



Dysphagia in Parkinson's Disease

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Abstract

Dysphagia in Parkinson's can result in impaired safety, aspiration pneumonia, malnutrition and dehydration and consequently to a well-documented decline of quality of life (QOL) in patients diagnosed with Parkinson's (PwPD). The underlying neurodegenerative mechanisms in central and peripheral nervous system affect all phases of swallowing in PwPD, while marked heterogeneity has been observed in symptomatology of swallowing impairments within PwPD and atypical parkinsonian symptoms. Further research is needed to understand how early should we screen and assess for swallowing impairments

and nutritional status in PwPD, which will in turn have an effect on the optimal therapeutic technique selection and management. This chapter discusses current knowledge on the neurophysiological underpinnings of swallowing impairments in PD, the health outcomes, the relationship of non-motor symptoms with dysphagia and the clinical assessment and management options, among other important issues in PD management.

1 Introduction

Dysphagia in Parkinson's disease (PD) is a common and clinically important symptom in PD, characterised as multifaceted and affecting all phases of deglutition. Dysphagia was recognised by James Parkinson in his original description of the symptoms and signs of PD (Parkinson Parkinson 1817) in Parkinson, 1817.

Dysphagia in Parkinson's can result in impaired safety, aspiration pneumonia, malnutrition and dehydration and consequently to a well-documented decline of quality of life (QOL) in patients diagnosed with Parkinson's (PwPD). The underlying neurodegenerative mechanisms in central and peripheral nervous system affect not only the oral propulsion of the bolus, but also the propagation of the bolus through the pharyngeal stage towards the oesophagus. Given the neurodegenerative nature of the disease, the clinician assessing and managing PwPD is required to be adept in recognising not only the clinical signs of dysphagia but also the underlying pathophysiology and the evolution and variation of symptomatology with disease progression.

Varying estimates of the prevalence of dysphagia in PD have been identified according to the patient population studied and methodology used. An overall estimate prevalence of 11–81% of dysphagia in PwPD was estimated with a recent systematic review (Takizawa et al. 2016). A recent meta-analysis of studies in PD identified a mean dysphagia prevalence of 35% (range 16–55%) based on subjective swallowing outcomes, but this rose to 82% (range 72–87%) in studies using objective measurements (Kalf et al. 2012a). Factors associated with dysphagia in a large cohort study of 6462 PD patients included older age, longer disease duration and dementia; male sex was associated with increased sensitivity to the effects of ageing and disease duration (Cereda et al. 2014).

Here, we review the pathophysiology of dysphagia in Parkinsonism together with an overview of the neurophysiology of swallowing in

movement disorders, the dysphagic symptoms and health outcomes, the differences between the most prevalent parkinsonian syndromes with regard to dysphagia and more importantly the clinical profile of patients with dysphagia. Lastly, we review current and proposed assessment and management procedures.

2 Pathophysiology of PD

Parkinson's disease is a neurodegenerative disorder characterised by four core motor features: tremor, rigidity, bradykinesia and postural instability. Parkinson's disease (PD) is the second most frequent neurodegenerative disease with an incidence between 13.4 and 20.5/100,000 (Lo and Tanner 2013). The mean age at diagnosis of PD is 55 and most patients are between 50 and 80 years old (Twelves et al. 2003).

The motor features of PD are predominantly due to degeneration of dopaminergic neurons of the substantia nigra (SNc), pars compacta, which project to the input regions of the basal ganglia and modulate the activity of projection neurons. The loss of dopamine in pars compacta increases the overall inhibitory output of the basal ganglia and affects motor control. Atypical parkinsonian syndromes, characterised by a more aggressive disease course and multisystem involvement, are discussed below.

Accumulation of α -synuclein-positive Lewy bodies in dopaminergic neurons is thought to be responsible for neurodegeneration in PD (Spillantini et al. 1997). Lewy bodies appear as protein-containing inclusion bodies that develop inside nerve cells and displace other components, and are suspected as the pathological bases of PD (Del Tredici and Braak 2012). Alpha-synuclein is a presynaptic neuronal protein which in aberrant conformations mediates toxic disruption of cellular homeostasis and neuronal death. There is also increasing evidence for Lewy body pathology in non-dopaminergic neurons and those

outside the basal ganglia in PwPD, indicating that the pathophysiology of PD is complex and damage to different neuronal systems accounts for the heterogeneity of symptoms.

