioning	100 (100–100)	75 (55–100)
Frequency of symptoms	88 (75–100)	64 (95–100)

SWAL-QOL-NL, the Dutch version of the Swallowing Quality- of-Life Questionnaire.

Table 4. Internal consistency of MDADI and SWAL-QoL-NL subscales

Instrument	*Number of items*	*Cronbach's alpha*
MDADI		
Global	1	-
Functional	5	0.77
Physical	8	0.85
Emotional	6	0.79
Total	19	0.92
SWAL-QoL-NL		
Burden	2	0.90
Food selection	2	0.80
Eating duration	2	0.80
Eating desire	3	0.78
Fear	4	0.80
Sleep	2	0.82
Fatigue	3	0.85
Communication	2	0.76
Mental health	5	0.88
Social functioning	5	0.93
Symptoms	14	0.62

MDADI, M.D. Anderson Dysphagia Inventory; SWAL-QOL- NL, the Dutch version of the Swallowing Quality-of-Life Questionnaire.

Construct Validity

Moderate to strong correlations were found between the MDADI-F subscale and the domain "social functioning" of the SWAL-QOL-NL, between the MDADI- P subscale and the SWAL-QOL-NL domain "frequency of symptoms," and between the MDADI-E subscale and the SWAL-QOL-NL domain "mental health" (Table 5). The correlation coefficients between the do- mains "sleep" and "fatigue" of the SWAL-QOL-NL and the different subscales of the MDADI were either low or very low (Table 5). These results support the hypothesis about convergent and discriminant construct validity.

Table 5. Criterion validity: correlations between the MDADI subscales and SWAL-QOL-NL domains in the patient group

SWAL-QOL-NL domains	MDADI subscales				
	global scale p value	functional scale p value	physical scale p value	emotional scale p value	total scale p value
General burden	0.573 ≤0.001	0.488 ≤0.001	0.549 ≤0.001	0.571 ≤0.001	0.590 ≤0.001
Food selection	0.523 ≤0.001	0.513 ≤0.001	0.620 ≤0.001	0.577 ≤0.001	0.671 ≤0.001
Eating duration	0.484 ≤0.001	0.422 ≤0.001	0.598 ≤0.001	0.519 ≤0.001	0.563 ≤0.001
Eating desire	0.328 ≤0.001	0.372 ≤0.001	0.375 ≤0.001	0.369 ≤0.001	0.408 ≤0.001
Fear of eating	0.381 ≤0.001	0.333 ≤0.001	0.446 ≤0.001	0.450 ≤0.001	0.427 ≤0.001
Sleep	0.204 0.018	0.182 0.032	0.229 0.012	0.231 0.012	0.252 0.009
Fatigue	0.284 ≤0.001	0.110 ≤0.145	0.247 0.009	0.249 0.009	0.232 0.012
Communication	0.448 ≤0.001	0.458 ≤0.001	0.489 ≤0.001	0.513 ≤0.001	0.522 ≤0.001
Mental health	0.614 ≤0.001	0.591 ≤0.001	0.672 ≤0.001	0.701 ≤0.001	0.719 ≤0.001
Social functioning	0.653 ≤0.001	0.709 ≤0.001	0.663 ≤0.001	0.736 ≤0.001	0.754 ≤0.001
Frequency of symptoms	0.516 ≤0.001	0.451 ≤0.001	0.624 ≤0.001	0.523 ≤0.001	0.626 ≤0.001

MDADI, M.D. Anderson Dysphagia Inventory; SWAL-QOL-NL, the Dutch version of the Swallowing Quality-of-Life Questionnaire. In each SWAL-QOL-NL domain, the first number indicates Spearman's correlation coefficient.

Criterion Validity

Table 5 shows the correlations between the MDADI subscales and the SWAL-QOL-NL domains in the patient group. All correlations were significant, except for the correlation between the MDADI-F subscale and the SWAL-QOL-NL domain "fatigue."

Discussion

Instrumental assessment tools such as FEES or VFS provide valuable information about the nature and severity of a swallowing disorder but they do not provide any information on the dimension of how the swallowing impairment affects a patient's life. Dysphagia-specific health-related QoL questionnaires can help the patient formulate his/her perception of the swallowing disorder.[9-12] Moreover, these questionnaires enable clinicians to detect what is important to the patients; the subjective responses can be useful when discussing patients' motivation for therapy. Therapy effects of OD treatment in HNC patients can be further quantified using for example the MDADI or the SWAL-QOL-NL.

Clinical practice has a manifest need for validated, easy-to-use dysphagia-specific questionnaires that can be filled in quickly by patients with neurogenic OD. Such a questionnaire is currently not available in the Dutch language. In the present study the preferred dysphagia-specific QoL questionnaire to validate for neurogenic patients in the Dutch language was the MDADI as the MDADI was already validated for Dutch HNC patients and can be distributed for both patient groups during clinical practice at otorhinolaryngological outpatient clinics for OD. The MDADI questionnaire is considerably shorter and therefore more convenient for neurological patients compared to the validated alternatives available in the Dutch language (SWAL-QOL, Deglutition Handicap Index).[13,14] The items in the MDADI questionnaire are formulated in such a way that they do not contain any head-and- neck cancer-specific elements. This too was an argument for choosing this questionnaire, which had already been officially translated into Dutch. The time required to complete the MDADI questionnaire by neurogenic patients visiting the present outpatient setting was on average 5 min. The original MDADI study by Chen et al. [17] examined psychometric properties of the questionnaire comprising known-groups validity, reliability (internal consistency and test-retest), construct validity, and criterion validity. The results showed that the MDADI is a reliable and valid questionnaire to evaluate the impact of OD on HNC patients' health-related QoL.[17] However, the MDADI was never validated in a group consisting entirely of neurological patients. To our knowledge, this is the first study intended to validate the Dutch version of the MDADI questionnaire for patients with neurogenic OD.

Divergent statistical validation techniques were applied across the published MDADI validation studies in different languages (Dutch, Japanese, Portuguese, Italian, Chinese, Swedish, etc.).[14,24-30] These studies assessed different sets of psychometric properties such as floor and ceiling effects, known-groups validity, reliability (internal consistency and test-retest reliability), construct validity, criterion validity, and so on. To validate the MDADI questionnaire in patients with OD of neurological origin in the present study, the following aspects were examined: floor and ceiling effect, known-groups validity, internal consistency, construct validity, and criterion validity. Similar to the

study validating the MDADI for HNC patients, there was no floor and/or ceiling effect for the MDADI-T in neurogenic patients in the present study. Analysis of the individual MDADI subscales identified a ceiling effect for MDADI-G and -F. However, when all the subscales were observed in conjunction (MDADI-T), only 8.4% of the patients achieved high scores (thus a weak indication for a ceiling effect). Furthermore, the results showed that the distributions of the MDADI scores differed significantly between subjects with and without OD (patients vs. healthy control subjects). When comparing the results with those of the Swedish MDADI validation study [24], which is the only one that included a group of neurogenic patients, the internal consistency for the MDADI-T score of neurogenic patients was found to be the same as in the present study. For the floor and ceiling effects, similar results were found. The construct validity of the Swedish study could not be compared with that of the present study as the Swedish group had tested the MDADI against the Short- Form 36 and the Hospital Anxiety and Depression Scale.

The criterion validity ranged from acceptable to high. The correlations between the MDADI-T and the SWAL-QOL-NL domains “sleep” and “fatigue” were weak. The Dutch MDADI validation study by Speyer et al. [14] found a marginally higher correlation coefficient for “sleep” and “fatigue” but their results were similar to the findings in the present study. The reason for these weak correlations can probably be found in the fact that the specific domains “sleep” and “fatigue” of the SWAL-QOL-NL are not rep- resented by similar items in the MDADI questionnaire. The Dutch version of the MDADI is a valid questionnaire that allows clinicians to gain insight into the dysphagia-specific QoL of dysphagic patients with neurogenic disorders. Implementation of this questionnaire as part of a multidimensional swallowing assessment for neurological patients in daily clinical practice is recommended because it may add clinical value when used alongside instrumental swallowing assessment tools such as FEES and VFS, which visualize other dimensions of the swallowing impairment. Information on the dimension how the patient perceives the impact of OD on his/her health-related QoL, in combination with clinical and instrumental swallowing evaluation, provides the opportunity to offer a patient- tailored treatment program based on his/her needs and expectations. Consequently, it might improve patients’ compliance to and satisfaction about the treatment.

Limitations and Future Directions

With regard to reliability, only the internal consistency was studied. In the future, test-retest reliability could be examined by filling in the MDADI questionnaire at 2 different measurement times.[31] Responsiveness of the questionnaire could be examined as well if the MDADI could be filled in at several time points by the same patients with neurogenic OD. That would reveal whether the questionnaire captures changes in the health status, changes in disease progression, and changes due to therapy effects. Finally, the patient

population in this study was recruited in one location at an otorhinolaryngological outpatient clinic for OD.

Conclusion

The results of this study show that the Dutch translation of the MDADI is a psychometrically validated and suitable dysphagia-specific QoL questionnaire for patients with neurogenic OD.

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3

Voice- and swallow-related quality of life in idiopathic Parkinson's disease

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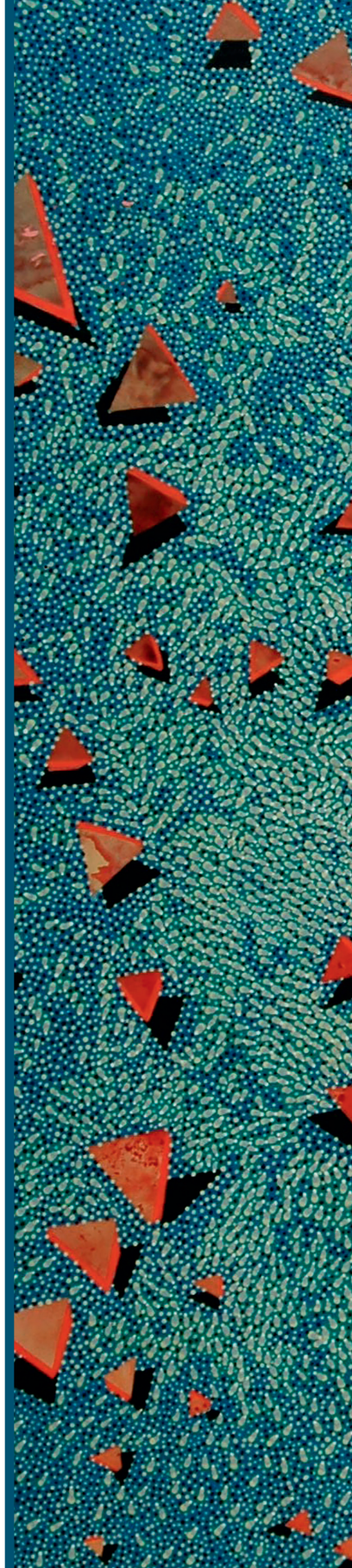

Abstract

Objectives/hypothesis
This study explores whether changes in OD and dysphonia-specific QoL are associated with progression of idiopathic Parkinson's disease (IPD). Furthermore, it examines the relationship between patients' perception of both voice and swallowing disorders in IPD.

Study design
Prospective clinical study, quality of life (QoL).

Methods
One-hundred mentally competent Patients with IPD with voice and swallowing complaints were asked to answer four QoL questionnaires (Voice Handicap Index, MD Anderson Dysphagia Inventory, Visual Analog Scale [VAS] voice, and Dysphagia Severity Scale [DSS]). Differences in means for the QoL questionnaires and their subscales within Hoehn and Yahr stage groups were calculated using one-way analysis of variance. The relationship between OD and dysphonia-specific QoL questionnaires was determined with the Spearman correlation coefficient.

Results
Scores on both voice and swallow questionnaires suggest an overall decrease in QoL with progression of IPD. A plateau in QoL for VAS voice and the DSS was seen in the early Hoehn and Yahr stages. Finally, scores on dysphonia-specific QoL questionnaires were significantly correlated with OD-specific QoL outcomes.

Conclusions
OD and dysphonia-specific QoL decreases with progression of IPD. A significant association was found between OD and dysphonia-specific QoL questionnaires. Healthcare professionals can benefit from OD and dysphonia-specific QoL questionnaires in a multidimensional OD and dysphonia-assessment protocol. The patient's perception of his/her swallowing and voice disorders and its impact on QoL in IPD should not be disregarded.

Introduction

Dysfunctions such as dysphonia and oropharyngeal dysphagia are common findings in idiopathic Parkinson's disease (IPD).[1, 2] Up to ninety percent of IPD patients will develop voice disturbances during the course of disease.[3] These may include breathy hoarseness, reduced loudness, and restricted pitch variability.[2, 4] Moreover, dysphonia is associated with concomitant swallowing disturbances [3]. Oropharyngeal dysphagia, bringing an increased risk of aspiration pneumonia, might be the most life-threatening dysfunction in IPD, with a prevalence ranging from sixteen to eighty-seven percent. [1, 5]

Validated and commonly used quality of life (QoL) questionnaires such as the Voice Handicap Index (VHI) [6] or MD Anderson Dysphagia Inventory (MDADI) [7] are useful tools to assess the patient's subjective perception of dysphonia and dysphagia, respectively. Although voice and swallowing disturbances can have a major impact on QoL in IPD, little is known about their impact on QoL as the disease becomes more severe.[8-10]

Skodda et al. [2] reported that voice disturbances, assessed with acoustic voice measures, increased with progression of disease. Also, dysphagia tends to become more severe with progression of disease, as described in a meta-analysis by Kalf et al.[1] This meta-analysis included several studies using single-item swallowing questions, surveys, gastro-intestinal QoL questionnaires, and swallowing speed measurements to assess patients' perception of their performance. However, the data used were clinically and statistically heterogeneous, and only a few OD and dysphonia-specific QoL questionnaires were included.

The aim of our study is to explore whether the patient's perception of voice and swallowing disturbances and the impact of these perceptions on QoL worsen with progression of IPD, as measured with validated and commonly used QoL questionnaires on voice and swallowing. A second point of interest is the relationship between these validated QoL questionnaires in IPD. To our knowledge, this is the first study to examine these questionnaires in that light for IPD.

Materials and methods

Participants
Patients with IPD having voice and swallowing complaints were recruited from diverse hospitals all over the Netherlands. IPD was diagnosed by a neurologist, and the severity of disease was assessed using the Hoehn and Yahr staging scale (H&Y scale).[11] The range of scores on this scale is 1–5, where 1 stands for unilateral involvement, usually with minimal or no functional disability, and 5 indicates confinement to bed or wheelchair unless aided.[11] The inclusion criteria were based on a broad definition of swallowing complaints. These ranged from mild to severe and covered difficulties in oropharyngeal

passage and bolus formation, slow eating, coughing while drinking, severe aspiration, abnormal amounts of residue, weight loss, etc. Similarly, dysphonic complaints ranged from mild to severe and covered breathy hoarseness, reduced loudness, harsh or rough voice, etc.

There were several exclusion criteria: being older than 85 years (presbyphagia); having had speech therapy during the previous six months (benefit of treatment and attention); scoring below 23 on a Mini Mental State Examination (MMSE) [12]; suffering from severe depression or having another known psychiatric diagnosis; not knowing Dutch; being illiterate or blind; undergoing an unstable period of IPD (periods with large fluctuations, especially in motor function); or having the medication regimen changed within the past six weeks. Also, patients with a history of radiotherapy or extensive surgery in the head and neck region were excluded. Written informed consent was obtained from all patients, and the study protocol was approved by the medical ethics committee of the Maastricht University Medical Centre.

Evaluation measurements

All patients underwent a standardized examination in the same hospital by the same multidisciplinary team in order to guarantee standardized data collection. The protocol stipulated the following: a clinical examination by a laryngologist; fiberoptic endoscopic evaluation of swallowing (FEES); videofluoroscopy of swallowing (VFS); videolaryngostroboscopy; a clinical observation of oral intake by a speech and language pathologist; QoL questionnaires; body mass index (BMI) measurement; and MMSE to ensure eligibility. For this study, we investigated results from the four QoL questionnaires on voice or swallowing issues: the Dutch versions of the MDADI [7] and VHI [6]; and two visual analog scales. The MDADI is a self-administered, psychometrically validated questionnaire used to assess the impact of dysphagia on QoL.[13] It consists of 20 items, 19 of which are divided into three subscales -- emotional (six items; MDADI-E), functional (five items; MDADI-F), and physical (eight items; MDADI-P) --, and one global assessment question (single item; MDADI-G) to evaluate the effect of swallowing disabilities on overall QoL. The functional subscale illustrates the impact of dysphagia on daily activities. The physical subscale refers to the patient's self-perception of swallowing difficulty. And the emotional subscale represents the patient's affective response to the swallowing disorder in terms of embarrassment, self-esteem, and self-consciousness. All items are rated on a five-point scale (1-5), where 1 corresponds to 'strongly agree' and 5 to 'strongly disagree'. The maximum total score is 100 and the minimum is 20. A low score indicates low functioning, a high score high functioning. The MDADI is considered to have good test-retest reliability.[13]

The Dutch version of the VHI was used to assess dysphonia-specific QoL. The VHI is a validated questionnaire measuring voice problems in daily life.[6] It consists of 30 items, again, divided into three subscales: emotional (VHI-E), functional (VHI-F), and

physical (VHI-P). Each item can be scored from 0 to 4, with 0 as 'never' and 4 as 'always'. Summing the scores on the 30 items yields a total VHI score ranging from 0 to 120. The higher the score, the higher the degree of patient-perceived vocal handicap.

The self-reports were scored by means of two visual analog scale (VAS) tools. A VAS is a psychometric response scale that can be used to measure subjective characteristics or attitudes. Patients specify their level of agreement with a statement or question by indicating a position along a continuous line between two end-points. First, a Dysphagia Severity Scale (DSS) was used to assess today's quality of swallowing and the extent of impairment experienced by the patient by scoring from 0 to 100, with 0 being 'can't swallow at all' and 100 standing for 'normal swallow' [13]. Next, to evaluate the self-reported voice function and the extent of voice impairment experienced by the patient, a three-item outcome VAS voice was used.[14] The first item refers to the overall severity of the voice disorder (VAS severity), the second to the psychosocial impact of the disorder on one's occupational activities if relevant (VAS profession), and the third to the impact of the voice complaints on daily living (VAS social life). A score of 0 indicates 'normal voice' and 100 'severe voice impairment'. All examinations and questionnaires were performed during the 'on' motor phase (within 90–120 minutes after intake of antiparkinsonian medication) [15].

Statistical analysis

Descriptive data analysis of patient characteristics was performed, and normality was tested using the Shapiro-Wilk test. To determine the association between OD and dysphonia-specific QoL questionnaires, Spearman's correlation coefficient (r_s) was calculated. Differences in the means of the QoL questionnaires and their subscales that showed up with increasing H&Y stage were calculated using one-way analysis of variance (ANOVA). That test was followed by pairwise comparison of means using post-hoc Tukey HSD tests, involving corrections for multiple comparisons. Only three subjects with an H&Y score of 5 met the inclusion criteria. Therefore H&Y stages 4 and 5 were combined to create one 'severe' H&Y group (further referred to as H&Y stage 4+). All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 22.0 (Armonk, NY: IBM Corp.).

Results

Patient characteristics

A total of 100 mentally competent IPD patients with dysphonia and oropharyngeal dysphagia were enrolled in this study. Baseline characteristics are displayed in table 1.

Ninety-four percent (N=82) of the patients scored ten or more points on the VHI-T, indicating a pathologic VHI score (cut-off score of ten) [6]. All questionnaires were reviewed for possible floor and ceiling effects, noting the number of respondents who

obtained the lowest or highest possible scores. The floor or ceiling effect was considered negligible because less than four percent (N=3) of the respondents got the lowest or highest possible score for MDADI-T, and less than five percent (N=4) for VHI-T. On the DSS, nine reported the lowest or highest possible score; for the VAS voice 'severity', 'profession', and 'social life', the lowest or highest scores were reported by nine, ten, and seven respondents, respectively.

Table 1. Baseline characteristics

	Hoehn and Yahr scale				total
	1	2	3	4+	
Gender (M/F)	23/4	23/8	16/5	11/10	73/27
Median age (yr)	68	65	66	69	67
Completed correctly (patients)					
MDADI	26	28	18	19	91
DSS	26	30	18	19	93
VHI	24	28	15	19	86
VAS severity	25	27	20	21	93
VAS profession	20	22	15	14	71
VAS social life	25	26	20	21	92

Hoehn and Yahr scale 4+: the combined scale 4 and 5
Abbreviations; VHI: Voice Handicap Index,
MDADI: MD Anderson Dysphagia Inventory,
DSS: Dysphagia Severity Scale, M/F: male/female

Severity of disease

Both OD and dysphonia-specific QoL tended to decrease with progression of disease. As shown in figures 1 and 2, mean scores of dysphonia-specific QoL questionnaires rise with advancing H&Y stage, indicating that QoL decreases as IPD progresses. Significant differences in the means of the VHI-T, VHI-P, VHI-F (*p*-value: 0.008, 0.003, and 0.002 respectively), and of the VAS severity and VAS social life (*p*-value: 0.007 and 0.044 respectively) were revealed with increasing H&Y stage using ANOVA. Pairwise comparisons of means revealed significant differences in means of dysphonia-specific QoL between H&Y stages 1 and 4+, and between stages 2 and 4+ (table 2). VHI-E (*p*-value: 0.070) and VAS profession (*p*-value: 0.070) did not reveal significant differences with progression of disease.