The Braak hypothesis outlines a conceptual framework for disease evolution in PD. According to this scheme, Lewy body pathology occurs initially in the olfactory nucleus and dorsal motor nucleus of the vagus (stages I–II), before motor symptoms develop with involvement of the substantia nigra pars compacta and thalamus (stage III–IV) (Braak et al. 2004). The later involvement of neocortical regions in stages V–VI is associated with the development of dementia, a common outcome in PD (Hely et al. 2008).

In the hypothetical sequence of the progression of the disease, alongside the motor system, the cognitive and neurophysiological system presents changes (Kwan and Whitehill 2011), with patients showing a decrease in executive cognitive functions. Somatosensory deficits are also evident that account mainly for disrupted tactile, thermal, nociception and proprioceptive sensation in PD (Conte et al. 2013). All the aforementioned provide weight to the evidence that PD is a multisystem degenerative disorder comprising not only dopaminergic but also noradrenergic, serotonergic, cholinergic and probably other neurotransmitter systems (Wolters and Bosboom 2007).

The medical diagnosis of PD utilises the clinical diagnostic criteria from the UK Parkinson's Disease Society Brain Bank (Spillantini et al. 1997), including the diagnosis of parkinsonism symptoms, such as bradykinesia and at least one of the following: muscular rigidity, 4–6 Hz rest tremor and/or postural instability. Exclusion criteria for the diagnosis of PD include negative response to large doses of levodopa, history of repeated stroke and stepwise progressive parkinsonism, as well as clinical features indicating a diagnosis of atypical parkinsonism.

On the other hand, the clinical progression of PD and the severity can be rated with the Hoehn and Yahr Scale which classifies the stage of PD (Hoehn and Yahr 1967):

1. Unilateral involvement only
2. Bilateral involvement without impairment of balance
3. Mild to moderate disability with impaired postural stability, but still physically independent

4. Severe disease; can still walk or stand unassisted
5. Wheelchair bound or bedridden unless aided

The Unified Parkinson's Disease Rating Scale (UPDRS) (Lang et al. 2013), although time consuming, is a generalised tool to follow up the course of PD in the longer term, including not only motor symptoms, but also mood, behaviour, activities of daily living and treatment complications. Swallowing disorders and drooling are also examined in UPDRS with two questions addressed to the patient.

2.1 Atypical Parkinsonian Syndromes

Conditions including multiple system atrophy (MSA), progressive supranuclear palsy (PSP) and corticobasal syndrome (CBS) are collectively termed atypical parkinsonian syndromes. These conditions are usually relatively poorly responsive to dopaminergic medications compared to PD, and show a more aggressive disease course, with average life span of around 7 years in PSP and MSA (O'Sullivan et al. 2008). Each of these conditions displays characteristic multisystem involvement. MSA occurs in both parkinsonian (MSA-P) and cerebellar (MSA-C) subtypes, and is characterised by prominent and early autonomic involvement, with postural hypotension and urinary and bowel symptoms (Stefanova et al. 2009). The underlying pathology is an α -synucleinopathy, but glial cell involvement predominates over neuronal involvement with particular neurodegenerative changes in the basal ganglia and cerebellum (Ozawa et al. 2004). PSP is characterised by early falls, vertical supranuclear gaze palsy and cognitive/behavioural impairment, due to underlying tau pathology (Litvan et al. 1996a).

In a clinico-pathological study of parkinsonian syndromes with post-mortem diagnostic confirmation, significantly longer latency to develop dysphagia was seen in those with PD (130 months) compared to MSA (67 months) and PSP (42 months) (Muller et al. 2001). Latency to dysphagia was significantly correlated with total survival time in all parkinsonian syndromes, and the authors reported that early dysphagia within a year of symptom onset had high specificity for

the diagnosis of atypical parkinsonism (Muller et al. 2001). Litvan and colleagues reported dysphagia in 80% of PSP patients after a mean 2 years of clinic visits (Litvan et al. 1996b). A recent meta-analysis of predictors of survival in atypical parkinsonism identified early dysphagia as an adverse prognostic marker in PSP (Glasmacher et al. 2017).