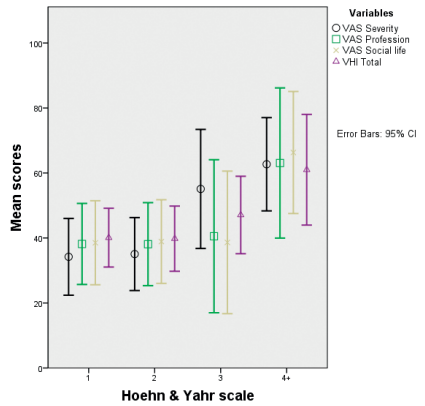

Figure 1. Mean scores of VAS voice and questionnaire subscales per Hoehn and-scale

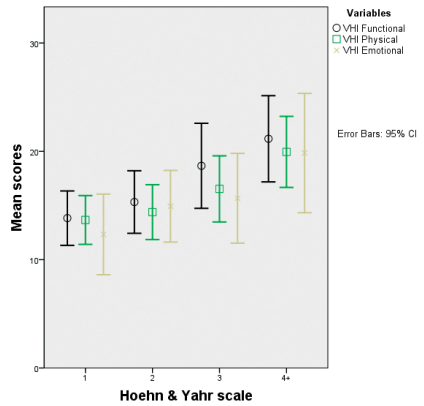

Figure 2. Mean scores of VHI questionnaires per Hoehn and Yahr scale

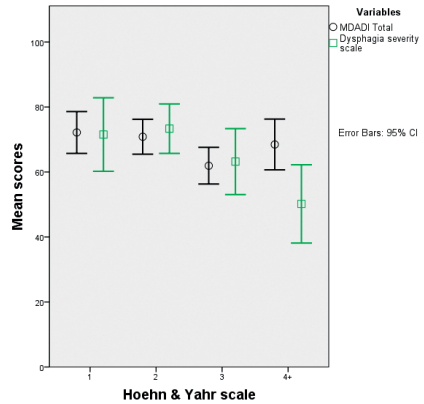

Figure 3. Mean scores of MDADI and DSS questionnaires per Hoehn and Yahr scale

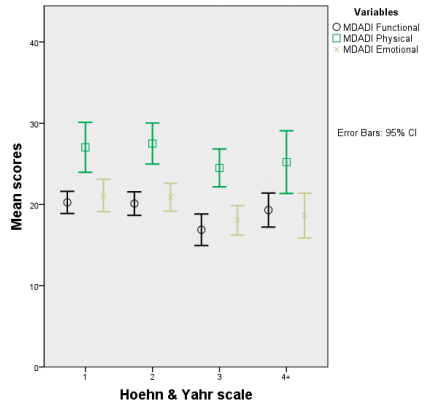

Figure 4. Mean scores of MDADI questionnaire subscales per Hoehn and Yahr scale

OD-specific QoL questionnaires showed slightly lower mean scores with advancing H&Y stage, suggesting a lower QoL at higher H&Y stages (figures 3 and 4). Only DSS revealed some significant differences in means (table 2), indicating that OD-specific QoL tends to decline with progression of IPD (*p*-value: 0.012).

Table 2. Differences in means of quality of life questionnaires by pairwise comparison of the four Hoehn and Yahr stages

Questionnaires (score: min-max)	Compared Hoehn and Yahr stages					
	Stage	**1**			**2**		**3**
	Stage	2	3	4+	3	4+	4+
Visual analog scales							
VAS severity (0 - 100)		- .929	-13.240	-22.088*	-12.311	-21.159*	- 8.848
VAS profession (0 - 100)		1.591	- 4.767	-24.786	- 6.358	-26.377	-20.019
VAS social life (0 - 100)		4.040	- 2.360	-19.293	- 6.400	-23.333*	-16.933
VHI total (0 - 120)		-4.810	-11.033	-21.114*	- 6.224	-16.305*	-10.081
VHI emotional (0 - 40)		-1.419	- 4.285	- 6.766	- 2.866	- 5.346	- 2.481
VHI physical (0 - 40)		- .503	- 3.658	- 6.217*	- 3.156	- 5.714*	- 2.558
VHI functional (0 - 40)		-1.201	- 4.821	- 7.642*	- 3.620	- 6.440*	- 2.821
MDADI total (100 - 20)		.915	9.141	5.650	8.226	4.735	- 3.491
MDADI emotional (30 - 5)		.218	2.711	2.461	2.493	2.243	- .250
MDADI physical (25 - 4)		.330	2.537	1.887	2.867	2.217	- .650
MDADI functional (40 - 8)		.152	3.009*	.859	2.857	.707	- 2.150
DSS (100 - 0)		-4.531	6.936	17.085	11.467	21.616*	10.149

Hoehn and Yahr stage 4+: Combined Hoehn and Yahr stage 4 and 5
Abbreviations; VHI: Voice Handicap Index, MDADI: MD Anderson Dysphagia Inventory, DSS: Dysphagia Severity Scale
* p-value at $\alpha < 0.05$ (ANOVA)

Correlation analysis

To evaluate the association between patients' self-reported perception of swallowing, on the one hand, and their voice complaints on the other, Spearman's correlation coefficient was calculated per questionnaire and subscale. The results are displayed in table 3. All dysphonia-specific QoL questionnaires are significantly correlated with OD-specific QoL questionnaires. In other words, patients reporting decreased dysphonia-specific QoL (higher scores on VAS voice and/or VHI) report a decline in OD-specific QoL (lower scores on DSS and/or MDADI) as well. The strongest correlation is seen between DSS and VAS voice scores. In addition, strong correlations are observed between the physical, functional, and emotional subscales of MDADI and VHI.

Table 3. Associations between OD and dysphonia-specific quality of life questionnaires using Spearman's correlation coefficients

	MDADI total	**MDADI emotional**	**MDADI physical**	**MDADI functional**	**DSS**
	r_s *(95% CI)*	r_s *(95% CI)*	r_s *(95% CI)*	r_s *(95% CI)*	r_s *(95% CI)*
VHI total	-.412* (-.595 ; -.201)	-.412* (-.597 ; -.168)	-.274* (-.470 ; -.055)	-.403* (-.591 ; -.171)	-.425* (-.581 ; -.245)
VHI emotional	-.383* (-.569 ; -.150)	-.389* (-.589 ; -.169)	-.224* (-.436 ; -.008)	-.378* (-.571 ; -.174)	-.368* (-.548 ; -.164)
VHI physical	-.427* (-.591 ; -.204)	-.430* (-.592 ; -.223)	-.353* (-.535 ; -.126)	-.385* (-.569 ; -.159)	-.340* (-.534 ; -.138)
VHI functional	-.409* (-.600 ; -.171)	-.374* (-.568 ; -.126)	-.284* (-.483 ; -.063)	-.409* (-.607 ; -.164)	-.445* (-.609 ; -.264)
VAS severity	-.347* (-.545 ; -.110)	-.360* (-.556 ; -.110)	-.229 (-.452 ; .018)	-.393* (-.573 ; -.169)	-.508* (-.603 ; -.302)
VAS profession	-.318* (-.538 ; -.062)	-.288* (-.511 ; -.019)	-.205 (-.448 ; .078)	-.291* (-.530 ; -.040)	-.430* (-.621 ; -.215)
VAS social life	-.378* (-.579 ; -.134)	-.376* (-.583 ; -.126)	-.241 (-.462 ; .013)	-.377* (-.569 ; -.139)	-.463* (-.620 ; -.276)

Abbreviations; r_s: Spearman's correlation coefficient, CI: Confidence Interval, MDADI: MD Anderson Dysphagia Inventory, DSS: Dysphagia Severity Scale, VAS: visual analog scale, VHI: Voice Handicap Index
* p-value at $\alpha < 0.05$ (r_s)

Discussion

The aim of this study was to explore whether a patient's perception of voice and swallowing disturbances worsens with progression of IPD. Using MDADI, VHI, DSS, and VAS voice, we found a significant worsening of OD and dysphonia-specific QoL when IPD progresses (table 2). Patients with advanced IPD reported a significantly worse voice outcome on VAS voice, VHI, and its subscales compared to patients in the earliest stages of IPD. As for swallowing, the means of DSS, as well as MDADI and its subscales had the tendency to decrease as the disease progressed (figures 3 and 4). However, only the DSS mean scores differed significantly with advancing H&Y stages (table 2).

Previous studies also suggest that swallowing disturbances have a major impact on QoL in patients with IPD.[1, 2, 8, 10] Plowman-Prine et al. [16] reported that a decrease in OD-specific QoL, as measured by the SWAL-QOL (a validated OD-specific QoL questionnaire), is positively correlated with a decrease in overall health-related QoL (Parkinson's Disease Questionnaire-39) in IPD. That study found no relationships between swallow-specific QoL and disease duration or severity in a group of 36 IPD patients. In another study using the SWAL-QOL, Carneiro et al. [17] compared the QoL of 62 IPD patients at different H&Y stages. They found a significantly lower score on the SWAL-QOL in groups in the later stage compared to those in the early stage, especially on the items 'sleep', 'eating duration', and 'symptom frequency'. In the present study, we have found significant differences in the means of DSS between H&Y stages 2 and 4+ (*p*-value: 0.009) (table 2), but not between H&Y stages 1 and 4+ (*p*-value: 0.187). For MDADI, only MDADI-F showed significant differences in means between H&Y stage 1 and 3 (*p*-value: 0.045), and 2 and 3 (*p*-value: 0.060) (table 2). Differences in means between H&Y stage 1 and 4+ and between 2 and 4+ were not statistically significant (*p*-value: 0.872 and 0.922, respectively).

Gamboa et al. [18] subjected 41 IPD patients to acoustic analysis, phonetometric measurements, and a non-blinded laryngoscopy. They found that the clinical profile, severity, and duration of IPD did not influence patients' perception of their voice performance. In a study by Majdinasab et al. [19], 23 IPD patients completed the VHI. Whereas no association was demonstrated between VHI outcomes, or its subscales, and the H&Y scale. Although, compared to Unified Parkinson's Disease Rating Scale section 3 (UPDRS-III) scores, a positive correlation with VHI-T was found.[19] In the present study, however, a significant decrease in dysphonia-specific QoL was found with advancing H&Y stages for the VHI, VAS voice, and their subscales. Although, UPDRS-III includes a broader range of parameters, in determining disease severity such as axial symptoms, the H&Y scale, as used in the present study, is an easy-to-use tool for a wide range of health-care professionals such as speech and language pathologists and otolaryngologists.

Both OD and dysphonia-specific QoL tend to decline with progression of disease. It is noteworthy that all questionnaires, including their subscales, showed no significant differences in mean scores when H&Y stage 1 was compared to stage 2 (table 2). It is concluded that dysphonia as well as dysphagia might be present in the earliest phase of IPD, even though, in the patient's perception, these symptoms start worsening at H&Y stage 3.

A reason for this plateau in a patient's self-perception at the earliest stages might lie in individual compensatory vocal and/or swallow techniques or mechanisms. Driven by sensory afferent input, compensatory mechanisms may develop by recruitment of better-preserved parallel motor loops.[20, 21] Moreover, IPD patients tend to have sensory

deficits that may compromise perceptual judgment. Such deficits have the potential to contribute to motor problems too.[22] These deficits are not only seen in swallowing but also in other sensorimotor actions. In the later stages, the degeneration could attack the higher centers responsible for sensorimotor integration. If so, overt problems in voice and swallowing could be even more debilitating. The adaptive strategy cannot be maintained, and at that point oropharyngeal dysphagia manifests itself.[21, 22]

Another explanation for the decline in QoL in the higher H&Y stages might be the 'wearing-off effect' of long-term dopaminergic treatment.[23, 24] Although the response of dysphonia and dysphagia to dopaminergic treatment is limited, this medication may initially improve motor symptoms such as bradykinesia, rigidity, and postural instability [25]. As the effect wears off, these symptoms can worsen, perhaps impacting the voice or swallowing function as muscular rigidity increases.[20] Midi et al. [26] showed that higher scores on total motor components of the UPDRS-III were associated with high scores on the VHI. Moreover, they found a positive correlation between speech problems and a masked facial expression on the UPDRS-III and the total VHI score.[26]

Finally, the plateau in a patient's self-perception at the earliest stages of IPD is calling for some caution because a larger sample size may smooth out the plateau.

All dysphonia-specific QoL questionnaires used in the present study are significantly associated with the OD-specific QoL questionnaires. For IPD, a patient's perception of increased voice disturbances will therefore most likely correlate with a perception of increased swallowing disturbances. This finding strengthens the hypothesis that dysphonia and dysphagia in IPD have a somewhat similar underlying pathophysiology.[27, 28] Since phenomena such as silent aspiration and latent dysphagia are common in IPD, one may assume that patients complaining of voice disturbances are very likely to experience swallowing disturbances as well. That possibility should subsequently be assessed using instrumental measures such as VFS or FEES. However, further evidence is needed to verify the exact association between concomitant voice and swallowing disorders in IPD.

Limitations

Only three participants with an H&Y score of 5 were included, and these participants were assigned to the modified H&Y stage 4+. The reason for this low number of patients with a score of 5 might lie in the exclusion criterion of cognitive dysfunction (MMSE<23). Although the validity of QoL questionnaires in patients with cognitive impairments has been investigated, conflicting results were reported.[29, 30] Therefore, to reduce possible bias due to cognitive dysfunctions in the present study, patients with an MMSE<23 were excluded. It was decided to create a modified H&Y stage 4+ that reflects a population with severe IPD (H&Y category 4 and 5) but includes mentally competent patients

(MMSE>22). Another limitation of the study might be the inclusion of IPD patients having voice and swallowing complaints. This might influence the results, since IPD patients in the mild stages can have no swallowing complaints despite abnormal instrumental evaluations.

The individual variability in IPD (level of activity, time to diagnosis, etc.), or subtypes of IPD (tremor-dominant, rigid-akinetic, etc.) were not evaluated per H&Y stage. Although relevant parameters, which may influence the progression of disease and symptom onset [31], a sample size of one-hundred IPD patients is believed to be insufficient to correct the results for these parameters.

The VHI and MDADI are psychometrically validated questionnaires to assess the impact of dysphonia and dysphagia on QoL. However, both questionnaires were not specifically validated for IPD, which might have implications for the interpretation of the results. Accordingly, these instruments should be used with caution in this population. On the other hand, both questionnaires were previously used in other studies regarding IPD.[8, 19, 26]

Conclusion

This study revealed that, as IPD progresses (advancing H&Y stage), both OD and dysphonia-specific QoL will decrease. Regardless of disease progression, a decline in dysphonia-specific QoL is associated with a decline in OD-specific QoL. In clinical practice, health-care professionals should be aware of this relationship between the patient's perception of voice and swallowing dysfunctions as assessed with QoL questionnaires (MDADI, VHI, DSS, and VAS voice), and the relationship between these perceptions and the severity of IPD. In that light, health-care professionals would benefit from introducing OD and dysphonia-specific QoL questionnaires into a multi-dimensional voice- or swallow-assessment protocol in IPD. The detection of the patient's perception of voice and swallowing disorders and the impact of their perception on QoL in IPD should not be disregarded.

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4

Swallowing assessment in Parkinson's disease; Patient and investigator reported outcome measures are not aligned

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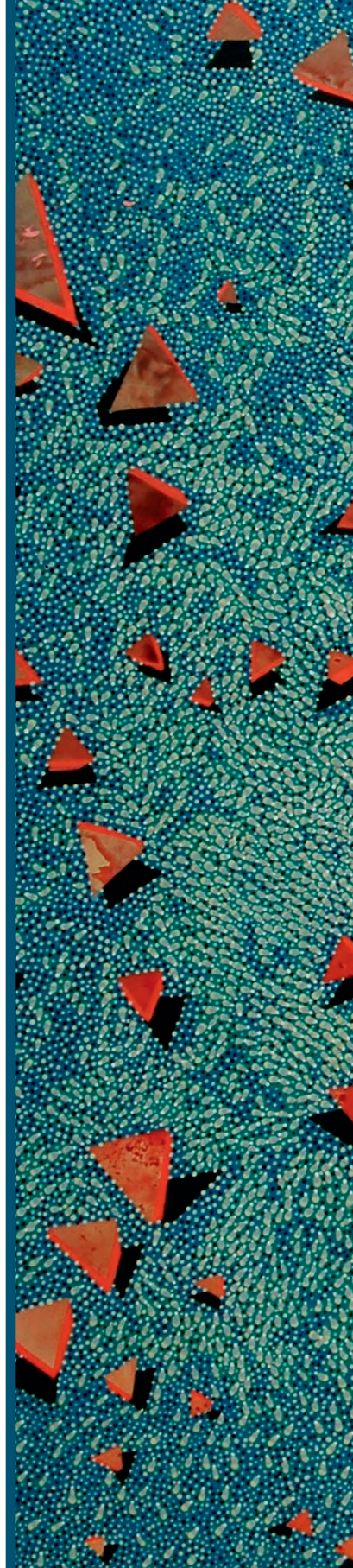

Abstract

This study determines the relationship between patient and investigator reported outcome measures (PROMs versus IROMs) on oropharyngeal dysphagia (OD) in Parkinson's disease (PD). The PROMs used are the MD Anderson Dysphagia Inventory (MDADI) and the Dysphagia Severity Scale (DSS). The IROMs used are fiberoptic endoscopic evaluation of swallowing (FEES) and videofluoroscopy of swallowing (VFS). Ninety dysphagic PD patients were included. Multilayer perceptron (MLP) neural network analysis was used to investigate the relationship between PROMs and IROMs on OD in PD. MLP neural network analysis showed a moderate agreement between PROMs and IROMs, with an area under the curve between 0.6 and 0.7. Two-step cluster analysis revealed several clusters of patients with similar scores on FEES and/or VFS variables, but with significant different scores on MDADI and DSS variables. This study highlights that there are PD patients with similar FEES and/or VFS findings that cannot be lumped together under the same pathophysiological umbrella due to their differences in PROMs. Since the exact origin of these differences is not fully understood, it seems appropriate for the time being to take into account the different dimensions of OD during the swallowing assessment so that they can be included in a patient-tailored treatment plan.

Introduction

Oropharyngeal dysphagia (OD) is a common non-motor symptom in idiopathic Parkinson's disease (PD).[1, 2] The burden of OD in PD is immense, as it affects health-related quality of life (QoL) [3-5], and may lead to complications such as aspiration pneumonia.[6, 7] Even in an early PD stage, patients report a lower OD-specific QoL compared to healthy control subjects.[3] However, patients with a moderately advanced PD disease stage do not report the worst OD-specific QoL compared to the patients in the early disease stages.[3] It appears that the OD-specific QoL only decreases further when the patients are in advanced Hoehn and Yahr (H&Y) stage.[3] This suggests that the decline of self-report OD-specific QoL stagnates despite the progression of PD during its early H&Y stages or that PD patients develop compensatory swallowing strategies or coping mechanisms that inhibit the decline of OD-specific QoL despite the progression of OD. In case of the latter, an inconsistency is expected between the patient reported outcome measures (PROMs) and the investigator reported outcome measures (IROMs) on swallowing.

The inconsistency between patient self-report OD-specific QoL and the actual swallowing function using fiberoptic/flexible endoscopic evaluation of swallowing (FEES) or videofluoroscopy of swallowing (VFS) has been described in several studies on OD due to other underlying disorders such as acute stroke, myotonic dystrophy and head and neck cancer.[8-11] Silent aspiration occurs in about 20% of the PD patients and is one of the main risk factors for developing aspiration pneumonia.[12, 13] For PD, the relationship between the results of validated self-report OD-specific QoL questionnaires and of instrumental tools such as FEES or VFS has not been reported in the literature before.

Therefore, the objective of the present study was to determine the relationship between PROMs and IROMs on swallowing in PD patients. To further explore the characteristics of this relationship, clinically relevant subgroups of patients within the study population, based on similar PROMs and/or IROMs, were identified and studied.

Materials and Methods

Participants

PD patients with dysphagic complaints were recruited from all over the Netherlands between 2007 and 2011. A neurologist clinically diagnosed the PD according to the UK Parkinson's Disease Society Brain Bank and the H&Y scoring system.[14, 15] The majority of the patients was referred by their speech and language pathologist (SLP) who had identified clinically relevant symptoms of OD during a clinical swallowing examination. Individuals were enrolled in the study if they were in a stable period of PD (periods without large fluctuations, especially in motor function). The exclusion criteria were: being older than 85 years (presbyphagia); having had speech therapy during the previous

six months (benefit of treatment and attention); scoring below 23 on a Mini Mental State Examination (MMSE) [16]; suffering from severe depression or having a psychiatric diagnosis; not being able to speak Dutch; being illiterate or blind; having a history of stroke, and having the antiparkinsonian medication regimen changed within the past six weeks**.** Also, patients with a history of extensive surgery or cancer of the head and neck region were excluded. Written informed consent was obtained from all patients and the medical ethics committee (MEC) approved the study protocol (MEC 05-237)**.**

Evaluation Protocol

All patients underwent a standardized examination protocol in the same tertiary referral university hospital by the same multidisciplinary team in order to guarantee standardized data collection. The examination protocol included an otorhinolaryngological examination, done by a laryngologist, checking the integrity of the cranial nerves and the upper aerodigestive tract; the MMSE; FEES; VFS; and patient self-report OD-specific QoL questionnaires, namely the MDADI and DSS. All examinations and questionnaires were performed at the same day during the 'on' motor phase (within 90–120 minutes after intake of antiparkinsonian medication).[17]

The MDADI is a self-administered, psychometrically validated OD-specific questionnaire. It is designed to assess the impact of OD on health-related QoL, although some MDADI items are also related to functional health status (FHS).[18-20] For the current study the validated Dutch MDADI version for neurogenic OD was used.[21] Like the original English version, the validated Dutch translation of the MDADI consists of 20 items pooled in 4 subscales: the global scale (1 item); the functional scale (5 items); the physical scale (8 items); and the emotional scale (6 items).[21, 22] The global assessment question (MDADI-G) evaluates the effect of OD on overall QoL. The functional scale (MDADI-F) illustrates the impact of OD on daily activities. The physical scale (MDADI-P) measures the patient's self-perception of the physical impact of OD. The emotional scale (MDADI-E) represents the patient's affective response to the swallowing disorder in terms of embarrassment, self-esteem, and self-consciousness. All items are scored on a 5-point scale (1-5), where '1' corresponds to 'total agreement' and '5' to 'total disagreement'. Responses on all domains were summed to calculate the MDADI total score (MDADI-T). The minimum score is 20, indicating poor functioning, and the maximum possible score is 100.

The DSS is a visual analogue scale that was used to assess patient's perception of the severity of the swallowing impairment on the day of the examination.[23] The DSS score ranges from 0 (extreme swallowing impairment or inability to swallow) to 100 mm (no swallowing impairment).

The FEES examinations were performed by an experienced laryngologist together with the SLP. First, patients had to perform three swallows of 10 cc thin liquid (water) followed by three swallows of 10 cc thick liquid (applesauce - One 2 fruit®) and three

bite-sized crackers (Delhaize mini toast 80 gr®). All liquids were dyed with 5% methylene blue (10 mg/ml). The viscosity of the liquid bolus consistencies was measured at 25°C and 50 s-1 of shear rate resulting in 1 mPa·s for thin liquid (International Dysphagia Diet Standardization Initiative (IDDSI) level 0) and 1200 mPa·s for thick liquid (IDDSI level 3).[24] A flexible fiberoptic endoscope, Pentax FNL-10RP3 (Pentax Canada Inc., Mississauga, Ontario, Canada), was used during the FEES examination. The tip of the endoscope was in 'high position', just above the epiglottis, where the scope could not interfere with closure of the laryngeal vestibule [25]. FEES images were obtained using an Alphatron Stroboview ACLS camera, Alphatron Lightsource, IVACX computerized video archiving system (Alphatron Medical Systems, Rotterdam, The Netherlands), and recorded on a DVD. No topical anesthetic or nasal vasoconstrictor was used during the exam.