3 Pathophysiology of Dysphagia in PD

Safe deglutition requires the timely coordination of several muscle groups from the upper aerodigestive system and is controlled by a topographically diverse brain network. In summary, cortical and subcortical areas communicate with motor nuclei in the brainstem for the execution of the swallow. Swallowing patterned response is a result of polysynaptic connections with several neurotransmitters transferring information across and within brain areas, such as the sensorimotor cortex, the supplementary motor areas (SMA), the premotor cortex, basal ganglia, brainstem and cerebellum.

In order to understand how changes in central nervous system (CNS), as well as peripheral system in PD, may result in changes in efficiency and safety of swallowing, we include here Fig. 1 showing the brain and peripheral areas important for the completion of swallowing in health with respect to movement disorders only, while recognising a more detailed map is required to explain neurophysiology of swallowing. The connections within the swallowing network are direct and indirect and specific neurotransmitters control the function of these connections (excitatory, inhibitory). In Fig. 1, the nature of the connections is also shown with different colours displaying the functionality of those, for instance excitatory (i.e. providing glutamatergic input), inhibitory (i.e. GABA) or modulatory (e.g. dopaminergic).

The brain areas activated in deglutition are represented bilaterally but asymmetrically (independent of handedness). This communication between the areas of CNS is important for the sensorimotor integration and subsequent motor

execution, the formulation of the motor plan and the initial drive and lastly the modulatory executive function for the swallow. The oral preparatory phase is under voluntary control, while the pharyngeal stage is an automatic, involuntary sequence of neuromuscular events following the elicitation of the swallowing response, but sufficient cortical and subcortical drive can also override this sequence with regard to the trigger of the swallow and the control of the swallow motor response.

Moreover, the oesophageal phase of deglutition is involuntary with different neurological control in the striated and smooth part of the oesophagus. The activation of the motor units in the swallowing centre regulates the peristalsis in the cervical oesophagus mediated by the vagal fibres. On the other hand, the peristalsis of the smooth part of the oesophagus and lower oesophageal sphincter relaxation is controlled by sacral and parasympathetic nuclei in the spinal cord and the enteric nervous system (ENS). Of interest for the oesophageal problems in PwPD, the dorsal motor nucleus of the vagus (DMV) of the medulla, responsible for the extrinsic innervation and the ENS, has shown α -synuclein pathology, even at the early PD stages (Wakabayashi et al. 1993; Braak et al. 2006).

In deglutition, the areas of the basal ganglia and thalamo-cortical connections deliver the information between the higher centre areas and the brainstem allowing the correct execution of voluntary movements. Several hypothetical models are proposed about the functional changes in PD in the basal ganglia circuitry (Blandini et al. 2000), due to the degeneration of dopaminergic neurons and how these changes in neurotransmitters exert functional changes to the activation of the network and therefore to the brain areas interconnected. Dopaminergic denervation in PD leads to imbalances in the activity of striatal projection neurons which regulate motor activity. A relative underactivity of the direct pathway, which facilitates desired movements, and overactivity of the indirect pathway, which suppresses unwanted movement, lead to bradykinesia, the cardinal clinical sign of PD (Albin et al. 1989). Whereas bradykinesia and rigidity have been proposed as

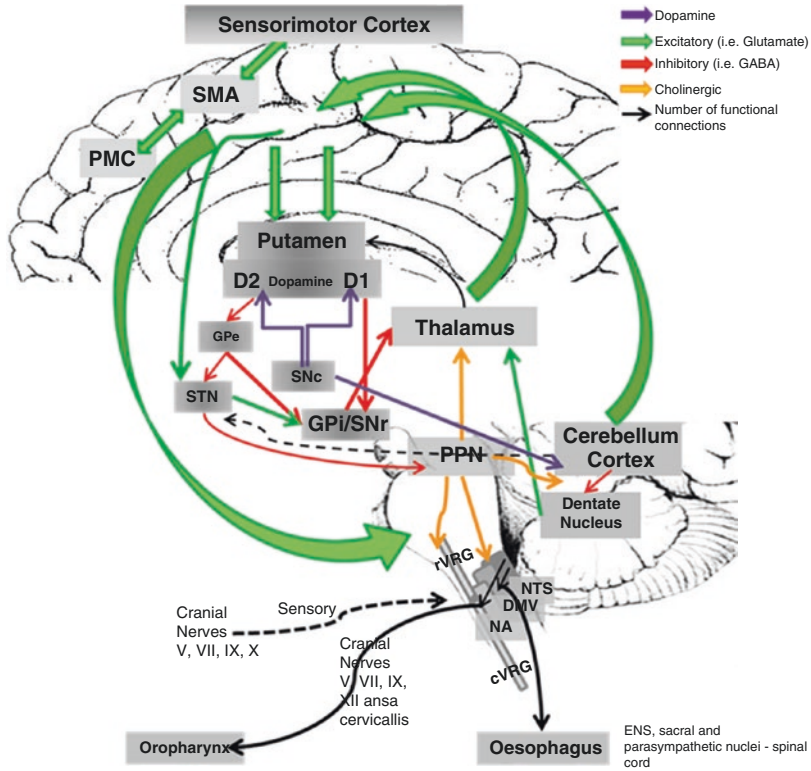


Fig. 1 Simplified diagram of the major functional connections between cortical and subcortical brain areas implicated in voluntary deglutition *in health*. The nature of the main functional connections is shown with green (excitatory) and red arrows (inhibitory). Of importance in this context, dopaminergic (purple) and cholinergic (orange) connections are also shown. In medullary area, connections between motor nuclei are reciprocal and it has been shown that the swallowing patterned response is polysynaptic and several neurotransmitters are involved (i.e. acetylcholine, serotonin, vasopressin and others).

Key: SMA supplementary motor area, PMC premotor cortex, D1, D2 dopamine receptors subtypes, GPe globus pallidus external, GPi globus pallidus internal, STN subthalamic nucleus, SNc substantia nigra pars compacta, SNr substantia nigra reticulata, PPN pedunculopontine nucleus, NA nucleus ambiguus, NTS nucleus tractus solitarius, DMV dorsal nucleus vagus, rVRG, cVRG rostral and caudal ventral respiratory group, housing the inspiratory and expiratory neurons, ENS enteric nervous system, GABA γ -aminobutyric acid

causes for dysphagia in PD, the lack of consistent clinical evidence for reversal of dysphagia by dopaminergic medications (see below) suggests that additional mechanisms for swallowing dysfunction must be involved. The basal ganglia form a critical component of parallel cortico-basal ganglia-thalamo-cortical loops sub-serving different motor, associative and limbic functions (Alexander et al. 1990), which has led to neurophysiological investigation of the role of cortical dysfunction in dysphagia, as described below.

In the brainstem, areas of the nucleus tractus solitarius (NTS), DMV and nucleus ambiguus (NA) involved in the delivery of information to

the periphery for the execution of the swallow and their operations depend on information from the periphery for initiation and accommodation of differences in the material ingested (thick vs. thin liquids, etc.). The NTS is involved in relaying visceral afferent sensations from the oesophagus and stomach, but is not pathologically involved in PD. Motor neurons of the NA of the vagus nerve contribute to coordination of muscles in the oropharyngeal phase of swallowing (Jean 2001). Brainstem pathology is observed in the different parkinsonian syndromes and may be hypothesised to contribute to swallowing dysfunction. However, NA is not affected by

α -synuclein pathology in PD, unlike the DMV (Braak et al. 2004), whereas selective loss of ventrolateral NA neurones occurs in MSA (Benarroch et al. 2006).

The relative lack of involvement in PD of brainstem neuronal regions involved with swallowing suggests that other centres which modulate their activity may be crucial to the understanding of dysphagia. Two important areas in movement disorders, the pedunculopontine nucleus (PPN) and the cerebellum, have been shown to play an important part in the swallowing process as well. Located in the midbrain tegmentum, the PPN is reciprocally connected with the basal ganglia, and projects to motor areas of the brainstem (Benarroch 2013). Cholinergic neurons of the PPN undergo neurodegeneration and cell death in PD, MSA and PSP (Schmeichel et al. 2008; Zweig et al. 1989; Zweig et al. 1987), and are increasingly implicated in gait disorders in those conditions. Given its projection to neurons such as those of the NA and NTS, the PPN is also thought to be implicated in impaired regulation of swallowing in parkinsonian syndromes (Cersosimo and Benarroch 2012).

Of importance to dysphagia in PD, due to the close link between breathing, swallowing and apnoea, in the brainstem the nuclei of the rostral and caudal ventral respiratory group (rVRG and cVRG), housing the inspiratory and expiratory neurons, receive input from PPN as well. In PwPD, respiratory impairments and cough impairments have been documented as well as an association with dysphagia and particular aspiration during swallowing (Troche et al. 2011).