During the VFS, patients were offered three trials of thin liquid low-density barium 40% weight/volume (Micropaque suspension® 1000 g/l) and three trials of thick liquid (50 cc applesauce - One 2 fruit® + 150 gr barium powder – E-Z-HD® 984.5 mg/g powder for oral suspension) followed by three bite-sized crackers (Delhaize mini toast 80 gr®) coated with barium paste. The viscosity of the liquid bolus consistencies was measured at 25°C and 50 s-1 of shear rate resulting in 12.05 mPa·s for thin liquid (IDDSI level 0) and 1900 mPa·s for thick liquid (IDDSI level 4).[24] Similar to what was done during the FEES examination, each participant swallowed the bolus consistencies upon command and in the same sequence (thin liquid, thick liquid, and bite-sized cracker). The field of the videofluoroscopic image included the lips, the oral cavity, the cervical spine, and the proximal cervical esophagus (in lateral position; dental prosthesis in position). Videofluoroscopic images were obtained with a Philips Diagnost 97 system (Philips Medical Systems, Eindhoven, The Netherlands) and recorded at twenty-five frames per second using a mini-DV camera-recorder Panasonic AG-DVC30 (Matsushita Electric Industrial Co., Osaka, Japan).

For each FEES and VFS swallow visuoperceptual ordinal variables (Table 1) were scored at varying speed (slow motion, normal, frame-by-frame speed) by two observers who followed a training program described in previous studies.[18, 26] The observers were blinded to patient identity, medical history, and to each other's rating scores (independent rating). Each observer was asked to limit the evaluation period to a maximum of 2 hours in order to maintain optimal attention and reduce fatigue-related bias.

Table 1. Definition and ordinal scale of the visuoperceptual fiberoptic/flexible endoscopic evaluation of swallowing (FEES) and/or videofluoroscopy of swallowing (VFS) variables.

Variable	Definition	Scale
Piecemeal deglutition[a] (FEES and VFS)	Sequential swallowing on the same bolus	0 = 1 swallow, no additional swallows; 1 = 1 swallow with 1 additional swallow; 2 = 1 swallow with 2 additional swallows; 3 = 1 swallow with 3 additional swallows; 4 = 1 swallow with 4 or more additional swallows.
Preswallow posterior spill[a] (FEES)	Preswallow loss of bolus into the pharynx	0 = no posterior spill; 1 = trace; 2 = more than trace, but less than 50%; 3 = >50% of the bolus; 4 = whole bolus flows into the pharynx without swallowing.
Postswallow vallecular pooling (FEES and VFS)	Pooling in the vallecula after the swallow	0 = no pooling; 1 = mild to moderate pooling (filling of less than 50 % of the vallecula); 2 = severe pooling (filling of more than 50 % of the vallecula up to complete filling);
Postswallow pyriform sinus pooling (FEES and VFS)	Pooling in the pyriform sinuses after the swallow	0 = no pooling; 1 = mild to moderate pooling (filling of less than 50 % of the pyriform sinuses); 2 = severe pooling (filling of more than 50 % of the pyriform sinuses up to complete filling);
Penetration aspiration scale (FEES and VFS)	Penetration and/or aspiration according to the Rosenbek scale	8-point scale

[a]Not scored for bite-sized cracker, since piecemeal deglutition and preswallow posterior spill can be normal aspects of swallowing during solid bolus processing/mastication.

Statistical Analysis

Observer Agreement Analysis

Observer agreement analysis was performed using a weighted kappa index of agreement (intraobserver and interobserver) for all visuoperceptual ordinal FEES and VFS variables.

Neural Network Analysis

To elaborate the clinically complex relationship between PROMs and IROMs on OD in PD, a multilayer perceptron (MLP) neural network analysis was used. An MLP neural

network analysis is a relatively modern statistical technique to process complex (non-) linear data. This statistical approach can be used for many purposes and is especially useful for data containing several kinds of variables (ordinal, binary, continuous, etc.). The most common purposes of MLP neural network analysis are pattern recognition, forecasting, and modeling of complex relationships between data.[27] In health care it has been used for several diagnostic purposes such as manometry for OD in PD.[28] To reach the objective of this study an MLP neural network, from now on referred as MLP, was used to model the complex relationship between PROMs, IROMs, and demographic patient characteristics. The MLP is composed of an input layer to receive the signal, an output layer that makes a decision or prediction about the input, and in between those two, an arbitrary number of 'hidden' layers that are the true computational engine of the MLP. Feed forward networks such as MLPs are like tennis. Your aim is to score a point. Every time you miss, you have to learn from your mistake to improve the next serve. You can think of this tennis of guesses and answers as a kind of accelerated science, since each guess is a test of what we think we know, and each response is feedback, letting us know how wrong we are. So, to model the data, an MLP uses one or more 'input nodes', and one or more 'output nodes'. In this study the input nodes were the PROMs (MDADI subscales and DSS) and demographic patient characteristics and the output nodes were the IROMs (FEES and VFS variables). The MLP technique was used to determine the relationship between each input node and output node resulting in a 'hidden node'. This hidden node is a robust weight between each input and output node describing their relationship to each other. In this way multiple hidden nodes will be obtained. Besides the weights between the input and output nodes, the MLP determines the weight between the hidden nodes as well. These steps result in multiple layers of hidden nodes. Every input, output, and hidden node is therefore connected to each other resulting in a complex network of weights. By training this MLP, the robust weight will become more accurate. The purpose of training the MLP is to find the optimal combination of weights resulting in the smallest error. To train the neural network, a training set is used. The input data (PROMs and demographic patient characteristics) of the training set was offered one by one to the network. Based on the robust weights between the input, output, and hidden nodes the output data could be calculated. This PROMs output data can then be compared to the actual output data of the IROMs and the differences between these two were marked as error. Finally, this error was used to recalculate the weight between all input, output, and hidden nodes resulting in the smallest possible error. These steps of training were repeated several times in order to develop the MLP based on the input and output data with the smallest error. This form of training is called back propagation. In this study the training set comprised 70% of the samples chosen at random. The training steps were repeated 50 times and the results were averaged.[27]

The extent to which the MLP can predict the output data from the input data can be visualized in a receiver operating characteristics curve (ROC-curve). In case of an

adequate neural network and a sufficient agreement between the input and output data, the neural network will predict the outcome data correctly to a large extent based on the input data. This accuracy can be calculated with an area under the curve (AUC). A high AUC, means an adequate neural network and a strong relationship and agreement between the PROMs and IROMs.[29]

Since several OD-specific variables (MDADI, DSS, FEES, and VFS) and demographic patient-related variables (age, gender, and H&Y scale) were used, there was a high chance of having a missing value on one of them. A complete case analysis would tremendously decrease the population size of the study. Therefore, besides the complete case analysis, multiple imputation was performed in the MLP analysis using fully conditional specification to account for missing values. By using multiple imputation, the missing values were estimated within the standard error. These estimations were repeated 200 times. In this way, 90 patients could be included in the MLP analysis and 200 unique datasets were created to develop the MLP feed forward network. The complete case analysis was used to verify that the imputation was valid.

To improve statistical power in the MLP analysis, patients were divided in three clinical patient labels based on the FEES and VFS ordinal variable outcome: *glossopalatal, pooling* or *aspiration*. It was possible for one patient to have multiple clinical labels. Patients received the *glossopalatal* label if either their FEES and/or VFS exam was scored impaired (score of 1 or higher) on one or more of the following variables during one or more bolus consistencies: preswallow posterior spill and/or piecemeal deglutition. Likewise, patients were assigned to the clinical patient label *pooling* if their swallowing exam was scored impaired (score of 1 or higher) on postswallow vallecular and/or pyriform sinus pooling. The clinical patient label *aspiration* was assigned to patients presenting penetration and/or aspiration according to the penetration-aspiration scale by Rosenbek et al.[30] If patients did not have an impaired score on these FEES and/or VFS variables, then they were used as a control group for this particular clinical patient label.

Two-step Cluster Analysis

Usually patients are divided in groups based on known demographic characteristics such as gender or whether they have a disease or not. By using two-step cluster analysis, patients are divided in clusters based on all available data. It is a tool to find 'hidden' clusters or patterns within the multivariate data that otherwise would not be found. The goal of two-step cluster analysis is to categorize patients by minimizing the within-cluster variation and maximizing the between-cluster variation. This leads to homogenous 'natural' clusters of patients with similar characteristics based on the multivariate data. With these newly formed clusters, additional statistical analysis can be done.[31]

To obtain a better insight into the possible characteristics of this relationship between PROMs and IROMs, a two-step cluster analysis was used to explore whether there are clusters of patients with similar outcomes on FEES or VFS resulting in similar clinical patient labels, but with different outcomes on MDADI or DSS scores. One-way analysis of variance F-overall tests for means (ANOVA) was used to determine the mean differences of the MDADI and DSS scores between the clusters of patients. Bonferroni post-hoc analysis was carried out to correct for multiple testing. A p-value $\leq .05$ was considered statistically significant. Fisher exact test was used to identify significant differences in demographic patient characteristics (age, gender, H&Y scale) between the different clusters within each clinical patient label. A complete case analysis was used for the two-step cluster analysis. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 23 (IBM, Armonk, NY).

Results

Participants

This study included ninety PD patients with swallowing complaints, of which sixty-seven were male. The median age was 67 years (range: 42-82 years) and the median H&Y score was 2 (range: 1-5). All patients were on a total oral diet, although seven patients (8%) required a modified texture diet. The mean MDADI-T score for the total group was 69 and the mean DSS score was 68 (standard deviation 14 and 24, respectively). The duration of the Parkinson's disease since diagnosis was at least 5 years. The floor or ceiling effect was considered negligible as few patients got the lowest or highest possible score for MDADI-T and DSS (4% and 10%, respectively). All patients used levodopa except for seven (8%) of the ninety PD patients. These patients did not use any antiparkinsonian medication. Due to the small number of patients without levodopa use, this was not included in the Fisher exact test. However, care was taken to ensure that all measurements in patients on levodopa were performed during the 'on' motor phase. The "on-off" phenomenon in PD refers to a switch between mobility and immobility in levodopa-treated patients, which occurs as an end-of-dose worsening of motor function.[17]

Observer Agreement Analysis

All FEES and VFS variables had sufficient intra- and interobserver agreement (i.e., weighted Cohen's kappa >0.6) and further inferences were drawn based on the data of the observer with the highest intraobserver agreement scores.

Multilayer Perceptron (MLP) Neural Network method

Table 2 shows the mean AUC, and the 95% confidence interval (CI) per clinical patient label. The mean scores of the MDADI-T and DSS were determined per clinical patient label.

Table 2. Mean results of the neural network analysis per clinical patient label

Clinical patient label	Glossopalatal	Pooling	Aspiration
Number of patients[a] (n=90)	51	36	19
Mean MDADI-T (score range 20-100)	68	67	64
Mean DSS (score range 0-100)	67	67	60
Mean AUC[b]	0.64	0.65	0.70
95% CI	0.62-0.65	0.63-0.67	0.67-0.72

Abbreviations; MDADI-T: MD Anderson dysphagia inventory - total score, DSS: Dysphagia severity scale, AUC: area under the curve, CI: confidence Interval.
[a]Patients can have more than one clinical patient label.
[b]Calculation of AUC and 95% CI were obtained after multiple imputation and averaging of 50 runs of MLP analysis for all (*n*=200) imputed datasets.

Two-step cluster analysis

For each clinical patient label a two-step cluster analysis was performed to identify clusters of patients sharing similar outcomes on FEES or VFS, but with different outcomes on MDADI or DSS scores. This analysis revealed three new clusters of patients within the clinical patient label glossopalatal, two clusters for the clinical patient label pooling, and three new clusters for the clinical patient label aspiration. Using Fisher exact test, no significant differences (p-value >.05) for confounders (age, gender, H&Y scale) were found between the different clusters of patients within each clinical patient label.

Clinical Patient Label Glossopalatal

For the clinical patient label *glossopalatal* three clusters of patients were found. A complete case analysis of seventy-eight patients was carried out for this clinical patient label. The mean MDADI subscale and DSS scores are listed in Table 3. Cluster 1 (33%; *n*=26/78) and 2 (32%; *n*=25/78) contain patients presenting preswallow posterior spill and/or piecemeal deglutition, and cluster 3 (35%; *n*=27/78) consists of patients who did not present preswallow posterior spill and/or piecemeal deglutition during FEES and/or VFS.

The mean MDADI subscale and DSS scores per patient cluster are presented in Figure 1. The mean MDADI subscale and DSS scores were significantly different (*p*<.001) between the two clusters of patients presenting preswallow posterior spill and/or piecemeal deglutition (cluster 1 and 2). Although patients in cluster 1 and 2 have similar scores on the IROMs, the mean scores of the PROMs of patients in cluster 2 were significantly higher (higher swallow-specific QoL) compared to patients in cluster 1 (Figure 1). For the patient cluster without signs of preswallow posterior spill and/or piecemeal deglutition (cluster 3) the mean MDADI subscale and DSS scores were significantly higher (higher swallow-specific QoL) compared to cluster 1. However, cluster 2 and 3 showed similar

mean PROMs scores. Only the mean MDADI-P and mean DSS score were significantly different between patients in cluster 2 and cluster 3 (*p*=.008 and p=.022 respectively). The mean MDADI-E and MDADI-F score did not significantly differ between cluster 2 and 3 (p=.088 and p=.052 respectively). It seems that although cluster 2 and 3 have different scores on the IROMs, their mean scores on the PROMs were fairly similar.

Table 3. Means (95% CI) of the MDADI subscale and DSS scores for each patient cluster within the clinical patient labels. The mean difference of the MDADI and DSS scores between the clusters of patients was determined using the one-way analysis of variance F-overall test for means (ANOVA).

Glossopalatal

Cluster	Preswallow posterior spill and/or piecemeal deglutition		MDADI-F	MDADI-P	MDADI-E	DSS
1	Impaired	*Mean (95% CI)*	17 (15-19)	22 (20-24)	17 (16-19)	48 (41-56)
2	Impaired	*Mean (95% CI)*	23 (22-24)	32 (30-34)	24 (23-25)	83 (77-89)
3	Normal	*Mean (95% CI)*	21 (19-22)	28 (25-30)	22 (20-23)	69 (60-78)
		p-value	.00	.00	.00	.00

Pooling

Cluster	Vallecular and/or pyriform sinus pooling		MDADI-F	MDADI-P	MDADI-E	DSS
1	Impaired	*Mean (95% CI)*	19 (19-20)	27 (26-28)	21 (20-21)	66 (64-70)
2	Normal	*Mean (95% CI)*	20 (20-21)	27 (26-28)	21 (20-22)	67 (65-72)
		p-value	.44	.79	.53	.79

Aspiration

Cluster	Penetration and/or aspiration		MDADI-F	MDADI-P	MDADI-E	DSS
1	Normal	*Mean (95% CI)*	22 (21-23)	29 (28-31)	23 (22-24)	73 (66-79)
2	Impaired	*Mean (95% CI)*	21 (19-22)	28 (25-30)	21 (19-23)	60 (49-71)
3	Normal	*Mean (95% CI)*	13 (12-12)	19 (16-22)	15 (13-17)	55 (41-69)
		p-value	.00	.00	.00	.02

Abbreviations; CI: confidence interval. DSS: dysphagia severity scale
MDADI-: MD Anderson Dysphagia inventory; F: functional, P: physical, E: emotional.

Clinical Patient Label Pooling

For the clinical patient label pooling, only two clusters of patients could be identified. Cluster 1 (46%; n=36/78) contains patients presenting postswallow vallecular and/or postswallow pyriform sinus pooling and cluster 2 (54%; n=42/78) consists of patients

without these signs of OD. No significant differences in the mean MDADI subscale and DSS scores were found between both patient clusters (Table 3).

Clinical Patient Label Aspiration

Figure 2 shows the three clusters of patients for the clinical patient label aspiration. Cluster 1 (58%; n=45/78) and cluster 3 (18%; n=14/78) contain patients who did not present penetration and/or aspiration during FEES and/or VFS. Cluster 2 (24%; n=19/78) consists of patients presenting penetration and/or aspiration. The mean MDADI subscale and DSS scores are listed in Table 3.

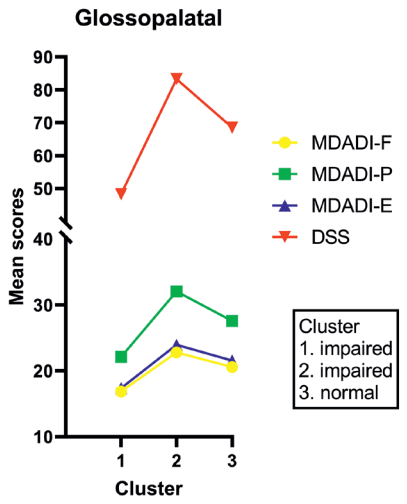

Figure 1. Mean MDADI subscale and DSS scores per patient cluster for the clinical patient label glossopalatal (presence of pre-swallow posterior spill and /or piecemeal deglutition

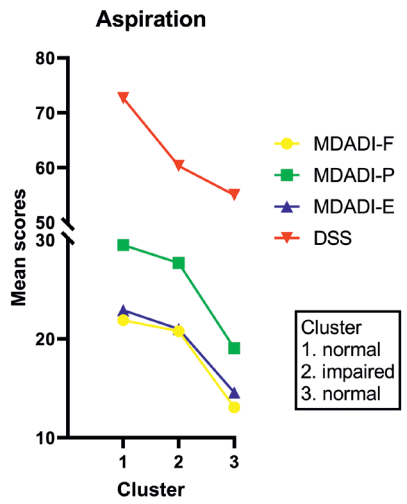

Figure 2. Mean MDADI subscale and DSS scores per patient cluster for the clinical patient label aspiration (presence of penetration or aspiration)

For the patients without signs of penetration and/or aspiration (cluster 1 and 3), the mean MDADI subscale (p<.001) and DSS (p=.041) scores were significantly different between cluster 1 and 3. Although these two patient clusters have similar scores on the IROMs, the mean scores of the PROMs of patients in cluster 1 were significantly higher (higher swallow-specific QoL) compared to patients in cluster 3 (Figure 2).

No statistically significant differences in the mean MDADI subscale (p>.176) and DSS (p=.155) scores were found between patients with signs of penetration and/or aspiration (cluster 2) and patients from cluster 1 without these signs of OD. This means that although the scores on the IROMs were significantly different between cluster 1 and 2, the mean scores of the PROMs were similar.

For cluster 3 however, the mean MDADI subscale scores were significantly different compared to the scores of patients in cluster 2 (p<.001). The mean DSS scores did not significantly differ between patients in cluster 2 and cluster 3 (p=1.000). So, although patients in cluster 3 did not present signs of penetration and/or aspiration, their mean MDADI subscale scores were significantly lower (lower swallow-specific QoL) compared to patients who did have signs of penetration and/or aspiration (cluster 2).

Discussion

The objective of the present study was to determine the relationship between PROMs and IROMs on OD in PD. Only a relationship with a moderate agreement (AUC = 0.6-0.7) between the PROMs and IROMs on OD in PD was found. This suggests that there is some sort of inconsistency between the signs of OD identified by clinicians using FEES and/or VFS and patient self-report OD-specific QoL questionnaires.

This inconsistency between PROMs and IROMs is not new in the literature on neurogenic dysphagia. In a cohort of 119 PD patients, Nienstedt et al. found that only 50% of the patients with severe aspiration (Penetration Aspiration Scale score>6 [30]) during FEES reported swallowing complaints in the relevant domains of the Unified Parkinson Disease Rating Scale (UPDRS) II and in the non-motor symptoms questionnaire (NMS). The majority of these patients described their difficulties as 'slight restrictions in swallowing'.[32] Pflug et al. used a single question to evaluate whether PD patients experienced swallowing impairment and compared this outcome to signs of OD using FEES.[33] Only 6% (*n*=5/119) of the PD patients showed a normal pharyngeal swallow during FEES. However, 73% (*n*=87/119) denied any swallowing impairment. The majority of the PD patients without OD complaints showed pharyngeal pooling of dyed water (52%; *n*=45/87), bread (93%; *n*=81/87), and biscuit (86%; *n*=75/87) and 16% (*n*=14/87) showed aspiration [33]. Only 12-27% of the PD patients with signs of swallowing impairment during FEES reported swallowing complaints.[32, 33] The current study also showed a moderate agreement between PROMs and IROMS in dysphagic PD patients. However, it is important to emphasize that previous studies described PROMS using OD symptom and FHS questionnaires and did not report on OD-specific QoL questionnaires**.**

To further elaborate this moderate agreement between PROMs and IROMs in the present study, a two-step cluster analysis was performed. It was hypothesized that there are clusters of patients with similar outcomes on FEES or VFS resulting in similar clinical patient labels, but with different outcomes on MDADI or DSS scores. The cluster analysis could help to understand why some PD patients with similar signs of OD during FEES or VFS have swallowing complaints and others don't. Using the two-step cluster analysis, patients of cluster 1 in the *glossopalatal* label (Figure 1) showed signs of OD during FEES and/or VFS and at the same time the lowest mean MDADI subscale and DSS scores, representing a poor swallow-specific QoL. However, the clinical patient label

glossopalatal also contained patients of cluster 2 who had the highest mean MDADI subscale and DSS scores (highest swallow-specific QoL), and signs of OD on the IROMs. In the attempt to identify confounders that could predict the differences in the level of swallow-specific QoL presented by patients in cluster 1 and 2, patient characteristics were added to the analysis. However, the variables age, gender, H&Y scale, and the score on the other clinical patient labels could not be identified as confounders. 'The exact reason for the significantly different mean scores on the PROMs in patients with similar IROMs was therefore not found in this study.

A similar result was seen for the clinical patient label *pooling*. Only two clusters were found: one with signs of postswallow vallecular and/or postswallow pyriform sinus pooling and the other without. Interestingly, the mean MDADI subscale and DSS scores did not significantly differ between both clusters. Apparently, the level of swallow-specific QoL did not seem to depend on the presence or absence of pharyngeal pooling.

There are numerous hypotheses regarding the pathophysiology of OD in PD. Different sites in the nervous system may be affected.[34] A possible explanation for the inconsistency between PROMs and IROMs on OD in PD may be that the different sites of pathology in the nervous system may affect the swallowing function and the subjective perception of this in a different way. So, the phenotype of OD of an individual PD patient seems to encompass more than just the biomechanical swallowing function measured by IROMs. The OD phenotype includes the dimension of 'the subjective perception of the swallowing disorder by the patient' as well. PROMs and IROMs really seem to represent different dimensions of OD that together determine an OD phenotype in an integrated manner. The most well-known hypothesis of the pathophysiology of OD in PD is the lack of dopamine in the basal ganglia [35]. Functional magnetic resonance imaging (fMRI) studies in healthy subjects showed increased activation in parts of the basal ganglia namely the globus pallidus and putamen during swallowing.[36] Restoring the dopamine levels in these areas using dopaminergic medication or deep brain stimulation seemed to significantly improve swallowing in some PD patients.[37] However, several studies showed no significant improvements or worsening of OD using dopaminergic medication or deep brain stimulation, suggesting that there are different pathophysiological mechanisms in developing OD.[34, 37] Another site of pathology in PD are the non-dopaminergic pathways which might be affected by the development of Lewy bodies. Lewy bodies are abnormal aggregations of mainly alpha-synuclein proteins and are related to neuronal cell loss.[38] These Lewy bodies appear in the brainstem and cortex as PD progresses and were found in important pathways related to swallowing such as the dorsal nuclei of the glossopharyngeal and vagal nerve.[39] Lewy bodies were not only found in the central nervous system, but also in the enteric nervous system, and in the sensory and motor nerves of the pharyngeal wall.[40, 41] A possible hypothesis is that these different sites of pathology relate to different phenotypes of OD in PD, and require different diagnostic and therapeutic approaches.