Involvement of the peripheral as well as CNS is increasingly recognised in PD (Nolano et al. 2008). Several clinicopathological studies have identified PNS pathology in PD that may be relevant to swallowing. α -Synuclein pathology has been found in both motor and sensory pharyngeal nerves compared to age-matched controls, and is associated with an increased incidence of dysphagia (Mu et al. 2013a, b). More recently, degeneration and α -synucleinopathy have been shown in sensory nerve terminals of the upper aero-digestive tract in PD (Mu et al. 2015). Pharyngeal muscles in patients with PD

show evidence of denervation, fibre atrophy and fibre-type grouping which may also contribute to dysphagia (Mu et al. 2012). Type I fibre atrophy could have been a result of hypomobilisation if the PD patients had modifications in oral consumption of food due to dysphagia. Involvement of the peripheral neuromuscular system may therefore play a key role in dysphagia in PwPD.

4 Neurophysiological Studies for Dysphagia in PD

Owing to the advances in neuroimaging, neurostimulation and electrophysiology, the number of neurophysiological studies to describe and delineate the changes in swallowing neural network in PD is increasing (Michou et al. 2013).

Evidence from animal studies and animal PD models in relation to swallowing has been interesting. In animals, PD is induced with the use of a neurotoxin, such as 6-hydroxydopamine, 6-OHDA, infused to areas such as the striatum, substantia nigra and/or medial forebrain and this can serve as a model of PD, although it does not recapitulate non-dopaminergic or extra-nigral aspects (Ungerstedt 1968). Specific testing protocols of orolingual deficiencies have been trialled in animals too (videofluoroscopy (Russell et al. 2013)). Some of the behaviours tested in animals may not be as similar as in humans and could involve reduced force and delayed timing in a complex licking task (Guggenmos et al. 2009; Ciucci et al. 2011, 2013), but it seems that tongue force rehabilitation regime (licking behaviour) on animals to medial forebrain could have an effect on halting deterioration: changes that are centrally mediated rather than peripherally (Ciucci et al. 2013). Different results were observed in rats with a different PD-induced model following lingual resistance training (Plowman et al. 2014).

In a longitudinal and cross-sectional 3-year study (Kikuchi et al. 2013) with PwPD with and without dysphagia, hypometabolism in the SMA as well as anterior cingulate cortex correlated to dysphagia. A strong decrease of the overall task-related cortical activation for completion

of swallowing tasks by PwPD was found with magnetoencephalography (MEG) (Suntrup et al. 2013). Additionally, only the non-dysphagic patients with PD showed a shift of peak activations towards lateral motor, premotor and parietal cortices, whereas activity in the supplementary motor area was markedly reduced. Authors concluded that adaptive cerebral changes apparently compensate for deficient motor pathways, since the non-dysphagic had shown recruitment of better preserved parallel motor loops.

Clinical neurophysiological techniques have been used to evaluate the differences in dysphagia between PD and atypical parkinsonian syndromes. Alfonsi and colleagues evaluated swallowing mechanisms with electromyography in PD, MSA-P and PSP compared to controls (Alfonsi et al. 2007) and found that early in the course of the disease of the atypical parkinsonian syndromes there is a reduction in the duration of the inhibition of the cricopharyngeal muscle activity compared to PwPD.

5 Dysphagia in PD: Clinical Features

Table 1 presents the characteristic clinical features and symptoms of dysphagia in PD across the stages of deglutition. Although dysphagia in Parkinsonism is frequently described as a non-motor symptom (NMS), the patterned response of swallowing has an important motoric component and relies on sensory information and feedback from the periphery—allowing for the modulation of the motor execution of swallowing.

As clearly shown in Table 1, dysphagia manifests a range of different signs and symptoms in PwPD. This symptomatology has been observed with assessment techniques (videofluoroscopy, VFS, fibre-optic endoscopic examination swallowing (FEES) and multichannel impedance and manometric assessments) described below. During the oral phase, bolus manipulation is shown to be one of the main symptoms causing accumulation of residue in the oropharyngeal area and piecemeal deglutition. Impaired preparatory lingual movements and mastication often

lead to abnormal bolus formation. Lingual bradykinesia is described mainly in the advanced stages of the disease, while contributing factors to the observed oral motor abnormalities could also be the disease-related tremor, bradykinesia and rigidity. In terms of mastication, PwPD have shown to present impairments due to jaw mobility and oral control. Velocity and stability and coordination of movements in the oral stage of the swallow seem to be reduced and disordinated, due to rigidity, jaw tremor and incomplete masticatory cycle.

During the pharyngeal phase, there is marked variability amongst patients. Patients have shown prolongation of bolus transfer timings and consequently stasis in the vallecular space and pyriform sinuses. One of the symptoms observed is incomplete cricopharyngeal sphincter relaxation (Ali et al. 1996), which can be either of intrinsic origin (hypertonic sphincter) or a result of the reduced forward and upward movement of the hyolaryngeal complex and even the weak propulsion forces and weak pharyngeal contractions. Reduction in sensation has also been observed in PwPD and it is now recognised that swallowing and airway sensory function change with disease progression (Hammer et al. 2013). Sensory loss of mechanoreceptors at the level of the base of the tongue (Leow et al. 2012) could also account for increased residue in the vallecular spaces. As a result of the pharyngeal dysfunction, penetration in the laryngeal vestibule and tracheobronchial aspirations are common in PwPD. Although further research is required, hypo-pharyngeal intrabolus pressures and reduced peak pharyngeal pressures have also been reported in PwPD (Ali et al. 1996). The presence of Zenker's diverticula, probably as a consequence of the impaired upper oesophageal sphincter function and high hypo-pharyngeal pressures, has also been reported (Byrne et al. 1994).

Oesophageal phase impairments are very frequent and appear early in the course of the disease (Sung et al. 2010; Bassotti et al. 1998). The nature of oesophageal impairments includes gastro-oesophageal reflux, diffuse oesophageal spasms and fragmented peristalsis. Abnormalities in lower oesophageal sphincter may contribute to reflux.

Table 1 Presents the list of the documented dysphagia signs in PwPD

Phase of deglutition	Findings on formal assessment	References
Oral/preparatory	Oropharyngeal bradykinesia	Bushmann et al. (1989), Umemoto et al. (2011), Nilsson et al. (1996)
	Tongue pumping	Argolo et al. (2015a), Nagaya et al. (1998)
	Smaller tongue movements	Van Lieshout et al. (2011), Leopold and Kagel (1996)
	Piecemeal swallowing	Nagaya et al. (1998), Argolo et al. (2015b)
Pharyngeal	Reduced pharyngeal constriction	Ellerston (2016)
	Premature spillage	Warnecke et al. (2016), Moreau et al. (2016)
	Vallecular residue	Argolo et al. (2015b), Warnecke et al. (2016), Moreau et al. (2016), Kim et al. (2015a), Lim et al. (2008), Fuh et al. (1997), Michou et al. (2014)
	Reduced velopharyngeal pressure	Jones and Ciucci (2016)
	Residue in pyriform sinuses	Argolo et al. (2015a), Fuh et al. (1997), Michou et al. (2014), Kim et al. (2015b)
	Reduced hyoid bone movement	Kim et al. (2015b), Ciucci et al. (2008)
	Decreased epiglottic rotation angle	Kim et al. (2015a)
	Shorter swallowing apnoea	Troche et al. (2011), Gross et al. (2008)
	Prolonged transit times	Nilsson et al. (1996), Argolo et al. (2015b), Kim et al. (2015a), Lin et al. (2012), Sung et al. (2010)
	Altered sensory processing	Pitts et al. (2016)
	Delayed laryngeal closure	Fuh et al. (1997), Leopold and Kagel (1997a)
	Incomplete CP relaxation	Kim et al. (2015a), Sung et al. (2010), Ali et al. (1996)
	Aspiration/penetration	Argolo et al. (2015b), Ellerston (2016), Warnecke et al. (2016), Moreau et al. (2016), Fuh et al. (1997), Hegland et al. (2016), Rajaei et al. (2015), Pitts et al. (2010), Johnston et al. (1995), Hunter et al. (1997), Robbins et al. (2008)
	Silent aspiration	Bushmann et al. (1989), Fuh et al. (1997), Stroudley and Walsh (1991), Nobrega et al. (2008), Monteiro et al. (2014)
Repetitive swallowing	Sung et al. (2010)	

Table 1 (continued)