Besides the different sites of pathology which may relate to different phenotypes of OD in PD, the occurrence of compensatory mechanisms may be another attribute to the different phenotypes. Some PD patients develop compensatory mechanisms that prevent them from having swallowing complaints.[42] Using magneto-encephalography (MEG) a shift in cortical activation during swallowing was found from the affected supplementary motor area to the lateral motor, premotor, and inferolateral parietal cortices in PD patients without clinical signs of OD. PD patients with clinical signs of OD did not show this shift on MEG.[42] Next to this compensatory shift in cortical activation several other compensatory strategies such as bolus modification and volume adjustment by taking smaller sips or bites may spontaneously be developed by PD patients.[43] This may improve patient's self-perception of swallowing, and also the safety and efficiency of swallowing, but does not necessarily improve the biomechanics of their actual swallowing disorder.

Multiple reasons may underlie this moderate agreement between PROMs and IROMs on OD in PD. The absence of a support network, the level of cognitive impairment, or the presence of neurobehavioral conditions such as mood disorders or optimism may affect a patient's perception of swallowing.[44] This study highlights that there are PD patients with similar FEES and/or VFS findings that cannot be lumped together under the same pathophysiological umbrella due to their differences in PROMs. This research has an important clinical relevance since it can give rise to differentiations in OD management for PD in the future.

Limitations of the Study

The present study has some limitations. Deep learning methods such as MLP analysis require a sufficient amount of input data in order to give reliable outcomes. Although several techniques were used to improve the statistical power, analyses with larger sample sizes may result in different outcomes. Moreover, specific confounders responsible for different clusters of patients within the same clinical patient label could not be identified. Maybe if other confounders were used in the statistical analysis, other clusters or OD phenotypes might have come forward. Data on possible confounders such as the precise duration of PD were certainly considered but often not clear. Patients came from all over the Netherlands and their medical history was obtained from the referring neurologist. The letters did not always provide clarity about the date of onset of PD.

Conclusion

In conclusion, the present study confirms inconsistencies between the signs of OD found using FEES and/or VFS and the burden of OD a patient may experience. There are PD patients with similar IROMs based findings that cannot be lumped together under

the same pathophysiological umbrella due to their differences in PROMs. Since the exact origin of these differences is not fully understood, it seems appropriate for the time being to take into account the different dimensions of OD during the swallowing assessment so that they can be included in the patient-tailored treatment plan.

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PART II

An update on treatment of dysphagia and dysphonia in Parkinson’s disease

5

Treatment effects for dysphagia in Parkinson's disease: a systematic review

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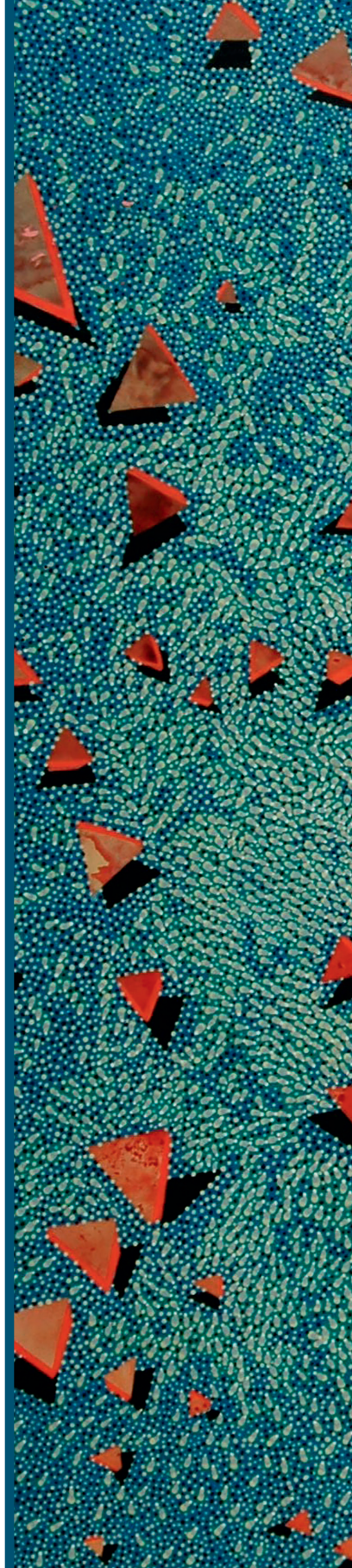

Abstract

Background
Dysphagia remains a common problem in Parkinson's disease (PD). Previous systematic reviews on therapy effects for oropharyngeal dysphagia in PD have shown a lack of evidence. In the past 5 years several placebo or sham-controlled trials with varying results have been published.

Objective
The aim of this systematic literature review is to summarize and qualitatively analyze the published studies on this matter.

Methods
Studies published up to December 2013 were found via a systematic comprehensive electronic database search using PubMed, Embase, and The Cochrane Library. Two reviewers independently assessed the studies using strict inclusion criteria.

Result
Twelve studies were included and qualitatively analyzed using critical appraisal items. The review includes rehabilitative (exercises, electrical stimulation, bolus modification etc.) and pharmacologic treatment. Some well-designed controlled trials were included. However, none of the included studies fulfilled all criteria for external and internal validity. A meta-analysis was not carried out as most of the studies were not of sufficient quality to warrant doing so.

Conclusion
Expiratory Muscle Strength Training (EMST) and Video-Assisted Swallowing Therapy (VAST) may be effective dysphagia treatments solely or in addition to dopaminergic therapy for PD. However, these preliminary results warrant further investigation concerning their clinical applicability, and further research should be based on randomized sham-controlled trials to determine the effectiveness and long-term effects of different therapies for dysphagia in PD.

Introduction

Parkinson's disease (PD) is characterized by motor symptoms including tremor, rigidity, postural instability, and bradykinesia. These symptoms are due to a gradual loss of dopaminergic neurons located in the substantia nigra [1]. However, many non-motor symptoms can manifest in PD, including autonomic dysfunction, neuropsychiatric symptoms, etc. [1, 2, 3] The pathophysiology of the underlying oropharyngeal dysphagia is poorly understood. Dysfunction of the swallowing central pattern generator (brainstem) and degeneration of the substantia nigra seem to be important causes, and disturbance of nondopaminergic neural networks may be a major contributing factor.[1,4,5]

One of the main causes of death in PD is pneumonia (4-30%).[2, 6, 7] This is a multi-factorial problem which includes an altered oropharyngeal bacterial flora, immunocompromised health status, and aspiration due to swallowing disturbances, of which the latter occurs with a prevalence of 16% to 87%.[8, 9] Treating dysphagia might be one of the cornerstones to prevent pneumonia in patients with PD.

Furthermore, swallowing disturbances can have a major impact on quality of life in patients with PD.[10, 11] Swallowing disturbances impair social interaction, give a feeling of fatigue, and decrease the pleasure and ability to select and consume various foods.[12] Therefore, treating dysphagia in PD is necessary in order to improve quality of life and to reduce mortality rates due to aspiration pneumonia.

Traditionally, swallowing is divided into four stages. The swallowing stages can be seen as a complex, sequential response along a continuum of automaticity, with the esophageal stage being most automatic and the oral preparatory stage the least.[12] In PD, disturbances may manifest in any stage of the swallowing process (oral preparatory, oral, pharyngeal, and esophageal stage). Abnormal bolus formation due to impaired lingual movements, aspiration due to delayed laryngeal movements, and impaired upper esophageal sphincter movements are common findings in PD.[13]

Various treatments for dysphagia in PD have been described including surgical interventions, bolus modification, neuromuscular electrical stimulation, postural and airway protective maneuvers, and pharmacological interventions. Previous systematic reviews on different aspects of dysphagia treatment in PD show a lack of sufficient evidence due to the absence of controlled trials and due to small sample sizes.[3, 15-17] Other systematic reviews have reported the effects of deep brain stimulation (DBS) and repetitive transcranial magnetic stimulation on dysphagia.[18, 19] The aim of the current systematic review is to evaluate the latest literature concerning the effects of treatment for dysphagia in PD and to provide an evidence-based overview to aid in clinical decision making.

Methods

Identification and selection of studies

Two authors independently carried out the literature search using the electronic databases PubMed, Embase, and the Cochrane Library. They performed a search as listed in table 1. The search was limited to articles published since June 2008 until December 2013. A previous systematic review by Baijens et al. [15] summarized the literature concerning the same subject until May 2008. Only articles on the effects of therapy for oropharyngeal dysphagia in Parkinson's disease were included. Studies describing treatment for esophageal dysphagia were excluded. In- and exclusion criteria are listed in table 2. The reference lists of all the included articles were searched for additional literature, but did not yield any additional studies. It was decided to exclude patients with DBS since dysphagia has often been described as a side-effect of DBS.[18] A systematic review regarding this subject by Troche et al. [18] however, found no significant effect on swallowing after DBS in most included studies.

Table 1. Systematic syntax

PubMed
((((“Parkinson Disease”[Mesh]) OR (“Parkinsonian Disorders”[Mesh]) OR (“Parkinson Disease, Secondary”[Mesh])) AND (“Deglutition Disorders”[Mesh] OR “Pneumonia, Aspiration”[Mesh] OR “Respiratory Aspiration”[Mesh])) OR ((deglut* OR swallow* OR dysphag* OR aspirat*) AND ((hypokinetic syndrome) OR Parkinson* OR (paralysis agitans))))
Embase
((swallowing/ or dysphagia/ or aspiration pneumonia/ or food aspiration/ or pulmonary aspiration/ or aspiration/) and (parkinsonism/ or Parkinson disease/)) or ((deglut* or swallow* or dysphag* or aspirat*) and (hypokinetic syndrome or Parkinson* or paralysis agitans))
The Cochrane library MeSH terms
([deglutition disorder] OR [Pneumonia, Aspiration] OR [Respiratory Aspiration]) AND ([parkinson disease])
The Cochrane library free-text
(deglut* or swallow* or dysphag* or aspirat*) and ((hypokinetic syndrome) or Parkinson* or (paralysis agitans))

Data analysis and assessment of study quality

The quality of the overall study design was determined using the A-B-C rating scale by Siwek et al. [20] Level A refers to high-quality randomized controlled trials, level B refers to well-designed, nonrandomized clinical trials, and level C refers to consensus or expert opinions. Furthermore, no validated instrument for assessing the methodological quality of therapy effect studies is available.[21] Therefore, a list of criteria for quality assessment was compiled, as derived from the studies of Jüni et al. [22], Crowe et al. [23], Katrak et al. [24], and the Cochrane Handbook for Systematic Reviews of Interventions by Higgins and Green.[21]

Table 2. In- and exclusion criteria

Inclusion criteria
Design
Peer-reviewed journal articles
English, German, French, Spanish, Portuguese or Dutch language articles
Studies with pre- and post-intervention data
N ≥ 10
Participants
Patients diagnosed with Parkinson's disease
Patients with or without swallowing disorders
Patients without Deep Brain Stimulation (DBS)
Adults
Exclusion criteria
Studies presenting a consensus or an expert opinion
In vitro laboratory studies in experimental set-up
Studies involving experiments on animals
Studies involving experiments on cadavers

Data extraction was performed by two independent reviewers and consisted of analysis of critical appraisal criteria per included study. The very few differences in rating were settled by consensus agreement after a discussion. If consensus could not be reached, a third review author was consulted for adjudication. The critical appraisal criteria were rated as 'yes', 'no' or as 'unknown' when insufficient information was provided and are summarized in figure 1. Criteria 1-2 were used to assess generalizability (external validity) and criteria 3-12 to assess reliability and risk of bias (internal validity). The present quality assessment tool, like many other validated ones, does not incorporate a quality score.[21] Finally, a meta-analysis was not carried out as most of the studies were not of sufficient quality to warrant doing so.

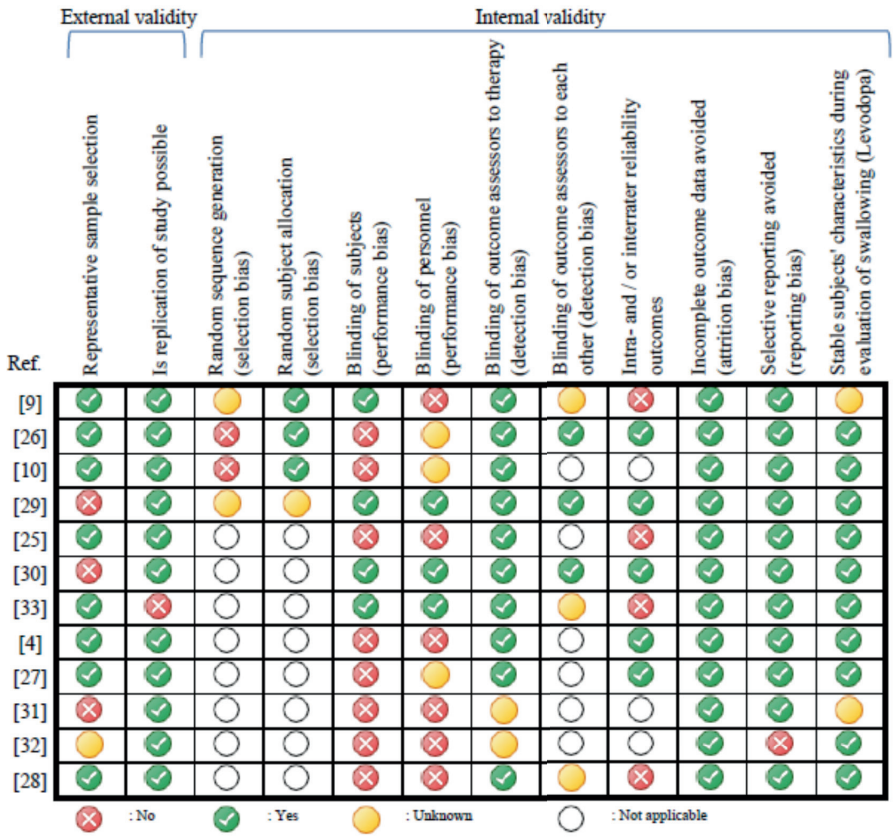

Figure 1. Summary of methodological quality and risk of bias [21-24]

Results

General results

In total, 1442 articles were found in PubMed, Embase, and the Cochrane library databases, as displayed in figure 2. A first selection was made based on abstract and title by two independent reviewers. Next, the definite inclusion was made using the original full-text articles and the in- and exclusion criteria (table 2). Finally, twelve articles were included for subsequent review.

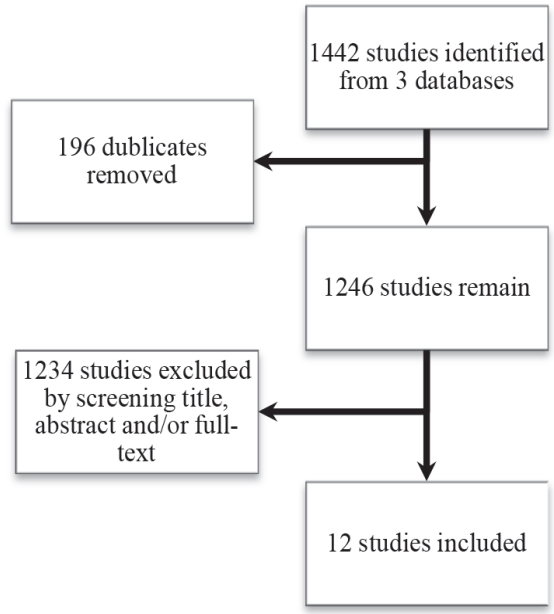

Figure 2. Flow diagram of study selection

Tables 3 and 4 summarize the data per study. They describe rehabilitative and pharmacologic treatments for dysphagia in PD. The classification of treatments was based on previous literature.[15, 25] Surgical or dental treatment interventions for dysphagia in PD were not identified. The first column of each table represents the level of evidence according to Siwek et al. [20] The Hoehn and Yahr scale (H-Y scale) [26] was used to assess the disease severity if present. Therapy, evaluation techniques, outcome parameters, "on/off" motor phase ("on" motor phase means within 90–120 minutes after the intake of antiparkinsonian medication), statistical analysis, and authors' key findings of the twelve articles were reviewed and summarized.

Methodological quality of included studies

Four level A and eight level B studies were included. Figure 1 summarizes the critical appraisal criteria per study. None of the included articles met all critical appraisal criteria. Seven studies fulfilled all criteria for external validity [4, 10, 11, 27-30] and five studies fulfilled one criterion.[31-35] Two studies met eight of the ten criteria for internal validity, thereby representing a low risk of bias [31, 32], while two studies met six or seven criteria.[28, 35] All other studies met less than six criteria for internal validity.[4, 10, 11, 27, 29, 30, 33, 34] Criteria on external and internal validity could not be scored on 14 occasions because of insufficient reporting.

Rehabilitative treatments

Table 3 summarizes the data of the included studies on rehabilitative treatments. The studies are grouped according to the type of intervention. Nine studies concerning rehabilitative treatment were found.

Argolo et al. [27] examined 15 dysphagic Parkinson's patients. They all received the same oral motor exercises for 5 weeks supervised by a speech-language pathologist to increase the strength and range of motion of the mouth, larynx, and pharynx, to ameliorate oral control of the bolus, to enhance coordination between breathing and swallowing, and to improve airway protection. Therapy effect was evaluated using a standardized videofluoroscopy of swallowing (VFS) pretherapy and following 5 weeks of training with different amounts of thin and thick liquids, puree, and soft solid foods. The Swallowing Quality of Life (SWAL-QOL) questionnaire was used to assess therapy effects on quality of life. Descriptive data and statistical analysis showed some improvements in VFS parameters. On the SWAL-QOL questionnaire, only fear and symptom frequency significantly reduced after training.

Pitts et al. [27] and Troche et al. [29] used an Expiratory Muscle Strength Training (EMST) device to evaluate its effect on voluntary cough parameters [29] and VFS parameters (table 3).[29, 31] At baseline and after a 4-week training period (table 3) the participants were asked to swallow a thin liquid barium bolus during VFS. VFS parameters were evaluated by a speech-language pathologist blinded for treatment. Penetration/aspiration scale (P/A scale) [36] scores significantly decreased after training. Subsequently, voluntary cough measures were evaluated using an oral pneumotachograph and spirometry. A significant increase in cough volume acceleration was found after training, which suggests that creating shearing forces and removing unwanted material from the airway improved.

Video-assisted Swallowing Therapy (VAST) is based on a visual cueing mechanism to improve motor and coordination skills in swallowing. Manor et al. [10] evaluated this treatment in forty-two Parkinson's patients in a randomized controlled trial. All patients were instructed about compensatory techniques and conventional swallowing exercises in five sessions during 2 weeks. Patients were ordered to use these techniques at home during drinking and eating for the next 4 weeks. Twenty-one patients received VAST during each session adjunct to these swallowing exercises and compensatory techniques. The VAST included a guided observation of a normal swallowing process, and their own distorted swallow using FEES during the first session. These videos, and a video with a newly learned compensatory swallowing, were used to improve and re-evaluate the distorted swallowing pattern during the next 4 therapeutic sessions. After the fifth session, swallowing was evaluated using FEES (table 3). At baseline the most common swallowing disorder was food residue in the pharynx. After VAST, the food residue significantly improved compared to conventional swallowing exercises solely.

Besides the FEES, several patient-self-reports showed significant subjective swallowing improvements in favor of the VAST group.

Three studies described the effects of a single session of surface electrical stimulation (SES) of the neck in dysphagic patients with PD.[11, 28, 32] Baijens et al. [28] described SES in 10 patients with PD and 10 age and gender matched healthy control subjects. Three different electrode positions on the neck were applied in random order per subject. For each electrode position, the current was turned "on" or "off" in random order. VFS parameters (table 3) were scored by experienced raters who were blinded to the group, electrode position, and status of the electrical current (on/off). Few significant effects were observed in dysphagic Parkinson's patients after a single session using different electrode positions. In both patients and healthy control subjects, however, significant results for VFS parameters were found when the current was "off", suggesting placebo effects.

SES versus traditional logopedic dysphagia treatment in PD was evaluated by Heijnen et al. [11] and Baijens et al. [28] Participants were quasi-randomly assigned to the three treatment groups (table 3). The sample sizes of both studies overlapped about 85%. All three groups received traditional logopedic dysphagia treatment, consisting of the following interventions: diverse airway-protecting maneuvers, postural compensation maneuvers, bolus modification and oral intake of various foods, swallowing saliva, and oral motor exercises. Besides this treatment, two groups received submental SES, either motor-level or sensory-level (traditional treatment and SES at the same time). To evaluate the possible subjective swallowing improvements, Heijnen et al. [11] used the Dysphagia Severity Scale (DSS) and two quality of life questionnaires (MD Anderson Dysphagia Inventory [MDADI], SWAL-QoL). Baijens et al. [28] used FEES and VFS to evaluate swallowing. FEES and VFS parameters were scored by raters blinded for each other's ratings, treatment group, and moment of measurement (pre- or posttreatment). In both studies some improvements were found following traditional logopedic dysphagia treatment, however, no statistical group differences due to SES were found.