Phase of deglutition	Findings on formal assessment	References
Oesophageal	Odynophagia	Su et al. (2017)
	Gastro-oesophageal reflux	Su et al. (2017), Bassotti et al. (1998), Park et al. (2015), Leopold and Kagel (1997b)
	Lower oesophageal sphincter obstruction/aberration	Su et al. (2017), Leopold and Kagel (1997b)
	Diffuse oesophageal spasm	Sung et al. (2010), Su et al. (2017), Bassotti et al. (1998), Eadie and Tyrer (1965)
	Ineffective/fragmented peristalsis	Sung et al. (2010), Su et al. (2017), Bassotti et al. (1998), Leopold and Kagel (1997b)

These signs are observed through formal assessments with the use of FEES, VFS or multichannel impedance and manometric assessments

Abnormal stomach emptying pattern and early satiety affecting in turn pharmacokinetics have been reported and are important to consider when assessing and managing dysphagia in PD. Although there is not enough supporting evidence, PwPD who do not appear to show abnormalities in the oropharyngeal phase of the swallowing in formal imaging assessments may present changes in oesophageal phase even before clinically important dysphagia symptoms (Gibberd et al. 1974). Accumulation of alpha-synuclein in the ENS and DMV has been related to the development of the gastrointestinal tract abnormalities in PD (Cersosimo and Benarroch 2012). It is also unclear whether and to what extent the oropharyngeal problems contribute to the oesophageal dysmotility (Derrey et al. 2015). Disease severity and duration do not seem to correlate to findings of oesophageal dysmotility in PwPD (Castell et al. 2001).

Alongside the dysfunction of the upper gastrointestinal tract, there is increasing evidence for premotor pathological and symptomatic involvement of the lower GI tract in PD, with constipation being the most notable such symptom: a large longitudinal study of 6790 men showed a significantly increased risk of PD in men with <1 bowel movement/day compared to those with more frequent bowel movements (Abbott et al. 2001). Constipation has also been associated with increased density of incidental Lewy body

pathology and reduced substantia nigra neuronal density in those without PD (Abbott et al. 2001; Petrovitch et al. 2009). There is emerging evidence for α -synuclein pathology in the colon of PD patients, which is supportive of an extension of the Braak hypothesis that Lewy body pathology may start in the gut and progress rostrally to the brainstem (Braak et al. 2003).

Furthermore, age, gender, disease duration and dementia have been reported to be independent *contributing factors for swallowing impairments in PwPD* (Cereda et al. 2014). Impairments in the oral and pharyngeal phase were associated to bradykinesia as recorded on UPDRS scale (Kim et al. 2015b), but further evidence is required. Importantly, several PwPD may not identify the presence of minimal changes in swallowing process and therefore sensitive clinical formal assessments should take place.

The range of symptoms shown in Table 1 indicates the heterogeneity in the deglutitive profile of PwPD with dysphagia. In addition, differences in symptomatology between the atypical parkinsonian syndromes and PwPD have also been observed (Umemoto et al. 2017). However, further research will allow us to compile a specific profile of differential symptomatology in the future.

Not all patients will experience these symptoms and not at the same period during disease progression. This is another indication for the

clinician who manages PwPD that the clinical assessment needs to be thorough. *Parkinson's disease is a multisystem neurodegeneration and differences in the degree of or rate of degeneration of different levels of CNS system may account for differences in phenotypic features with regard to swallowing function.*

6 Relationship to Other Non-motor Symptoms

Non-motor symptoms are increasingly recognised as a major contributor to symptom burden and impaired QOL in patients with PD. Many of these symptoms are mediated by involvement of non-dopaminergic and extra-nigral sites in the nervous system (Lim et al. 2009). Voice problems and dysphonia (Skodda et al. 2011) seem to be closely related to the presence of swallowing impairments in PD (Muller et al. 2001; van Hooren et al. 2015).

Several of the NMS in PD will have an impact on swallowing function and will have to be closely considered in therapeutic procedures. These NMS include fatigue, cognition, olfaction and taste changes as well as somatosensory changes centrally and from the periphery. Although less frequent than the olfactory problems (Kashihara et al. 2011), taste loss has a direct effect on appetite and is clinically relevant for malnutrition.