Table 3. Rehabilitation treatments

Level of evidence [18]	Ref.	Subjects and Hoehn & Yahr scale (H-Y) [24]	"on" or "off" motor phase	Intervention	Evaluation techniques and Outcome parameters	Statistical analysis	Authors' conclusion
A (randomized clinical trial)	[9]	N = 42 G1: N = 21, G2: N = 21 H-Y: I-IV	Unknown	All subjects received 5 half an hour sessions of conventional swallowing therapy for 2 weeks G1: conventional swallowing therapy solely G2: additional video-assisted swallowing therapy (VAST). Both groups received a 6th session 4 weeks after the 5th session.	FEES outcomes: temporal- and visuoperceptual parameters; SWAL-QOL; SWA-CARE; POE; SDQ	Multivariate analysis of variance, paired comparison analysis	As a result of the intervention, food residue significantly improved in both groups. However, the improvement in the VAST group was significantly greater than in the control group. Parameters for penetration or aspiration didn't show any group differences. Additionally, all questionnaires showed significant swallowing improvements in favor of the VAST group direct after training and 1 month after training.
A (randomized clinical trial)	[26]	N = 90 G1: N = 30, G2: N = 30, G3: N = 30 H-Y: I-V	"on"	All subjects received traditional logopedic dysphagia treatment. G1: traditional logopedic dysphagia treatment solely. G2: additional motor-level SES of the suprahyoid musculature. G3: additional sensory-level SES of the suprahyoid musculature.	FEES and VFS outcomes: visuoperceptual parameters.	Proportional odds models, intra- and intermeasurer reliability analysis	Analysis of VFS parameters showed a group independent significant improvement in piecemeal deglutition. Subsequently, on FEES, preswallow posterior spill and delayed initiation pharyngeal reflex showed significant improvements after any therapy. No additional effect of SES was observed.
A (randomized clinical trial)	[10]	N = 88 G1: N = 30, G2: N = 30, G3: N = 30 H-Y: I-IV	"on"	All subjects received traditional logopedic dysphagia treatment. G1: traditional logopedic treatment solely. G2: additional motor-level SES of the suprahyoid musculature. G3: additional sensory-level SES of the suprahyoid musculature.	SWAL-QOL; DSS; MDADI; FOIS	Wilcoxon signed rank test, Mann-Whitney U test,	Analysis showed significant therapy effects for the total group on both quality of life questionnaires. However, no statistically significant group differences were found on both MDADI and SWAL-QOL.
A (randomized clinical trial)	[29]	N = 60 G1: N = 30 EMST device, G2: N= 30 sham group H-Y: II-IV	"on"	One training session at baseline with an expiratory muscle strength training (EMST) device and during 4 weeks, 5 days a week, 5 sets of 5 breaths at home. Sham group: identical EMST device, however the device was made non-functional by removing the pressure release valve.	VFS outcomes: temporal-, spatial-, and visuoperceptual parameters; Pressure manometry: MEP; SWAL-QOL	Repeated-measures analysis of covariance, regression analysis, intra- and intermeasurer reliability analysis	EMST may be a restorative treatment for dysphagia in those with PD. The mechanism may be explained by improved hyolaryngeal complex movement.
B (prospective cohort study)	[25]	N = 15 H-Y: I-IV	"on"	Oral motor exercise, twice a day, five days a week of which 1 day supervised by a speech-language pathologist, for five weeks.	VFS outcomes: temporal-, and visuoperceptual parameters; SWAL-QOL	Multiple linear regression, correlation of Spearman	Motor swallowing exercises may reduce swallowing disorders in PD patients without lingual pumping and dental absence and impact quality of life positively in individuals with PD.

Level of evidence [18]	Ref.	Subjects and Hoehn & Yahr scale (H-Y) [24]	"on" or "off" motor phase	Intervention	Evaluation techniques and Outcome parameters	Statistical analysis	Authors' conclusion
B (case-control study)	[30]	N = 20 G1: N=10 healthy controls, G2: N=10 PD H-Y: I-III	"on"	Single session SES using different electrode positions on the neck. Electrode positions and electrical current status were randomly applied.	VFS outcomes: temporal-, spatial-, and visuoperceptual parameters;	Regression analysis, intra- and intermeasurer reliability analysis	Only a few significant effects of a single session of SES using different electrode positions were observed in this study. Significant results for temporal and spatial variables were found regardless of the status of the electrical current in both groups suggesting placebo effects.
B (case-control study)	[33]	N = 20 H-Y: II-IV	"on"	Five minutes of gum chewing	Laryngeal and respiratory bellows connected to laptop computer and a PowerLab system • Swallow frequency • Swallow latency	Analysis of variance, post hoc trend analysis, t-test	For both swallow frequency and latency significant changes were found comparing baseline outcomes, during chewing, and direct after chewing. Swallow frequency decreased after chewing over time, reaching baseline at 5.317 minutes.
B (case- control study)	[4]	N = 13 H-Y: II-V	"on"	Thermal-tactile stimulation (TSS) on anterior faucial arch immediately pre-swallow versus no stimulation.	VFS outcomes: temporal parameters.	Wilcoxon signed rank test, intra- and intermeasurer reliability analysis	TSS significantly reduced temporal measures of the pharyngeal phase of swallowing in the PD population. Significant results may be attributed to the role of sensory stimulation in improving motor function in PD.
B (prospective cohort study)	[27]	N = 10 H-Y: II-III	"on"	One training session at baseline using the EMST device and self-training at home during 4 weeks, 5 days a week, 5 sets of 5 breaths a day.	VFS outcomes: visuoperceptual parameters. Pressure manometry: MEP Oral pneumotachography: cough flow waveform outcomes: • Inspiration phase duration (IPD), • Compression phase duration (CPD), • Expiratory phase rise time (EPRT), • Expiratory phase peak flow (EPPF), • Cough volume acceleration	Wilcoxon signed rank test, Bonferroni correction, intrameasurer reliability analysis	P/A scale scores and MEP significantly decreased after EMST. Concerning voluntary cough outcomes, there was a significant decreased CPD and EPRT following EMST, stating an increased effectiveness in voluntary cough actions. IPD and EPPF didn't show significant changes. EMST is a viable treatment modality for a population of participants with PD at risk of aspiration.

VFS = Videofluoroscopy of swallowing; FEES = fiberoptic endoscopic evaluation of swallowing; PD = Parkinson's Disease; G1 = group 1; G2 = group 2; G3 = group 3; MEP = Maximum Expiratory Pressure
SWAL-QOL = dysphagia specific quality of life questionnaire; DSS = Dysphagia Severity Scale; MDADI = MD Anderson Dysphagia Scale; SES = Surface Electrical Stimulation
P/A scale = penetration / aspiration scale; SWAL-CARE = Swallowing Quality of Care; POE = Pleasure of Eating; FOIS = Functional Oral Intake Scale, SDQ = Swallowing Disturbances Questionnaire

Regan et al. [4] used thermal-tactile stimulation to improve a delayed pharyngeal swallowing reflex in PD by providing sensory stimulation via a cold probe to the anterior faucial arches. Thirteen participants were asked to swallow 5 ml thin liquid barium and a paste bolus, before and after application of the cold probe to the anterior faucial arches. The VFS swallows were judged by a rater, blinded to patient identity, and severity of disease. The duration of three of the four temporal VFS parameters significantly decreased following treatment. These findings support the hypothesis that thermal-tactile stimulation can speed up the involuntary pharyngeal swallow.

The effect of gum chewing on swallow frequency and latency was evaluated in a case-control study by South et al. [35] Two bellows positioned on the larynx and chest connected to a laptop were used for measuring the swallow frequency and latency before, during, and immediately after chewing gum. Twenty non-dysphagic Parkinson's patients were asked to chew gum for 5 minutes and to breathe normally without talking. For both swallow frequency and latency, significant changes were observed when comparing before and during chewing, during and direct after chewing, and before and immediately after chewing gum. After chewing gum the number of swallows gradually decreased over time.

Pharmacologic treatments

Müller et al. [33] described the effect of dopaminergic treatment in de novo PD. After a 12 month follow-up, 171 Parkinson's patients participated of whom 31 received no dopaminergic treatment and 140 received dopaminergic treatment (table 4). Using the Unified Parkinson's Disease Rating Scale (UPDRS) autonomic symptoms including dysphagia were assessed at baseline and after 12 months. After 12 months the dopaminergic treatment group revealed a significant decrease in the severity of dysphagia.

Table 4. Pharmacologic treatments

Level of evidence [21]	Ref.	Subjects and Hoehn & Yahr scale (H-Y) [22]	Intervention	Evaluation techniques and Outcome parameters	Statistical analysis	Authors' conclusion
B (prospective cohort study)	[31]	N = 171 G1: N = 31, G2: N = 64, G3: N = 76 H-Y: I-III	G1: no treatment G2: L-dopa only G3: dopamine agonist(s) only or both L-dopa and dopamine agonist(s).	Unified Parkinson's disease rating scale (UPDRS)	t-test, McNemar test, Wilcoxon signed rank test	Some significant changes in severity of dysphagia scored with UPDRS were found after dopaminergic treatment. The results encourage to optimize dopaminergic treatment in patients suffering from dysphagia, as improvement may be achieved in some individuals and prevent discomfort and complications like aspiration.
B (case-control study)	[32]	N = 36. G1: N = 14, G2: N = 22	G1: L-dopa 'on' and 'off'. G2: Healthy control subjects without intervention	UPDRS; Accelerometry: swallow duration; Surface EMG parameters; • Peak amplitude, • Burst area, • Burst duration, • Rise time, • Fall time, • Interburst latency	Wilcoxon signed rank test, repeated-measures analysis of variance	On UPDRS, global motor scores improved significantly after L-dopa treatment. However, EMG parameters didn't show significant changes. This study shows that L-dopa more effectively normalizes the coordination of the swallow response than individual muscle activations.

Table 4. *Continued.*

Level of evidence [21]	Ref.	Subjects and Hoehn & Yahr scale (H-Y) [22]	Intervention	Evaluation techniques and Outcome parameters	Statistical analysis	Authors' conclusion
B (prospective cohort study)	[28]	N = 16 H-Y: II-V	Injection of 125 U Botulinum toxin (BT-A) in both parotid glands	VFS outcomes: visuoperceptual parameters; Questionnaire concerning feeding complaints.	Descriptives, Wilcoxon signed rank test	There were no significant VFS swallowing differences and no significant differences on a dysphagia questionnaire after BT-A injection into the parotid glands.

VFS = Videofluoroscopic of swallowing; EMG = electromyography; G1 = group 1; G2 = group 2; G3 = group 3; L-dopa = Levodopa

In a study of Tawadros et al. [34] the swallowing function of fourteen Parkinson's patients and twenty-two healthy control subjects was evaluated in response to Levodopa (L-dopa). The Parkinson patients were asked to swallow several increasing amounts of standardized thin liquids during the "off" and "on" motor phase. Surface electromyography (EMG) and the UPDRS were used to evaluate therapy effects on swallowing. The Parkinson's patients showed a significant improvement on global motor scores on the UPDRS, however, improvements on dysphagia solely were not reported. Submental and laryngeal EMG parameters did not show significant effects following the intake of L-dopa.

Botulinum toxin-A (BT-A) injections in the parotid glands have been proven to be effective in reducing sialorrhoea in PD.[37] Nóbrega et al. [30] evaluated its effect on swallowing dynamics in PD. Sixteen patients answered a feeding complaints questionnaire and were asked to swallow several standardized barium boluses (thin and thick liquid, and half a biscuit). VFS was performed at baseline and 30 days following BT-A injections. After 30 days, sialorrhoea significantly decreased in severity. No significant VFS changes in dysphagia were seen 30 days after BT-A injections. Aspiration and penetration did not show significant treatment differences.

Discussion

Methodological comments

The aim of this systematic review is to update the literature concerning dysphagia treatments in PD since the literature study of Baijens et al. in 2008.[15] In this previous study, some positive group tendencies were found, however, sufficient evidence stating significant therapy effects could not be found due to a lack of well-designed studies.[15]

In this current literature review the methodological quality of the included studies (figure 1) has improved compared to the previous studies reported by Baijens et al. [15]. In the past five years, four level A randomized trials and eight level B non-randomized trials have been published on this matter (tables 3 and 4). However, figure 1 shows that none of the included studies met all critical appraisal criteria. Only two of the four randomized controlled trials described the method of randomization.[10, 11, 28, 31] Most studies used a substantial sample size (minimum: 10; maximum: 90) and all but one mentioned a PD severity score such as the H-Y scale [32]. Five of the eleven studies mentioning a H-Y scale, used a study sample with mild to moderate disease severity.[10, 11, 28, 32, 33] However, it is known that the number of patients with significant cognitive impairment increases in the higher levels of the H-Y scale excluding them from several types of treatment.[38]

The next methodological issues concern the topic of blinding. Criterion 5 (performance bias) had the most 'no' scores of all criteria (8/12) indicating that most studies had an inappropriate blinding of subjects for the treatment. Only four studies blinded the

study subjects [10, 31, 32, 35] and three blinded the executive personnel for treatment.[31, 32, 35] Most likely this methodological shortcoming is due to technical difficulties to either blind participants or executive personnel. Some studies didn't report whether there were one or more outcome assessors (detection bias) and if they were blinded to each other's ratings.[10, 30, 35] The majority of the studies determined the intra- and interrater reliability.[4, 28, 29, 31, 32] Only one study had a higher risk of reporting bias, since it failed to report sufficient data to reveal therapy effects in dysphagia.[34]

Therapy effects in literature

In PD the first treatment usually consists of dopaminergic treatment such as L-dopa. However, there is still no consensus whether L-dopa treatment has an effect on non-motor symptoms such as dysphagia.[15, 16, 39] In the current systematic review, only 2 level B studies were included regarding the effects of dopaminergic treatment on dysphagia (table 4).[33, 34] Some significant changes were found on the UPDRS questionnaire regarding dysphagia and no changes on submental and laryngeal EMG after dopaminergic treatment. However, the methodological quality of both studies is poor.

A meta-analysis of 5 trials by Menezes and Melo [16] showed that L-dopa does not improve dysphagia in PD. However, Sutton [39] reported several trials with small sample size rejecting this statement, again, some with questionable methodological quality as mentioned in the systematic review by Baijens et al. [15] Whether L-dopa affects dysphagia in PD or not remains unclear. Large well-designed randomized clinical trials are necessary to evaluate the therapy effects of L-dopa on the swallowing physiology.

In addition to dopaminergic treatment in PD, alternative treatments such as rehabilitative treatments (swallowing exercises, compensatory maneuvers, electrical stimulation, bolus modification etc.) can be considered for persistent dysphagia. Swallowing exercises, as evaluated by Argolo et al. [25], guided by speech- and language pathologists, are a valuable contribution to dopaminergic treatment for dysphagia in PD. Argolo et al. [27] reported that some VFS parameters improved after swallowing exercises. On the other hand, transit time measures were not reduced and subjective dysphagia persisted, although some subscores on quality of life questionnaires improved.

Furthermore, the exact role of traditional logopedic dysphagia treatment in PD should be specified. The studies of Baijens et al. [28, 32] and Heijnen et al. [11] reported a positive therapy effect of traditional logopedic dysphagia treatment. However, its exact content, frequency, and duration remain to be studied in detail to compile a clinical decision-making model for treatment options in this patient population. In conclusion, the combination of dopaminergic treatment and swallowing exercises may improve dysphagia, but it is not sufficient to target all aspects of the pathophysiology of dysphagia in PD.

Literature of good methodological quality on rehabilitative treatments used in addition to dopaminergic treatment for dysphagia in Parkinson's patients is scarce.[15] The studies of Pitts et al. [29] and Troche et al. [31] showed improvements in expiratory muscle strength in patients with PD and secondarily, improvements on the VFS P/A scale after 4 weeks of EMST (table 3). According to these results, EMST could be a potential cost-effective therapy, besides dopaminergic treatment and other logopedic swallowing exercises, in reducing laryngeal penetration and aspiration in PD. Since both studies used subjects with mild to moderately impaired swallowing, new evidence should focus on a broader spectrum of severity of PD and long-term outcomes of EMST.

In a randomized controlled trial by Manor et al. [10] VAST was evaluated in dysphagic Parkinson's patients with some positive results. In clinical practice, video-assistance combined with logopedic swallowing exercises might reduce dysphagia. Since the follow-up time was relatively short, the question remains how long the effect of VAST will last. It might be very time-consuming if video-assistance has to be repeated on a regular basis to maintain the positive effects on swallowing. Therefore, in the future, randomized controlled studies evaluating VAST in PD should focus on a longer follow-up time.

Subsequently, Regan et al. [4] investigated thermal-tactile stimulation on the faucial arches with a cold probe and its effect on dysphagia. They revealed some significant improvements in the timing of swallowing. Nevertheless, thermal-tactile stimulation seems a short-time optimization of the swallowing pathophysiology. Therefore, it might be hard to use thermal-tactile stimulation in clinical practice or at home. However, applying a cold probe on the faucial arches may contribute to the knowledge about the pathophysiology of the swallowing reflex in PD and may be an inspiration for developing further treatments.

The literature on SES for oropharyngeal dysphagia has been evaluated by Clark et al. until 2009.[40] Fourteen studies with many methodological problems were included in this review, reporting, however, promising results for dysphagia. Besides that, only one of the fourteen articles studied a subpopulation of PD.

SES had no significant therapy effect in PD in the methodological designs studied by Baijens et al. [28, 32] and Heijnen et al. [11] Therefore, SES of the neck does not seem to improve the pathophysiological aspects of swallowing in PD. These observations imply a need to carefully consider whether or not to use SES for oropharyngeal dysphagia in PD in clinical practice. Although no side-effects emerged during the experiments conducted in the studies, the possibility of their occurrence should not be disregarded when deciding to treat this patient population with SES.

Although botulinum toxin-A injections have been effective for treating sialorrhoea in PD, Nóbrega et al. [30] revealed no effects on swallowing. Chewing gum as evaluated by South et al. [35] significantly increased swallow frequency and decreased latency of swallowing. However, it lacked measurements to assess qualitative changes in swallowing physiology related to swallowing in a prandial context.

Limitations of the review

The present systematic review has some limitations with respect to the search strategy, quality, and data analysis. The systematic search generated twelve studies. One reason for this low number may be the inconsistent terminology used in therapy effect research. Furthermore, the search strategy may have been too specific or the number of selected databases too small. It is possible that eligible studies were missed despite the extended search (table 1). Also excluded was the gray literature for the reason that basic information such as authorship, publication date, or publishing body may not be discerned with certainty. Furthermore, the assessment of study quality was performed using critical appraisal criteria derived from other studies or tools.[21-24] There is no evidence that these criteria can be used to qualitatively analyze therapy effect studies. Another method of methodological quality assessment may have produced different results.

Conclusion

Few reports have been published on the effect of therapies for oropharyngeal dysphagia in PD. For dopaminergic treatment, consensus has yet to be reached whether it affects swallowing physiology or not. In case of persistent dysphagic symptoms despite pharmacological treatment, alternative approaches such as logopedic dysphagia treatment can be considered.[11, 27, 28, 32] Subsequently, several rehabilitative therapies, including EMST, and VAST, have been successful.[10, 29, 31] Much work still needs to be done to improve the management of oropharyngeal dysphagia in patients with PD. Further research should focus on several remaining gaps in our knowledge on treatment interventions for oropharyngeal dysphagia in PD. Well-designed randomized controlled studies using larger patient populations are necessary to evaluate clinical applicability and the potential therapeutic effects of new treatment techniques.

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6

The effects of surface electrical stimulation plus voice therapy in Parkinson's disease

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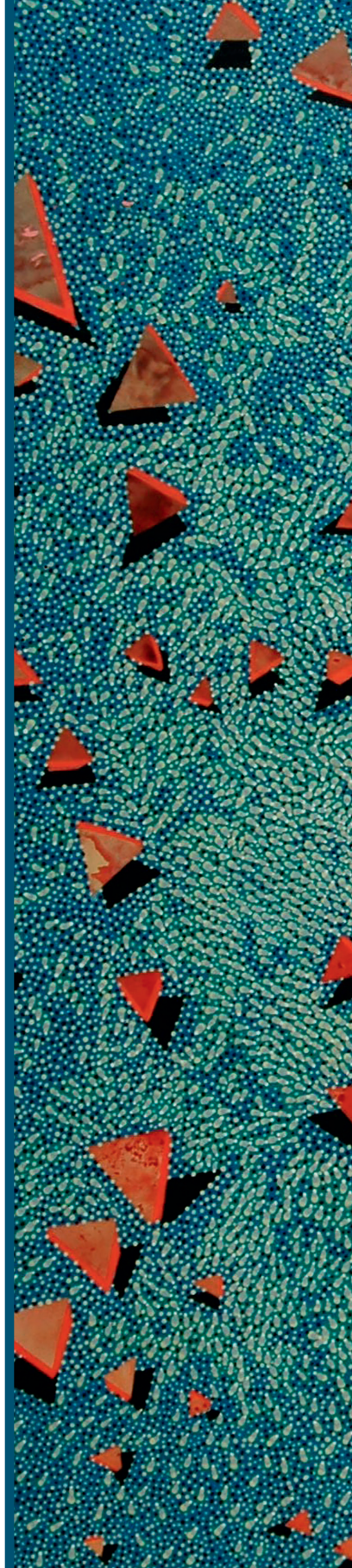

Abstract

Objective
To assess the effects of surface electrical stimulation (SES) plus voice therapy on voice in dysphonic patients with idiopathic Parkinson's disease (IPD).

Methods
Patients were assigned to three treatment groups (n=28 per group) and received daily treatment for three weeks, five days a week. All three groups received voice therapy (usual care). In addition, two groups received SES, either motor-level or sensory-level stimulation. A standardized measurement protocol to evaluate therapy effects included the Voice Handicap Index (VHI) and a videolaryngostroboscopy.

Results
VHI and videolaryngostroboscopic assessment revealed statistically significant differences between baseline and post-treatment across all groups, without any post-treatment differences between the three groups.

Discussion
Intensive voice therapy (usual care) improved Patients with IPD' self-assessment of voice impairment and the videolaryngostroboscopic outcome score. However, SES used as an add-on to usual care, did not improve Patients with IPD' self-assessment of voice impairment or the videolaryngostroboscopic outcome scores any further.

Introduction

Dysphonia is a common finding in idiopathic Parkinson's disease (IPD) and its treatment remains a challenge.[1-3] Dysphonia is often accompanied by other disturbances in the upper aerodigestive tract such as hypokinetic dysarthria and oropharyngeal or esophageal dysphagia.[3] During the course of the disease, up to ninety percent of IPD patients will develop voice complaints including breathiness, hoarseness, reduced loudness, vocal tremor, restricted pitch variability, etc. [2-4] Voice disorders, among others, may affect speech intelligibility and can have a major impact on health-related quality-of-life in IPD as they interfere with the communicative abilities of the patient.[5, 6] As with other IPD-related dysfunctions, dysphonia can be initially treated with levodopa as this medication is usually prescribed to improve the overall motor-function of the patient.[7-10] If symptoms persist, other therapeutic approaches such as voice therapy (for instance Lee Silverman Voice Treatment [LSVT LOUD]) or in specific cases surgical treatment (i.e. vocal fold augmentation) may be considered.[7, 8] These treatments may improve dysphonia-specific quality of life and voice functionality, but so far no treatment can completely halt the inevitable decline. The question is whether surface electrical stimulation (SES) can be of added value in the rehabilitation of voice complaints.

There are currently no large-scale investigations on voice rehabilitation using SES of the neck combined with voice therapy (usual care) in IPD patients. As in sports medicine, where adjunctive electromyostimulation has been used to enhance the effects of muscle training, it is hypothesized that voice therapy with adjunctive SES may enhance the vocal function.[11]

Guzman et al. have carried out a study in this context concluding that SES in combination with voice therapy might be a useful intervention to improve voice quality in patients with a superior laryngeal nerve injury.[12] Furthermore, seven patients with bilateral vocal fold bowing were enrolled in a study by Lagorio et al. [13] Voice therapy with adjunctive SES seemed to reduce vocal fold bowing resulting in improved acoustic, laryngeal, and patient-reported outcome measures in this study.[13]

The rationale of SES is twofold: first, the stimulation of the nerve and its motor end plate, and consequently the muscle fibers, resulting in re-education of functional muscle contraction patterns mainly being a peripheral effect.[14, 15] Second, when SES is applied to the skin at low current levels, it activates the sensory nerve endings in the surface layers of the skin providing sensory feedback to the central nervous system that uses this feedback to make appropriate motor actions. Motor control is fundamentally the integration of this sensory information to generate desired movements or action.[16]

It is unknown if SES can improve voice quality in IPD patients by improving vocal fold function or if SES could be used as a cueing tool to improve sensory feedback and

internal cueing for voice production.[7, 8, 17] Based on the aforementioned mechanisms, the aim of this study was to describe the effects of SES plus voice therapy (usual care) on voice function in dysphonic IPD patients. The hypothesis is that dysphonic IPD patients could benefit from suprahyoid SES using different electrical current intensities as adjunct to voice therapy.

Materials and methods

Study population

IPD patients reporting voice complaints were recruited from hospitals all over the Netherlands. A neurologist clinically diagnosed the IPD according to the UK Parkinson's Disease Society Brain Bank and the Hoehn & Yahr (H&Y) scoring system.[18, 19] In- and exclusion criteria are listed in Table 1.

Table 1. inclusion and exclusion criteria

Inclusion criteria
Idiopathic Parkinson's Disease diagnosed by neurologist
Broad range of voice complaints
Exclusion criteria
Mini Mental State Examination (MMSE) Score <23
Unable to perform videolaryngostroboscopy due to anatomy or gaging
Severe depression
History of a concurrent neurological disease such as stroke
History of voice therapy during the past 6 months
Parkinson medication regime changed within past six weeks
Being non-Dutch speaker, illiterate or blind
History of a deep brain stimulator
History of radiotherapy or extensive surgery of the head in neck

Study design

Each patient was strictly allocated chronologically to a treatment group (alternation), i.e., the first patient to enter the study was placed in group 1, the second patient in group 2, the third patient in group 3, the fourth patient in group 1, and so on to obtain quasi-randomization. The IPD patients were blinded for this allocation during the baseline measurements. All patients received 30 minutes of treatment every day, except for the weekends, during three weeks (fifteen days). Voice therapy (usual care) included the following exercises: airway/breathing exercises to increase respiratory volumes and subglottal air pressure; postural exercises; oral motor exercises; loudness

training by active phonation and vocal fold adduction; and exercises to improve sensory awareness.[7, 8]

The aim of the voice therapy was to improve respiratory and laryngeal tract function. The content of this intensive training program was deemed to be consistent with theories of motor learning and skill acquisition, but also with principles of neural plasticity (i.e., the capacity of the nervous system to change in response to signals).[1, 3] Eighty-five speech and language pathologists (SLPs) affiliated with ParkinsonNet® and having experience in voice therapy for IPD took part in the study.[20] ParkinsonNet® is a national network of more than 3,400 healthcare providers of various disciplines specialized in IPD.[20] This large number of SLPs minimized the possibility of a therapist effect on group performance or on treatment outcome and enabled patients to receive treatment in their own neighborhood all over the country. All SLP's underwent a supervised SES training which was described in a previous study on dysphagic IPD patients.[21]

All three groups received voice therapy and group 2 and group 3, also received SES at the same time, making group 1 the control group. SES at motor-level threshold was applied in group 2 and SES at sensory-level threshold in group 3.

A commercially available electrical stimulator was used (VitalStim® Therapy; frequency 80 Hz, pulse width 700 µs, Chattanooga Group, Chattanooga, TN, USA). Two skin electrodes (VitalStim®, reference 59035) were placed on the suprahyoid skin slightly medially to the posterior horns of the hyoid bone near the presumed location of the superior laryngeal nerves and connected on each side of the midline of the neck (Figure 1). Adult electrodes are circular, have a 2.1-cm diameter, and provide 3.46-cm^2 surface area of stimulation via a carbon-silver substrate. This electrode position was based on previous SES studies in non-IPD patients with dysphonia and on the VitalStim® manual.[13-15] The suprahyoid triangle has suprahyoid muscles (mylohyoid and digastric muscles) and innervations from cervical and cranial nerves such as the trigeminal, hypoglossal with ansa cervicalis, and superior laryngeal nerves (internal and external branches) that are able to receive and transduce stimuli towards the central nervous system as sensory feedback.[16] The protocol for applying electrical current at a motor-level or sensory-level intensity was based on previous studies.[21,24,25] The treatment sessions and all examinations were performed within 90-120 minutes after the intake of antiparkinsonian medication during the "on" motor phase.[22] The "on-off" phenomenon in IPD refers to a switch between mobility and immobility in levodopa-treated patients, which occurs as an end-of-dose worsening of motor function [22].

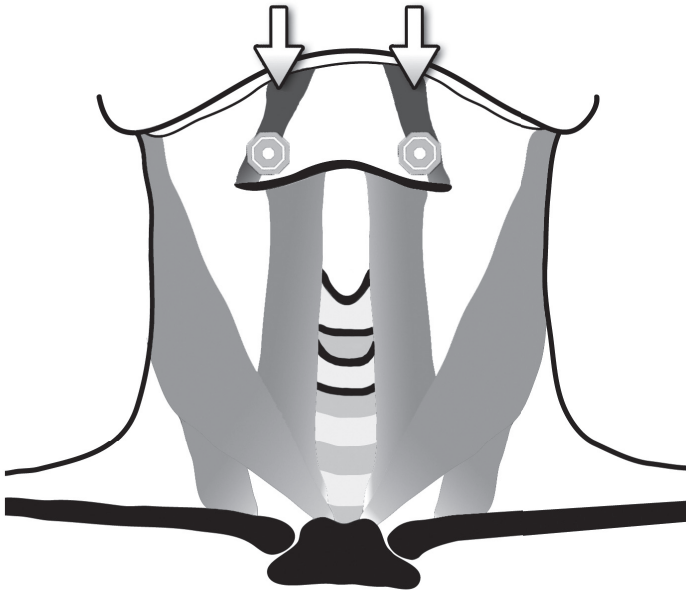

Figure 1. Electrode position (after cleaning, lifting, and shaving the skin): two self-adhesive electrodes (VitalStim®, reference 59035) placed horizontally on the suprahyoid skin slightly medially to the posterior hyoid horns near the location of the superior laryngeal nerves on each side of the midline of the neck (suprahyoid region). The arrows mark the electrodes. The electrodes have a 2.1-cm diameter, and provide 3.46-cm ^{2}surface area of stimulation via a carbon-silver substrate.

Outcome measures

All patients underwent a standardized assessment protocol including: a clinical examination (ear, nose, throat anatomical and cranial nerve integrity, postural behavior - gait, upper limb movement, etc.); the Voice Handicap Index (VHI) [23-25; and] a videolaryngostroboscopy. All measurements were performed within one week before the start of treatment and within one week following the end of therapy by the same laryngologist of the research lab. During baseline measurements, all patients and the laryngologist were blinded to treatment allocation.

The validated Dutch version of the VHI was used to measure the level of voice handicap and disability experienced by the patients.[23] It consists of 30 items divided into three subscales: emotional (VHI-E), functional (VHI-F), and physical (VHI-P). Each item can be scored from 0 to 4, 0 represents 'never' and 4 'always'. Adding the scores of the 30 items yields a total VHI score (VHI-T) ranging from 0 to 120. The higher the total score, the higher the degree of patient-experienced voice handicap.

A videolaryngostroboscopy was performed to assess laryngeal function during phonation and investigate the presence of any laryngeal pathology. The videos were recorded on a DVD at thirty frames per second using a flexible fiberoptic endoscope Pentax FNL-10RP3 (Pentax Canada Inc., Mississauga, Ontario, Canada) together with the Alphatron Stroboview ACLS camera, Alphatron Lightsource, Alphatron contact microphone, and IVACX computerized video archiving system (Alphatron Medical Systems, Rotterdam, The Netherlands). During the examination, patients were seated upright. The field of the image included the laryngeal vestibule, vocal folds, anterior and posterior commissure, and the arytenoids. Video recordings of vocal fold vibration were made during repeated stable phonation of a sustained vowel /a:/ or /i:/ at comfortable pitch and loudness. Each video contained a phonation time long enough to allow the registration of at least one 'complete cycle' of vibration. All selected videos were similar in length and clarity.

Visuoperceptual ordinal and nominal videolaryngostroboscopic variables were derived from reports of the Phonosurgery Committee of the European Laryngological Society (ELS) and scored by a panel of two observers (glottic closure, periodicity of vibratory cycles, vocal fold amplitude, and symmetry of mucosal displacement).[26-28] More details in the online only supplementary data file. All of these variables were scored for each videolaryngostroboscopic recording using varying speed (slow motion, normal, up to frame-by-frame) and repeated as often as necessary. The videolaryngostroboscopic recordings were randomly selected and both observers were blinded to the patients' identity, medical history, and for the measurement moment (baseline versus post-treatment). Prior to the assessment, the observers underwent consensus training for these measurements, as described previously.[26] To determine the intrapanel observer agreement level, 33% of the videolaryngostroboscopic recordings were rated twice by the panel of observers, again blinded and in randomized order. This multidimensional voice protocol was deemed appropriate to measure treatment effects in the present study. Details on statistical analysis are included in the online only supplementary material.

Patient characteristics

The study included 109 mentally competent patients with a diagnosis of IPD and dysphonic complaints. Twenty-five patients were excluded during the study due to change of antiparkinsonian medication (*n*=21), dental surgery (*n*=2), and unexpected comorbidity not related to therapy (*n*=2). None of the patients experienced adverse events as a result of the therapy. Adherence of the patients to therapy and their compliance for antiparkinsonian medication were ensured through a diary completed by the SLPs. Finally, each treatment group contained 28 patients (*n*=84; 20♀ and 64♂). Descriptive data analysis of patient characteristics was performed, and data normality was tested using Shapiro-Wilk tests. No significant differences were found in the baseline general characteristics between the three groups (Table 2) and the duration

of the IPD was at least five years. All patients used levodopa except for two patients in group 1, three patients in group 2, and two patients in group 3. They did not use any antiparkinsonian medication. The median current intensity used for group 2 was 10.5 mA (25th; 75th percentile: 7.3; 14.0) versus 3.3 mA (25th; 75th percentile: 3.0; 4.4) for group 3.

Table 2. Baseline patient characteristics

Treatment group	n	Gender (M; F)[I]	Age in years (median 25;75[II])	MMSE[III] (median 25;75[II])	H&Y scale [IV] (median 25;75[II])
1: Voice therapy	28	22; 6	69 (62; 74)	28 (26; 29)	2 (1; 4)
2: Voice therapy + motor level SES	28	21; 7	65 (60; 74)	28 (26; 29)	2 (1; 3)
3: Voice therapy + sensory level SES	28	21; 7	66 (60; 69)	28 (26.5; 29)	2 (2; 3)
Total group	84	64; 20	68 (60; 73)	28 (26; 29)	2 (1; 3)

[I] male; female
[II] 25th percentile; 75th percentile
[III] Mini mental state examination (range 0-30)
[IV] Hoehn and Yahr scale (range 1-5)

Results

Voice handicap outcomes

Ninety-two percent (n=77) of the patients correctly completed the VHI questionnaire at baseline and ninety percent (*n*=76) after treatment. The mean (standard deviation - SD) VHI-T score for the total group (*n*=84) was 46.4 (21.39) at baseline and 51.2 (18.6) post-treatment. At the baseline, the floor or ceiling effect was considered negligible as few respondents got the lowest or highest possible VHI-T score. Table 3 shows the descriptive statistics of the baseline data and the effect data of the VHI, the level of significance of the difference between post-treatment compared to baseline data for all groups (paired samples t-test), and the level of significance of post-treatment *between group* differences (one way ANOVA F-test for means). In group 2, a significant positive therapeutic effect for the VHI-E (*p*=.006), VHI-F (*p*=.026), and VHI-T (*p*=.033) subscales was found. Furthermore, in the total study population (*n*=77) a significant positive therapeutic effect (post-treatment versus baseline) was observed for the VHI-T (*p*=.003). However, when comparing the post-treatment *between group* scores of each VHI subscale, no statistically significant difference between the three groups was found (Table 3).

Videolaryngostroboscopy outcomes

The levels of intrapanel observer agreement for all videolaryngostroboscopic variables was determined. Agreement levels ranged from moderate to substantial (Cohens Kappa coefficient > 0.52-0.79). The frequency distribution of patients per category of the different videolaryngostroboscopic variables is shown in the online only supplementary data file, providing an indication of the average baseline voice function of the study population. None of the patients showed anatomical changes due to vocal fold pathology of organic origin such as polyps, vocal fold nodules, cysts, etc.

In addition to the complete case analysis, a mixed effects binary logistic model was used for the binary outcomes that were measured repeatedly. For this statistical method, the patients were divided in two clinical patient labels: a normal '0' versus abnormal '1' videolaryngostroboscopic status. Patients received the clinical label 'abnormal' videolaryngostroboscopic status if their videolaryngostroboscopic exam was scored impaired (score 1 or higher) in one or more of the measured videolaryngostroboscopic variables (see online only supplementary data file on statistics).

Table 3. Descriptive statistics of the baseline and the post-treatment Voice Handicap Index (VHI) data and the level of significance of the difference between post-treatment data compared to baseline data for all groups using the paired samples t test. Furthermore, the level of significance of post-treatment *between group* differences using the ANOVA F-overall test for means.

VHI subscales	Treatment group	*n*	Baseline data	Effect data[I]	*p*-value Post-treatment versus baseline	*p*-value Post-treatment *between group* difference
			Mean (SD)	Mean (SD)		
VHI-E	Group 1: Voice therapy	27	16.32 (8.97)	-2.35 (7.97)	.146	.525
	Group 2: Voice therapy + motor level SES	24	16.00 (10.78)	-3.11 (5.57)	**.006**	
	Group 3: Voice therapy + sensory level SES	26	16.14 (8.46)	-1.03 (6.07)	.367	
	Total group	77	16.15 (9.37)	-2.14 (6.55)	**.003**	
VHI-F	Group 1: Voice therapy	27	17.66 (7.17)	-1.33 (4.79)	.160	.057
	Group 2: Voice therapy + motor level SES	24	14.68 (8.81)	-2.60 (5.47)	**.026**	
	Group 3: Voice therapy + sensory level SES	26	17.89 (6.73)	-1.07 (4.46)	.222	
	Total group	77	16.83 (7.61)	-1.65 (4.89)	**.004**	
VHI-P	Group 1: Voice therapy	27	15.41 (6.06)	0.45 (5.03)	.635	.075
	Group 2: Voice therapy + motor level SES	24	13.64 (7.66)	0.46 (5.64)	.680	
	Group 3: Voice therapy + sensory level SES	26	16.48 (5.28)	-0.22 (4.77)	.810	
	Total group	77	15.17 (6.45)	0.23 (5.10)	.781	
VHI-T	Group 1: Voice therapy	27	48.44 (19.70)	-5.13 (14.85)	.112	.065
	Group 2: Voice therapy + motor level SES	24	40.83 (25.61)	-6.77 (13.91)	**.033**	
	Group 3: Voice therapy + sensory level SES	26	49.42 (18.45)	-2.68 (12.04)	.277	
	Total group	77	46.40 (21.39)	-4.77 (13.51)	**.003**	

Abbreviations: SD=standard deviation; SES=surface electrical stimulation; VHI-E=Voice Handicap Index Emotional subscale; VHI-F= Voice Handicap Index Functional subscale; VHI-P= Voice Handicap Index Physical subscale, VHI-T= Voice Handicap Index Total Score.
A *p*-value ≤.05 was considered statistically significant. [I] Effect data = post-treatment minus baseline data.

Table 4 shows the baseline versus post-treatment videolaryngostroboscopic status for each treatment group. In total, 63 patients were included in the logistic regression complete case analysis for the videolaryngostroboscopic outcome (Group 1 - voice therapy *n*=23; Group 2 - voice therapy + motor level SES *n*=21; Group 3 - voice therapy + sensory level SES *n*=19).

Table 4. Descriptive statistics in absolute numbers of the baseline and the post-treatment videolaryngostroboscopic status ('0' versus '1') per treatment group and for the total group (*n*=63).

	Normal	Abnormal	Total
	Post-treatment n (%)		
Group 1: Voice therapy *			
baseline n (%)			
- Normal	13 (56.5)	2 (8.7)	15 (65.2)
- Abnormal	7 (30.4)	1 (4.4)	8 (34.8)
- Total	20 (87.0)	3 (13.0)	23 (100.0)
Group 2: Voice therapy + motor level surface electrical stimulation †			
baseline n (%)			
- Normal	8 (38.0)	2 (9.6)	10 (47.6)
- Abnormal	3 (14.3)	8 (38.1)	11 (52.4)
- Total	11 (52.4)	10 (47.6)	21 (100.0)
Group 3: Voice therapy + sensory surface electrical stimulation ‡			
baseline n (%)			
- Normal	6 (31.6)	2 (10.5)	8 (42.1)
- Abnormal	4 (21.1)	7 (36.8)	11 (57.9)
- Total	10 (52.7)	9 (47.3)	19 (100.0)
Total group **			
baseline n (%)			
- Normal	27 (42.9)	6 (9.5)	33 (52.4)
- Abnormal	14 (22.2)	16 (25.4)	30 (47.6)
- Total	41 (65.1)	22 (34.9)	63 (100.0)

* Improved: 7/23 (30.5%), deteriorated: 2/23 (8.7%)
† Improved: 3/21 (14.3%), deteriorated: 2/21 (9.5%)
‡ Improved: 4/19 (21.1%), deteriorated: 2/19 (10.5%)
** Improved: 14/63 (22.2%), deteriorated: 6/63 (9.5%)

To assess the group effect, an interaction term with the videolaryngostroboscopic variables at baseline was included not showing any baseline group differences not even for the missing values. Thirty (47.6%) patients had an abnormal videolaryngostroboscopic status at baseline and 22 patients (34.9%) an abnormal status after treatment (odds ratio [OR] = 0.194, 95% confidence interval [CI] = 0.06 to 0.607, *p*=.003). The group effect was not statistically significant (*p*=.845). Taking into account the missing values, the mixed effects binary logistic regression analysis produced an OR of 0.470 (95% CI = 0.221 to 0.997, *p*=.049) Fourteen (22.2%) patients showed a positive treatment effect where the videolaryngostroboscopic status abnormal '1' at baseline changed into a normal status '0' post-treatment. After adjustment for age, gender, and the H&Y score in the logistic regression analysis, no statistically significant *between group* differences in the videolaryngostroboscopic outcome were found. Furthermore, six patients (9.5%) showed a negative treatment effect meaning that the videolaryngostroboscopic status normal '0' at baseline changed into an abnormal status '1' post-treatment. This 'reversed effect' was equally distributed over the three treatment groups (*n*=2 per group). To account for missing values, multiple imputation was performed. This technique produced a crude OR of 0.245 (95% CI = 0.081 to 0.741, *p*=.002) and an adjusted OR of 0.184 (95% CI = 0.054 to 0.633, *p*=.007). Sensitivity analyses, which were performed to test the effect of the treatment group, age, gender, and the H&Y score, showed similar results for both the crude and adjusted logistic regression analyses.

Discussion

In the present study the effect of SES as an adjunct to voice therapy (usual care) was investigated in dysphonic IPD patients. It was explored whether SES of the suprahyoid region changes videolaryngostroboscopic outcome scores and patients' self-assessment of voice impairment in daily life. Safety, feasibility, and acceptability of SES for dysphonia in IPD were high as none of the patients left the trial due to adverse events or noncompliance to therapy.

The pathophysiology of dysphonia in IPD is complex. It depends on the coordination of factors in both the peripheral and the central nervous system. Dysphonia can be caused by uncoordinated or disrupted signals along the dopaminergic and non-dopaminergic neural pathways.[1, 3] Previous studies described that IPD patients experience progressive voice impairment with the progression of their disease.[28-30] In this context, well-known voice characteristics of IPD are among others breathiness and reduced loudness due to vocal fold bowing or atrophy, vocal fold tremor and/or rigidity, and weakened diaphragmatic breathing.[31] On the grounds of clinical experience and the literature, we assumed that adding a peripheral stimulus at a sufficient intensity over the suprahyoid triangle with suprahyoid muscles and innervations from cervical and cranial nerves such as the trigeminal, hypoglossal with ansa cervicalis, and superior laryngeal nerves (internal and external branches) originating from the vagal nerve could alter the

videolaryngostroboscopic characteristics and the IPD patients' self-assessment of voice.[13, 32, 33]

A significantly positive therapeutic effect within group 2 for the VHI-E, VHI-F, and VHI-T (sub)scale was found. However, when comparing this therapeutic effect of group 2 with the VHI outcomes of group 1 and 3, the motor level SES did not have a significant additional therapeutic effect. The improvement (baseline versus post-treatment) on the VHI-T score in the total group suggests that intensive voice therapy does have a significant positive treatment effect. This positive therapeutic effect was also seen in the videolaryngostroboscopic results where fourteen (22.2%) patients showed an improved videolaryngostroboscopic status following treatment. Nevertheless, after adjustment for age, gender, and the H&Y score in the logistic regression analysis, no statistically significant *between group* differences in the videolaryngostroboscopic outcome were found. Furthermore, six patients, equally distributed over the three groups, showed a deterioration of the videolaryngostroboscopic status following treatment. Reasons for this may include spontaneous disease progression of the IPD or other variables not measured in our protocol such as pulmonary function parameters. Anyway, the findings of the present study confirm the results of previous studies showing the benefits of voice therapy in IPD.[7, 8, 34]

Thus, no enhancing effect of adjunctive SES was observed in the present study. The absence of a therapeutic effect of SES in this study might be explained as follows. According to other authors, excitability depends on the stimulation parameters applied.[35-38] The fixed stimulation variables (frequency 80 Hz, pulse width 700 µs, current intensity 0 to 25 mA) of the VitalStim® appliance may not have been appropriate to induce any therapy effect during 15 days of SES in dysphonic IPD patients. Another reason for the absence of group differences due to SES may be that snap skin electrodes are not a precisely targeted method of electrical stimulation for suprahyoid muscles and nerves. However, a previous study in 32 healthy subjects without any vocal pathology, with a similar placement of the electrodes as in the present study did result in increased vocal fold adduction during stimulation at rest.[33] Perhaps other anatomical subsites of the neck are more susceptible to the reception and transduction of electrical stimuli for voice rehabilitation in IPD patients.[38] Furthermore, the body of literature on studies using SES in the context of voice rehabilitation is poor and does not allow a direct comparison with our results. These studies were conducted mainly on healthy subjects or in patient groups that were not comparable with the current IPD group. Their study designs with regard to the applied type of electrical stimulator, stimulation paradigm, and voice assessment protocol were also not comparable.[13, 33, 39, 40]

A central cueing effect of the motor- or sensory level stimulus helping the patient to improve the vocal function was expected but ultimately not found in the present IPD sample.[17, 41] In IPD, a deficit in the basal ganglia can result in disturbed internal cueing

of automatic, sequential movements, such as gait, voice or swallowing. External cues provide temporal (timing) or spatial (size) stimuli associated with the initiation and ongoing facilitation of motor activity.[41] External cues can be applied in the form of visual, auditory, and tactile stimuli that can trigger movements or that can provide rhythmic or spatial support to the central nervous system improving the quality and timing of movements. Thus, the explanation that external cue training using SES reroutes the movement through a non-automatic pathway removing it from the automatic basal ganglia pathway, could not be used as a hypothesis in the present study.[41, 42]

Previously, in a small case series of patients (without IPD) with chronic dysphonia due to vocal fold bowing, SES applied over the superior laryngeal nerves and the cricothyroid muscles did significantly improve VHI scores.[13] This study inspired us to design the present larger quasi-randomized study for IPD patients. Likewise, in our study, a therapy effect was found, as indicated by improved videolaryngostroboscopic and VHI scores for all three groups together. However, this effect cannot be attributed to SES, as we did not find any significant post-treatment *between group* differences for the videolaryngostroboscopic and VHI scores. Instead, we can attribute the improvement in the three groups to exercises, since all groups received voice therapy. In itself, this is a valuable finding that can confirm the added value of voice therapy (usual care) for dysphonia in IPD patients. The present study results are preliminary and explorative, making further investigation also considering sham stimulation necessary.

Conclusion

This quasi-randomized controlled study revealed that intensive voice therapy (usual care) improved IPD patients' self-assessment of voice impairment and the videolaryngostroboscopic outcome score. However, SES did not improve IPD patients' self-assessment of voice impairment using the VHI questionnaire or the videolaryngostroboscopic outcome score. The application of SES for dysphonic complaints in IPD patients is unprecedented and these explorative conclusions are preliminary.

Online only supplementary data file

Patient baseline characteristics

Descriptive data analysis of patient characteristics was performed, and data normality was tested using Shapiro-Wilk tests. Table 2 is an overview of these descriptive data (gender, age, MMSE score and H&Y scale). A p≤.05 was defined as statistically significant. No significant differences were seen in the baseline characteristics between the three groups.

Voice Handicap Index pre and post treatment data

Descriptive statistics of VHI baseline data and effect data (post-treatment minus baseline data) were determined and is shown in table 3. Differences between the pre and post-treatment results were tested for significance using a paired samples t-test. Per VHI subscale and the VHI total groups the between group differences were tested using a one-way ANOVA F-test for means, followed by pairwise comparison of means using post-hoc Tukey HSD tests. Again, a p-value ≤.05 was considered statistically significant.

Intrapanel observer agreement for videostroboscopy

The level of intrapanel observer agreement for videolaryngostroboscopic measurements was obtained using Cohen's kappa coefficient for the videolaryngostroboscopic variables periodicity, symmetry, closure, and type of closure defect and the linear weighted kappa coefficient for amplitude. Definition, scale and Cohen's kappa coefficient are listed in the table below.

Table: Videolaryngostroboscopic ordinal and nominal variables derived from reports of the Phonosurgery Committee of the European Laryngological Society

Variable name	Definition	Scale	Kappa[III]
Amplitude, left and right vocal fold[I]	Extent of lateral movement of the medial free edge of each vocal fold during phonation (displacement from closed phase of the vibratory cycle to the maximal open phase)	0 = normal 1 = impaired 2 = absent	0.69
Periodicity, left and right vocal fold[I]	Temporal regularity of vibratory cycles	0 = normal 1 = impaired	0.79
Symmetry[I]	Symmetry of mucosal displacement	0 = normal 1 = impaired	0.52
Closure[I]	Degree of glottic closure during the closed phase of vibration	0 = normal 1 = impaired	0.79

Table: *Continued.*

Variable name	Definition	Scale	Kappa[III]
Defect[II]	Type of glottic closure: predominant mucosal closure patterns	0 = normal, no defect 1 = oval defect 2 = hourglass defect 3 = anterior defect 4 = posterior defect (<50%) 5 = complete defect (>50%)	0.67

[I] Visuoperceptual ordinal variable
[II] Visuoperceptual nominal variable
[III] Cohen's Kappa coefficient

Videostroboscopy pre and post-treatment data

Table: The baseline frequency distribution of patients per category of the different videolaryngostroboscopic variables given as absolute numbers and percentages per treatment group provides an indication of the average baseline voice function of the study population.

Variable name		Group 1: Voice therapy		Group 2: Voice therapy + motor level SES		Group 3: Voice therapy + sensory level SES	
		n = 25 [I] (%)		*n* = 24 [I] (%)		*n* = 24 [1] (%)	
Amplitude, left and right vocal fold		*Right*	*Left*	*Right*	*Left*	*Right*	*Left*
	0 = normal	23 (92%)	22 (88%)	18 (75%)	17 (71%)	18 (75%)	18 (75%)
	1 = impaired	1 (4%)	1 (4%)	2 (8%)	3 (13%)	1 (4%)	1 (4%)
	2 = absent	1 (4%)	1 (4%)	1 (4%)	1 (4%)	2 (8%)	1 (4%)
Periodicity, left and right vocal fold		*Right*	*Left*	*Right*	*Left*	*Right*	*Left*
	0 = normal	22 (88%)	21 (84%)	16 (67%)	16 (67%)	16 (67%)	15 (63%)
	1 = impaired	0 (0%)	0 (0%)	2 (8%)	2 (8%)	1 (4%)	1 (4%)
Symmetry	0 = normal	19 (76%)		16 (67%)		13 (54%)	
	1 = impaired	4 (16%)		4 (17%)		7 (29%)	
Closure	0 = normal	18 (72%)		12 (50%)		15 (63%)	
	1 = impaired	7 (28%)		8 (33%)		6 (25%)	
Defect	0 = normal	18 (72%)		12 (50%)		15 (63%)	
	1 = oval defect	0 (0%)		3 (13%)		0 (0%)	

Table: *Continued.*

Variable name		Group 1: Voice therapy	Group 2: Voice therapy + motor level SES	Group 3: Voice therapy + sensory level SES
		n = 25 [I] (%)	*n* = 24 [I] (%)	*n* = 24 [1] (%)
	2 = hourglass defect	1 (4%)	0 (0%)	0 (0%)
	3 = anterior defect	3 (12%)	0 (0%)	1 (4%)
	4 = posterior defect (<50%)	1 (4%)	2 (8%)	2 (8%)
	5 = complete defect (>50%)	2 (8%)	3 (13%)	2 (8%)

Logistic regression analysis was performed to evaluate the videolaryngostroboscopic outcome (pre versus post-treatment). To assess the group effect, an interaction term with the videolaryngostroboscopic variables at baseline was included to account for any baseline group differences. Furthermore, between group differences in the videolaryngostroboscopic outcome (baseline versus post-treatment) were adjusted for age, gender, and the H&Y score in the logistic regression model. In addition to the complete case analysis, where only patients with no missing values were included, a mixed effects binary logistic model was used for the binary outcomes that were measured repeatedly. This statistical method accounts for any baseline group differences and for dependency between repeated measurements (baseline vs. post-treatment) within the same patient for which an unstructured covariance matrix was used. For this statistical method, the patients were divided in two clinical patient labels: a normal '0' versus abnormal '1' videolaryngostroboscopic status. Patients received the clinical label 'abnormal' videolaryngostroboscopic status if their videolaryngostroboscopic exam was scored impaired (score 1 or higher) in one or more of the measured videolaryngostroboscopic variables (Table 1). Multiple imputation was performed too, using fully conditional specification to account for missing values. Since several patient-related parameters (i.e. age, gender, H&Y scale, and videolaryngostroboscopic status) were used, there was a high chance of having a missing value on one of them. A complete case analysis would tremendously decrease the population size not representing the current 'intention to treat' population. Therefore, besides the complete case analysis, multiple imputation was performed using fully conditional specification to account for missing values. In this way, 63 complete datasets were created. Treatment group, age, gender, H&Y score, and baseline videolaryngostroboscopic status were used as predictors. A two-sided $p \leq .05$ was defined as statistically significant. All statistical analyses were performed with IBM SPSS Statistics for Windows, Version 25.0 (Armonk, NY: IBM Corp.).

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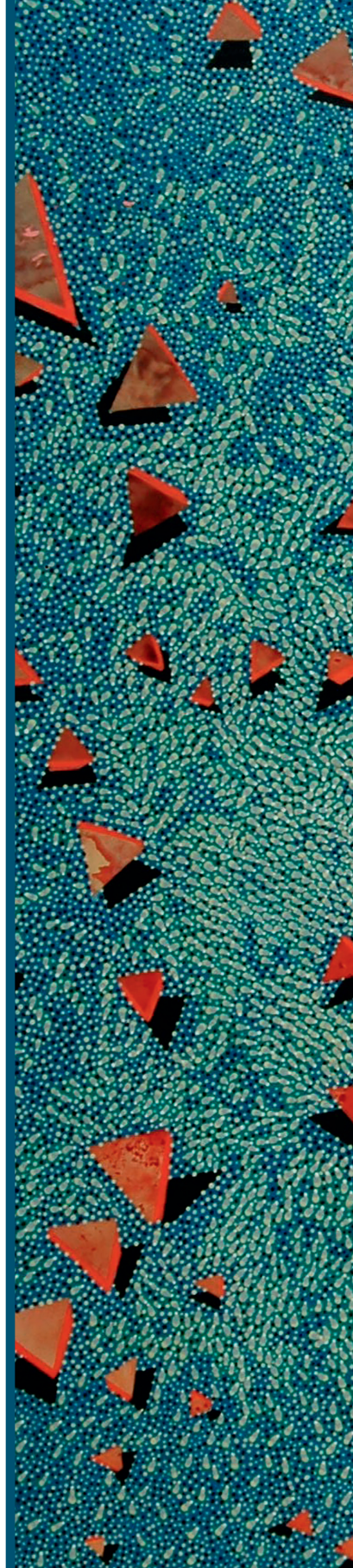
PART III

General discussion, impact paragraph and summary

7

General discussion and impact paragraph



General discussion and impact paragraph

The purpose of this thesis was two-fold: to elaborate the role of oropharyngeal dysphagia (OD) and dysphonia-specific patient-reported outcome measures (PROMs) in idiopathic Parkinson's disease (IPD); and to evaluate whether surface electrical stimulation (SES) of the suprahyoid region of the neck can be used as a novel add-on treatment to standard voice therapy for dysphonic patients with IPD.

OD and dysphonia can have a major impact on health-related quality of life (HR-QoL) of patients with IPD. [1-3] In severe cases OD can even be life-threatening. OD and dysphonia may interfere with communication, the pleasure of eating, prevent people from visiting social events such as a restaurant or birthday and may lead to a lowered self-esteem, feelings of depression, panic attacks or anxiety. [4-6] Because of this major impact on a patient's HR-QoL, a person-focused approach to the diagnosis, treatment, and follow-up of OD and dysphonia in patients with IPD is warranted.

The need for this person-focused approach is stressed out in chapter 4. Investigator reported outcome measures (IROMs) such as during fiberoptic endoscopic evaluation of swallowing (FEES) and videofluoroscopic swallowing study (VFSS) cannot evaluate the full impact of OD on a patient's daily life in a more holistic context. IROMs are merely tools to visualize and measure the biomechanical characteristics and severity of swallowing impairment. Nonetheless, IROMs are very helpful in the diagnosis and follow-up of OD in patients with IPD. By using FEES or VFSS, clinicians can e.g., assess the risk and underlying pathophysiology of aspiration and recommend specific dietary, postural or compensatory techniques based on the nature and severity of the abnormalities found. Furthermore, FEES or VFSS can provide visual feedback to the patients on their swallowing impairment and on the effect which postural and compensatory techniques may have. However, in chapter 4 it is interesting to see that visuoperceptual IROMs of OD are not necessarily related to the impact of OD on a patient's HR-QoL. Patients with IPD usually have multiple medical needs due to the many other symptoms of IPD. OD and dysphonia are just a few of them. The combination of PROMs and IROMs in the diagnostic work-up of OD and dysphonia should result in a more holistic representation of the extend and impact of OD and dysphonia. PROMs, such as the MD Anderson Dysphagia Inventory (MDADI) and the Voice Handicap Index (VHI), can be excellent tools to evaluate the burden of OD and dysphonia and to determine the impact on HR-QoL. [7, 8]

Chapter 4 shows that PROMs are not necessarily in line with IROMs in patients with IPD and OD. In chapter 4 multilayer perceptron neural (MLP) network analysis was used to investigate the relationship between PROMs and IROMs on OD in patients with IPD. MLP neural network analysis showed a moderate agreement between PROMs and IROMs. Subsequently, two-step cluster analysis revealed several clusters of patients with similar scores on IROMs, but with significantly different scores on PROMs. E.g., the

patients with moderate to severe OD based on IROMs can be divided in patients with or patients without a severely reduced HR-QoL based on OD-specific PROMS. The reason why some patients with IPD have a better OD-specific HR-QoL than others with similar signs of swallowing impairment is unclear. Maybe, these clusters of patients represent different phenotypes of OD in a more holistic context. This so-called phenotype of OD of an individual IPD patient seems to encompass more than just the biomechanical characteristics of swallowing impairment determined by IROMs in FEES or VFSS. A phenotype also seems to be determined by PROMs covering the burden of OD and the impact on HR-QoL in patients with IPD. It is known that in the peripheral and central nervous system, different anatomical sites of pathology can be found in patients with IPD and OD. [1, 9] It is likely that these different sites of pathology in the nervous system may explain the various combinations of PROM and IROM outcomes resulting in different phenotypes of OD in patients with IPD.

When IPD progresses OD and dysphonia tend to get worse. [2] The results found in chapter 3 show that the scores of the OD and dysphonia-specific PROMs do not significantly differ between patients with Hoehn & Yahr (H&Y) stage 1 versus 2. So, the patient's OD and dysphonia-specific HR-QoL does not seem to decrease during the early stages of IPD, in which a plateau is observed. From H&Y stage 3 a significant decrease of the PROM scores starts, compared to the early stages of disease (H&Y 1-2). Interestingly the range of the confidence intervals of the PROM scores in H&Y stage 3 seems wider than in the early stages of disease. It is likely that there is a greater variability within the H&Y stage 3 subgroup regarding the burden of OD and dysphonia and the impact of OD and dysphonia on HR-QoL.

As IPD progresses, more and more problem-solving adjustments made by the patient are needed, since biomechanical swallowing impairment will progress. [10] Due to the usually slow progression of IPD, patients have time to adapt and compensate for the losses in swallowing functionality they may have. In the beginning, subtle swallowing impairment goes unnoticed and problem-solving adjustments made by the patient are small and often subconscious. [2, 11] Think of cutting the food into smaller bite-sized boluses, adding more sauce to solid and dry dishes, or avoiding particular foods. These adjustments may not even lead to a reduced HR-QoL nor to physical, socioeconomic, and psychosocial burden. Patients can be unaware of their OD and think that it is part of their aging process, since swallowing function may slightly deteriorate with aging. Besides that, as IPD progresses, other IPD-related complaints may appear or worsen such as among others cognitive impairment or constipation. When these other complaints increase, the patient's perspective on OD and dysphonia may change, because OD and dysphonia may no longer be prominent in relation to other IPD-related impairments that can affect HR-QoL even more. To what extend the other IPD-related impairments affect HR-QoL and co-determine OD phenotypes is unknown. [11]

The aforementioned slow progression of IPD and of subclinical OD and dysphonia may cause a patient-delay in the diagnosis of OD and dysphonia. The patient will not seek help for an abnormality it does not perceive. Even when a patient visits the general practitioner (GP) or neurologist with complaints such as drooling or coughing during oral intake or reduced loudness of voice, the patient may still not be identified as being dysphagic or dysphonic. [12, 13] Patients with subclinical OD or dysphonia not having any severe complaints such as aphonia, malnutrition, chocking or aspiration pneumonia are less likely to be referred to a speech and language pathologist (SLP) or laryngologist. Doctor's delay is therefore also an issue. To reduce the risk of patient's and doctor's delay we should inform patients, family, informal caregivers, physicians, nurses, etc. about the high prevalence of subclinical OD and dysphonia in patients with IPD. With a prevalence of 80-90% it's not a matter of whether you get OD and dysphonia or not, but it's about when you get it. [12, 14] When patients, family, and caretakers of patients with IPD are more aware of the subtle signs of subclinical OD and dysphonia, it is more likely that the GP or neurologist will refer the patient at an earlier stage of the disease to an SLP with expertise in IPD. In a Dutch study by Talebi et al. [15] only a third of the patients with IPD visited an SLP during the course of the disease. The question remains, whether early consultation of an SLP by patients with subclinical OD or dysphonia will result in a better HR-QoL during the course of IPD and will reduce the occurrence of life-threatening events such as choking or aspiration pneumonia. On the other hand, SLPs can educate patients with subclinical OD or dysphonia and their family and caretakers to recognize subtle swallowing and voice problems and subsequently train patients to develop problem-solving adjustments to support compensatory and coping mechanisms. Patients who were treated by an SLP during the course of IPD were less likely to develop pneumonia. Especially when treated by an SLP with expertise in IPD. [15] So far, this aspect of early intervention is poorly integrated in the current clinical practice guideline. [16] In the Dutch clinical practice guideline for Parkinson's disease only a small paragraph covers OD, and information on dysphonia, speech, and communication in general is lacking. [16] The guideline recommends early referral of patients with IPD and complaints of OD to an SLP for screening, diagnosis, and OD treatment. The Dutch Association of Speech and Language Therapy and Phoniatrics (Nederlandse Vereniging voor Logopedie en Foniatrie – NVLF) developed a separate clinical practice guideline for speech and language therapy in patients with IPD. [17] However, despite the recommendations of the Dutch clinical practice guideline for Parkinson's disease and of the clinical practice guideline of the NVLF to refer patients early during the course of IPD, the majority of the patients will not visit an SLP at all. [15] The exact reason why many patients do not visit an SLP is unclear. We recommend to screen all patients at an early stage of IPD for OD and dysphonia and to incorporate this in the Dutch clinical practice guideline for Parkinson's disease.[16] Likely, this will lead to a better awareness of the patient and subsequently lead to early diagnosis and treatment of subclinical OD and dysphonia.

The main goal of OD and voice therapy is to decrease morbidity and mortality and to improve or maintain HR-QoL. The first step in the treatment of motor fluctuations and rigidity and as such OD and dysphonia is to start or optimize the dopaminergic medication. The body of evidence in the literature is limited and studies describing the effects of dopaminergic medication on swallowing and voice problems report conflicting results. [18-20] Besides dopaminergic medication, deep brain stimulation (DBS) for IPD may also have a beneficial effect on OD and dysphonia in selected cases. [21, 22] OD and/or voice therapy may have a beneficial effect but should preferably be started after optimalisation of the dopaminergic medication.

The goal of OD-specific therapy is to improve safety and efficiency of swallowing and improve HR-QoL. OD-specific therapy or conventional swallowing therapy for IPD usually consists of a combination of rehabilitative and compensatory techniques including exercises, dietary adaptations, and maneuvers. This may include among others, expiratory muscle strength training (EMST), effortful swallowing, bolus modification with thickened liquids and texture modified diets, postural or compensatory techniques to enhance airway protection and bolus passage. [17] Challenging aspects during the design of person-focused conventional swallowing therapy are cognitive impairment and/or sarcopenia, also being prevalent phenomena in patients with IPD [23]. Unfortunately, there is no high-quality evidence that conventional swallowing therapy can improve OD in patients with IPD. This conclusion is supported by the literature study in chapter 5. In this systematic review [20] some well-designed studies revealed promising results of rehabilitative techniques such as EMST or video-assisted swallowing therapy (VAST), however none of the studies provided unbiased high-level evidence supporting the effects of these techniques [24-27]. Several systematic reviews covering the latest literature have been published since then. [19, 28-30] But still there is a lack of evidence about which specific intervention or combination of interventions or techniques of conventional swallowing therapy are effective for patients with IPD. A consensus paper on the treatment of OD in patients with IPD was published by Schindler & Pizzorni et al. to establish an agreement on best practice treatment protocols for OD in patients with IPD based on the available literature and on expert opinion. [31] The authors suggested that conventional swallowing therapy should be based on instrumental findings such as FEES or VFSS and that therapy should target a specific pathophysiological aspect or aspects of swallowing function.

For voice therapy in IPD the body of evidence is limited too. The most frequently used rehabilitative technique for standard voice therapy is the Lee Silverman Voice Treatment (LSVT LOUD). [18, 32] Some studies revealed promising results of LSVT, but sample sizes are too small to provide high-level evidence supporting the effects of LSVT. [18, 32] Similar as for OD, cognitive impairment and/or sarcopenia make standard voice therapy challenging in patients with IPD. In chapter 6, we evaluated whether surface electrical stimulation (SES) of the suprahyoid region of the neck can be used as a novel add-on treatment to

standard voice therapy for dysphonic patients with IPD. Patients were referred to one of the eighty-five participating SLPs, affiliated with ParkinsonNet. [33] The standard voice therapy was carried out in a person-focused approach and consisted of a combination of e.g., LSVT, airway and breathing exercises, and oral motor exercises. PROMs such as the VHI and IROMs such as during videolaryngostroboscopy were used to evaluate the burden of dysphonia, to determine the impact of dysphonia on a patient's daily life, and to visualize biomechanical characteristics of dysphonia in a more holistic context. We found a statistically significant improvement of dysphonia-specific PROMs and IROMs after fifteen consecutive sessions of standard voice therapy of 30 minutes daily for three weeks. SES used as an add-on treatment to standard voice therapy did not result in an additional improvement of dysphonia-specific PROM and IROM outcomes.

Altogether, based on this thesis, the current literature, and the consensus paper by Schindler & Pizzorni et al. we recommend a person-focused approach to conventional swallowing therapy in patients with IPD. A one-size fits all therapy seems a utopia considering the enormous amount of clinically relevant interpersonal variations in this patient population. Person-focused conventional swallowing therapy should be based among others on IROMs during FEES or VFSS, patients' physical and cognitive capabilities, additional IPD-related needs and comorbidity, and OD-specific PROMs. [31] OD-specific PROMs and IROMs represent different dimensions of swallowing impairment and must be combined with information on physical and cognitive capabilities to support the process of shared decision making and the design of person-focused therapy. Furthermore, other factors should be taken into account, such as the wishes and capabilities of the informal caregivers such as the partner, family, and friends, but also the input of health professionals of the accommodation where the patient is living.

Similar as for OD no international consensus exists regarding best practice for dysphonia in patients with IPD. We recommend a person-focused approach to voice therapy in patients with IPD. Person-focused voice therapy should be based among others on IROMs during videolaryngostroboscopy, aerodynamic and acoustic measurements, patients' physical and cognitive capabilities, additional IPD-related needs and comorbidity, and dysphonia-specific PROMs. High-level scientific evidence or an international consensus on the number, length, interval, and strategic timing of treatment sessions for OD and dysphonia is lacking. However, since the risk of cognitive impairment and sarcopenia rises when the severity of IPD increases, we believe that the recommendation to intervene at an early stage of disease is justified.

In conclusion, based on this thesis the existence of so-called phenotypes of OD and dysphonia seems plausible. A phenotype encompasses multiple dimensions of a problem representing a combination of: biomechanical characteristics of swallowing impairment or dysphonia, a patient's perspective on OD or dysphonia, and multiple other IPD-related needs that co-determine these phenotypes leading to a more holistic integration

and representation of what OD and dysphonia encompass. The PROMs and IROMs described in this thesis can be used in this context and form the basis for designing a person-focused conventional swallowing therapy or voice therapy in daily clinical practice for patients with IPD. This thesis is a first step towards a multidimensional phenotyping of OD and dysphonia in patients with IPD. Future research is certainly needed to determine whether this phenotyping or profiling can be further optimized since patients with IPD within the same H&Y stage can still show a great variability in PROMs and IROMs on OD and dysphonia. This enormous variability within disease stages should also be taken into account during randomized controlled trials on the effects of new treatments for OD and dysphonia. Our SES experiment for dysphonia should be interpreted with caution too because variability may have affected the outcome of SES. In short, this thesis marks the start of further research and hopefully supports the update of current clinical practice guidelines for IPD.

Impact paragraph

Idiopathic Parkinson's disease (IPD) is with almost 10 million known cases worldwide the second most common neurodegenerative disease. [34] Oropharyngeal dysphagia (OD) and/or dysphonia will occur in more than 80% of the patients with IPD. [5, 14] That means millions of people suffer from OD and dysphonia disturbances due to IPD.

In this paragraph we discuss the impact of the results and conclusions of this dissertation. We address the importance of the use of patient-reported outcome measures (PROMs) in the diagnosis and treatment of OD and dysphonia in patients with IPD. Also, we discuss the impact OD and dysphonia may have on patients, family, and friends. Finally, we show how we have shared our findings to create awareness, to give rise to new scientific studies to improve quality of care, and to support the update of clinical practice guidelines.

The aim of this thesis is to improve the diagnostic work-up and treatment of OD and dysphonia in patients with IPD. Unfortunately, we still cannot cure IPD nor the related OD and dysphonia. Therefore, optimizing a person's health-related quality of life (HR-QoL) should be one of the cornerstones of conventional swallowing and voice therapy in patients with IPD. In this thesis we validated the Dutch translation of the MD Anderson Dysphagia inventory (MDADI) for patients with a neurological disorder. It is an easy-to-use tool and relatively short compared to several other available questionnaires. HR-QoL questionnaires such as the MDADI are a vital part of diagnosing OD in IPD. Moreover, we compared common OD and dysphonia-specific PROMs to find a possible relationship between OD and dysphonia-specific HR-QoL. We found that both OD and dysphonia give a similar loss of HR-QoL when IPD progresses. This means health-care professionals should be aware of the coexistence of both OD and dysphonia, even when one of the two is not so apparent.

Using these HR-QoL questionnaires, we found that a patient's HR-QoL is not always in line with the severity of OD evaluated with flexible endoscopic evaluation of swallowing (FEES) or videofluoroscopic swallowing study (VFSS). Patients with severe OD may have a mild reduction in HR-QoL and vice versa. That means that we cannot tell the severity of OD solely based on the impact OD has on a patient's life. This thesis creates awareness about these sometimes hidden swallowing disturbances, so patients will seek help at an early stage of the disease.

Based on this thesis the existence of so-called phenotypes of OD seems plausible. The results of this thesis eliminate knowledge gaps on the existence of so-called phenotypes of OD. This is a first step towards a multidimensional phenotyping of OD in patients with IPD. The conclusion of this thesis marks the start of further research on the integration of PROM and investigator-reported outcome measures (IROM) outcomes of OD and

dysphonia in patients with IPD and hopefully supports the update of current national and international clinical practice guidelines for IPD. This thesis should also provide the foundation for future research to optimize this phenotyping or profiling of patients with IPD and OD or dysphonia and also inspire researchers to optimize the design of future randomized controlled trials on the effects of new treatments for OD and dysphonia by taking phenotypes into account.

Detection of subclinical OD and dysphonia, prevention of sequala and/or rehabilitation of OD and dysphonia will enable patients with IPD to participate in social activities and increase the chances of community reintegration and maintenance of employment in case of juvenile IPD. To find a possible treatment for dysphonia in IPD we added surface electrical stimulation (SES) of the neck to standard care with standard voice therapy. We found a positive therapeutic effect of standard voice therapy, but no additional effect of SES.

The results of this dissertation were published in high-impact scientific journals. For complete transparency and to target a broad audience the results were published in open access journals when possible. The results from this dissertation have also been communicated through presentations at international congresses targeting an interdisciplinary audience of health professionals working with patients with IPD, e.g. the Annual Meeting of the Dysphagia Research Society (2014, Nashville Tennessee USA), the Annual Meeting of the European Society for Swallowing Disorders (2017, Barcelona Spain), and the Annual Meeting of the Deutschen Gesellschaft für Neurologie (2016, Mannheim Germany). Also, results were presented at a regional ParkinsonNet [33] conference for health professionals involved in IPD and for patients and relatives in October 2023.

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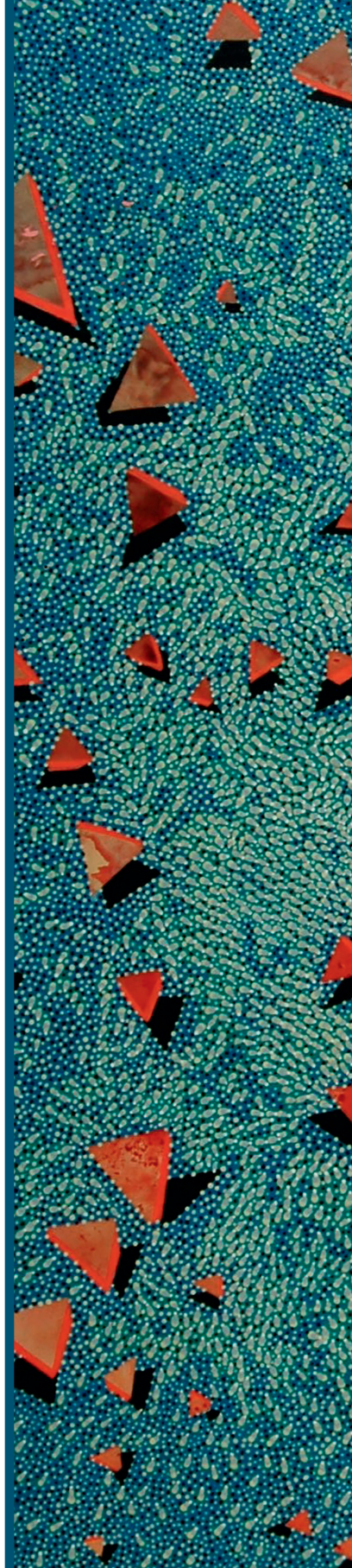
Summary



Summary

The research presented in this thesis discusses the impact of oropharyngeal dysphagia (OD) and dysphonia on the quality of life of patients with idiopathic Parkinson's disease (IPD). On the one hand, we evaluate the importance of patient-reported outcome measures (PROMs) regarding OD and dysphonia in patients with IPD. On the other hand, we are evaluating treatment options for OD and dysphonia, in particular surface electrical stimulation (SES) of the neck to improve dysphonia in patients with IPD.

IPD is characterized by several distinct symptoms: rest tremor, rigidity and postural disturbances. 1% of the total world population over the age of 60 suffers from IPD. More than 80% of patients with IPD also develop OD and/or dysphonia. **Chapter 1** elaborates on the problems that patients with IPD and their loved ones may experience and the challenges that healthcare professionals face with regard to the diagnosis and treatment of OD and dysphonia in IPD.

PROMs in patients with IPD and OD and dysphonia
In addition to Flexible Endoscopic Evaluation of Swallowing (FEES) and videofluoroscopic swallowing study (VFSS), PROMs are important outcome measures in diagnosing OD and dysphonia from a holistic point of view. PROMs are any status report of a patient's health coming directly from the patient. PROMs can be used to evaluate the individual's perception of their health. There are many different validated PROMs that are usually specific to a particular patient population with a particular symptom or disease. In **Chapter 2**, we validated the MD Anderson Dysphagia inventory (MDADI) in Dutch for patients with OD of a neurogenic etiology. The MDADI was already validated for the head and neck oncology population. Due to the validation for patients with OD of a neurogenic etiology, it is possible to use the same PROM to the vast majority of the patient population that comes to the ENT outpatient clinic with OD.

Chapter 3 describes the exploratory, prospective clinical study regarding whether changes in OD and dysphonia-specific quality of life are associated with progression of IPD. Both the outcomes of the OD (MDADI and DSS; dysphagia severity scale) and the dysphonia-specific PROMs (VHI; Voice Handicap Index and VAS Voice) worsen as IPD progresses. Remarkably, the decline in PROM outcomes is not proportional to the decline in IPD. Although OD and dysphonia may result in a decreased outcome on PROMs in the earliest stage of IPD (Hoehn and Yahr scale 1), in the patient's perception, these symptoms start worsening at a mor advanced stage of IPD (Hoehn and Yahr stage 3). In addition, this study shows that the outcomes of the OD and dysphonia-specific PROMs are related to each other. Thus, with a worsening of OD-specific PROM outcomes, there is most likely a similar deterioration in dysphonia-specific PROM outcomes.

In **chapter 4** we've compared the outcomes of OD-specific PROMs (MDADI and DSS) with the results of the FEES and VFS by using a neural network analysis. Neural network analysis is a modern statistical approach to processing complex data. The neural network must be trained to predict the outcome of the FEES and VFS based on the outcome of the PROM of a patient. By comparing the predicted outcome with the actual outcome of the FEES and VFS, the neural network learns from the error and predicts better next time. By repeating this experiment often, with different patients, a reliable neural network can be created, since the margin of error is getting smaller. This study included 90 patients with IPD and OD. After training the neural network, we conclude that there is only limited agreement between the outcomes of the PROMs and FEES and VFS. To obtain a better insight in this limited agreement, a two-step cluster analysis was performed. A two-step cluster analysis categorizes patients into one or more clusters, based on all available data. This creates clusters with patients that have many similarities in the given data. For example, we found two clusters of patients who showed no signs of laryngeal penetration or aspiration on FEES or VFS, where one of the two clusters had a relatively high outcome on PROMs and the other cluster had a relatively low outcome. In addition, there was a cluster that did show signs of laryngeal penetration or aspiration on FEES or VFS with a similar low outcome compared to the cluster with no abnormalities on FEES or VFS. Based on the outcome of the PROMs used, it is therefore impossible to predict what the outcome will be based on FEES or VFS. It is therefore important to include both parameters in the analysis of OD in patients with IPD, because the absence of complaints does not mean that there are no abnormalities.

An update on treatment of dysphagia and dysphonia in Parkinson's disease
A systematic literature review on the different treatment options for OD in patients with IPD is described in **Chapter 5**. Twelve studies were included regarding pharmacological and rehabilitation treatments. Of these, only 4 studies were randomized and the methodological quality of a number of studies was limited. No high-quality evidence that pharmacological of rehabilitation treatments improve OD in patient with IPD was found. However, a clinical trend was found that conventional swallowing therapy using rehabilitative and compensatory techniques has a positive effect on OD in patients with IPD. The role of pharmacological treatments such as dopamine replacement still remains unclear. A person-focused conventional swallowing therapy seems to be the best treatment strategy for the time being. Person-focused conventional swallowing therapy should be based among others on IROMs during FEES or VFSS, patients' physical and cognitive capabilities, additional IPD-related needs and comorbidity, and OD-specific PROMs

Chapter 6 describes the effects of SES of the suprahyoid region of the neck as a new adjunctive treatment in voice therapy for patients with IPD and dysphonia. Patients were quasi-randomized into 3 groups. The first group received standard voice therapy only, the second group received standard voice therapy and SES at the motor level, and

the third group received standard voice therapy and SES at the sensory level. Patients were referred to one of the eighty-five participating speech and language pathologists (SLPs) affiliated with ParkinsonNet. The person-focused standard voice therapy included Lee Silverman Voice Treatment (LSVT), airway and breathing exercises and oral motor exercises. We found that after 15 sessions of standard voice therapy of 30 minutes per day for three weeks, a statistically significant improvement on the outcomes of dysphonia-specific PROMs (VHI) and stroboscopy was found. SES as an adjunctive treatment did not result in an additional improvement of dysphonia-specific outcomes.

A

Appendices

Nederlandse samenvatting

In dit proefschrift doen we verslag van het onderzoek omtrent de impact die slik- en stemproblemen hebben op de kwaliteit van leven van mensen met de ziekte van Parkinson. Enerzijds evalueren we het belang van patiënt-gerapporteerde uitkomstmaten (PROMs) omtrent slik- en stemproblemen bij mensen met de ziekte van Parkinson. Anderzijds evalueren we de behandelmogelijkheden voor slik- en stemproblemen, in het bijzonder oppervlakte elektrische stimulatie van de hals om de stem te verbeteren bij mensen met de ziekte van Parkinson.

De ziekte van Parkinson is een veel voorkomende aandoening die zich kenmerkt door met name het trillen van de ledematen in rust, traagheid in bewegen en stijfheid van spieren. 1% van de totale wereldbevolking boven de 60 jaar leidt aan de ziekte van Parkinson. Meer dan 80% van de mensen met de ziekte van Parkinson ontwikkelt ook slik- en/of stemproblemen. In **Hoofdstuk 1** wordt stilgestaan bij de problemen die mensen met de ziekte van Parkinson en hun naasten kunnen ondervinden en de uitdagingen die er voor de zorgprofessionals zijn omtrent de diagnostiek en behandeling van slik- en stemproblemen bij de ziekte van Parkinson.

PROMs uitkomstmaten omtrent slik- en stemproblematiek bij de ziekte van Parkinson

PROMs zijn naast endoscopie van de slikact (FEES; Flexible Endoscopic Evaluation of Swallowing) en videofluoroscopie van de slikact (VFS) belangrijke uitkomstmaten om vanuit een holistisch oogpunt slik- en stemproblemen in kaart te brengen. PROMs geven weer hoe de problemen invloed hebben op het dagelijks leven van een patiënt en geven een weergave van hun sociale en emotionele welbevinden. Er zijn vele verschillende PROMs die meestal specifiek zijn voor een bepaalde patiëntenpopulatie met een bepaald symptoom of ziekte. De desbetreffende PROM geeft dan specifiek aan in hoeverre het desbetreffende symptoom of ziekte invloed heeft op de kwaliteit van leven of in hoeverre dit leidt tot functieverlies in het dagelijkse leven. In **Hoofdstuk 2** hebben we de MD Anderson Dysphagia inventory (MDADI) gevalideerd in het Nederlands voor patiënten met slikproblemen met een neurologische origine. In het verleden was deze reeds gevalideerd voor de hoofd-hals oncologiepopulatie. Door de validatie voor slikproblemen met een neurologische origine is het mogelijk om bij het overgrote deel van de patiëntenpopulatie die op het spreekuur komt met slikproblemen eenzelfde PROM af te nemen.

Hoofdstuk 3 beschrijft de observationele studie over hoe de uitkomsten van slik- en stemgerelateerde PROMs evolueren naarmate de ziekte van Parkinson vordert. Zowel de uitkomsten van de slik- (MDADI en DSS; dysphagia severity scale) als de stemgerelateerde PROMs (VHI; Voice Handicap Index en VAS Voice) worden slechter naarmate de ziekte van Parkinson vordert. Opvallend is dat de achteruitgang van de

PROM-uitkomsten niet evenredig verloopt met de achteruitgang van de ziekte van Parkinson. Bij beginnende ziekte van Parkinson (Hoehn en Yahr schaal 1) kunnen er wel al afwijkende uitkomsten worden gezien met de PROMs, echter deze verslechteren in de eerste fase niet tot nauwelijks. Pas in een latere fase van de ziekte van Parkinson (Hoehn en Yahr schaal 3) wordt ook een significante verslechtering van de uitkomsten van de slik- en stemgerelateerde PROMs gezien. Daarnaast laat deze studie zien dat de uitkomsten van de slik- en stemgerelateerde PROMs gerelateerd zijn aan elkaar. Dus bij verslechtering van de slikgerelateerde PROM-uitkomsten is er meest waarschijnlijk ook een vergelijkbare verslechtering van de stemgerelateerde PROM-uitkomsten.

Dat PROMs naast de FEES en VFS van belang zijn om de impact van slik- en stemproblemen in kaart te brengen bij de ziekte van Parkinson wordt bevestigd door de uitkomsten van de studie in **Hoofdstuk 4.** Deze studie vergelijkt de uitkomsten van slikgerelateerde PROMs (MDADI en DSS) met de uitkomsten van de FEES en VFS middels een neuraal netwerkanalyse. Een neuraal netwerkanalyse is een moderne statistische aanpak om complexe data te verwerken. Het neuraal netwerk moet getraind worden om op basis van de uitkomst van de PROM bij een patiënt, de uitkomst op de FEES en VFS te voorspellen. Door deze voorspelling te vergelijken met de daadwerkelijke uitkomst van de FEES en VFS, leert het neuraal netwerk van de fout en voorspelt het de volgende keer beter. Door dit experiment vaak te herhalen, met verschillende patiënten kan er een betrouwbaar neuraal netwerk ontstaan, omdat de foutmarge steeds kleiner wordt. In deze studie werden 90 mensen met de ziekte van Parkinson geïncludeerd die ook slikproblemen ervaarden. Na trainen van het neuraal netwerk concluderen we dat er slechts een beperkte overeenkomst is tussen de uitkomsten van de PROMs en FEES en VFS. Om deze beperkte overeenkomst te duiden werd een clusteranalyse verricht. Een clusteranalyse categoriseert patiënten in één of meerdere clusters. Niet op basis van één gegeven zoals geslacht, maar op basis van de alle gegeven data. Hierdoor ontstaan clusters met patiënten die veel overeenkomsten hebben in de gegeven data. Zo werden er bijvoorbeeld twee clusters gevonden van patiënten die *geen* tekenen van laryngeale penetratie of aspiratie vertoonden op FEES of VFS, waarbij er één van de twee clusters een relatief goede uitkomst had op PROMs en het andere cluster een relatief slechte score. Daarbovenop was er een cluster die *wel* tekenen van laryngeale penetratie of aspiratie vertoonden op FEES of VFS met een vergelijkbare slechte score als het cluster zonder afwijkingen op FEES of VFS. Op basis van de uitkomst van de gebruikte PROMs kan dus niet voorspelt worden wat de uitkomst zal zijn op de FEES of VFS. Het is dus van belang om beide parameters mee te nemen in de analyse van slikproblemen, omdat het niet hebben van klachten niet betekend dat er geen afwijkingen zijn.

Evaluatie van behandelmogelijkheden voor slik- en stemproblemen bij de ziekte van Parkinson

Een systematisch literatuuronderzoek over de verschillende behandelmogelijkheden voor slikproblemen bij de ziekte van Parkinson wordt beschreven in **Hoofdstuk 5**.

Twaalf studies werden geïncludeerd betreffende farmacologische behandelingen en logopedische revalidatie. Hiervan waren slechts 4 studies gerandomiseerd en was de methodologische kwaliteit van een aantal studies beperkt. Een onomstotelijk bewezen behandeling werd niet gevonden. Wel werd er een klinische trend gevonden dat logopedische revalidatie een positief effect heeft op slikproblemen. De rol van farmacologische behandelingen zoals dopaminesubstitutie blijft nog altijd onduidelijk. Een persoonsgerichte behandeling waarbij gekeken wordt naar de afwijkingen op FEES en VFS, maar zeker ook de uitkomsten van PROMs om zaken zoals het sociale en emotionele welbevinden te beoordelen lijkt vooralsnog de beste behandelstrategie.

Hoofdstuk 6 beschrijft de effecten van oppervlakte elektrische stimulatie (SES) van het suprahyoïdale gebied van de hals als een nieuwe aanvullende behandeling bij logopedische stemtherapie voor mensen met de ziekte van Parkinson en stemproblemen. Patiënten werden quasi-gerandomiseerd in 3 groepen. De eerste groep kreeg alleen logopedie, de tweede groep kreeg logopedie en SES op motorisch niveau en de derde groep logopedie en SES op sensorisch niveau. Patiënten werden doorverwezen naar één van de vijfentachtig deelnemende logopedisten, aangesloten bij ParkinsonNet. De persoonsgerichte logopedische behandeling, omvatte onder meer Lee Silverman Voice Treatment (LSVT), luchtweg- en ademhalingsoefeningen en mond motorische oefeningen. We vonden dat na vijftien sessies logopedie van 30 minuten per dag gedurende drie weken een statistisch significante verbetering op de uitkomsten van de stemgerelateerde PROMs (VHI) en stroboscopie werd gevonden. SES als aanvullende behandeling resulteerde niet in een extra verbetering van stemgerelateerde uitkomsten.

Curriculum vitae

Michel van Hooren werd geboren op 30 maart 1989 te Maastricht. Hij rondde zijn VWO af in 2007 aan het Porta Mosana College te Maastricht (voorheen Jeanne d'arc college). Aansluitend startte hij aan de Universiteit Maastricht zijn geneeskundestudie, welke in 2014 werd afgerond. Tijdens zijn studie werd de basis gelegd voor dit proefschrift. Na een korte periode als anios SEH/zaalarts te Atrium Medisch centrum locatie Brunssum en als arts-onderzoeker KNO (feasability of an eNose in head and neck cancer) onder dr. K.W. Kross startte hij in 2015 aan de opleiding tot KNO-arts in het MUMC+. Gedurende de opleiding doorliep hij twee perifere stages in respectievelijk het Catharina Ziekenhuis te Eindhoven onder dr. F.C.P.J. Adriaansen en Zuyderland Medisch centrum te Heerlen en Sittard/Geleen onder dr. V.E. Bergshoeff. Parallel aan de opleiding doorliep hij het 'plustraject' aan de Universiteit Maastricht getiteld: Health policy innovation and management; Financial management in healthcare. Aansluitend werd een differentiatie laryngologie en hals-chirurgie afgerond onder professor dr. B. Kremer, dr. L.W.J. Baijens en dr. JW Brunings. In 2020 werd de opleiding onder opleiders dr. J.R. Hof en professor dr. B. Kremer afgerond.

Na een korte periode als chef de clinique in het Zuyderland MC, startte hij in 2021 als staflid in het Maasziekenhuis Pantein te Boxmeer. Zijn belangrijkste aandachtsgebied zijn de laryngologie, benigne weke delen chirurgie en kinder-KNO. Daarnaast vervult hij verschillende organisatorische taken binnen de afdeling en neemt zitting in de landelijke expertisegroep cluster laryngologie. Zijn thuisbasis is Maastricht waar hij samenwoont met Anandi en hun kinderen Basile en Jules.

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