In a recent study (Cereda et al. 2014), dysphagia in PwPD with dementia was associated with male gender and disease duration, while in PwPD with no dementia symptoms, dysphagia was associated with male gender, age and disease duration. Cognitive problems have been observed to relate more to the oral phase impairments (Kim et al. 2015b). However, earlier reports mention that the presence of dementia did not influence the age at the time of death in patients with dysphagia (Bine et al. 1995). Cognitive problems, however, might have an immediate effect on the selection of the appropriate assessment and therapeutic approach.

Dysphagia in PwPD was also associated with bradykinesia and axial and postural instability

with gait disturbances (Moreau et al. 2016; Park et al. 2015). Of interest, depressive states and dysphagia seem to correlate (Han et al. 2011), but the relationship between depression and dysphagia will be discussed later on.

6.1 Drooling and Xerostomia

Both drooling and xerostomia are NMS reported by PD patients and affect not only the QOL but also their oral health (Barbe et al. 2017) and can result to debilitating conditions in PwPD (Bloem et al. 2009). Pathophysiological underpinning of drooling appears to be the α -synuclein observed in minor salivary glands (Folgoas et al. 2013) and the submandibular glands (Del Tredici et al. 2010).

Drooling is an important NMS that is closely linked to swallowing impairments in PwPD and it is reported more prominently in the 'off'-medication period. Patients, who experienced drooling, showed silent aspiration in formal assessments (Rodrigues et al. 2011) and pharyngeal stage swallowing disorders (Nobrega et al. 2008). Approximately 50% of PwPD experience ptialism (Martinez-Martin et al. 2007; Kalf et al. 2012b; Verbaan et al. 2007). Drooling correlated to overall patient dyskinesia (Park et al. 2015), while others believe that it does not correlate to disease duration or severity (Ou et al. 2015). It is now accepted that the reduction in the frequency of spontaneous swallowing may be the underlying pathology for the excess of saliva (Bagheri et al. 1999; Proulx et al. 2005) as well as hypomimia (Kalf et al. 2011).

On the other hand, xerostomia, the abnormal dryness due to insufficient secretions, is an important problem for PwPD (Barbe et al. 2017; Cersosimo et al. 2011). Xerostomia is usually related to levodopa dosage with higher doses increasing the xerostomia problem (Clifford and Finnerty 1995) or could be a side effect of the anticholinergic medication and can lead to changes in microflora and reduced oral health (Bakke et al. 2011) and change taste sensation, affecting swallowing function directly.

6.2 Lung Function and Cough

PD patients may present respiratory impairments and complications, including disturbances in ventilation (Gardner et al. 1986) and respiratory dysrhythmias (De Keyser and Vincken 1985), respiratory muscle weakness (de Bruin et al. 1993) and more.

Both inspiratory and expiratory muscles are affected in PD, while reflexive cough is more impaired than voluntary cough (Fontana et al. 1998). In addition, dopaminergic therapy may result in symptomatic respiratory disturbance in rare cases (Rice et al. 2002). In less advanced stages of the disease, it has been suggested that the motor rather than the sensory components of the cough reflex are impaired (Fontana et al. 1998). A recent study with classification of the patients according to their 'swallowing profile' as a response to dopaminergic medication showed that results on pulmonary function test were not as useful in differentiating PwPD with swallowing impairments (Sawan et al. 2016).

Coordination of breathing and swallowing is impaired in PwPD (Gross et al. 2008), with PwPD showing significant more post-swallow inhalation. Association of the reflexive cough (Troche et al. 2016), urge to cough (Troche et al. 2014a) and measurements of the voluntary cough (Ebihara et al. 2003) with penetration of material in the airways in PwPD has already been documented.

Although only small sample studies have been performed, it is a really interesting clinical research avenue because understanding the ineffective cough reflex might help not only in screening but also in choosing therapeutic approach for these patients (Pitts et al. 2009). In a recent study by Troche et al. (2016), sensitivity of cough reflex discriminated between patients who penetrated above the level of the vocal folds and those with more severe penetration/aspiration, but more studies are needed, given that other factors (such as disease duration) may play a role.

7 Medical Therapy of Parkinson's Disease and Effects on Dysphagia

7.1 Pharmacological Therapy

Dopamine replacement therapies have been the mainstay of PD treatment since the demonstration of the therapeutic effects of the dopamine precursor drug levodopa in the 1960s (Cotzias et al. 1967). Subsequent studies have confirmed the efficacy of levodopa in improving motor symptoms and quality of life in PD (Fahn et al. 2004; Group PDMC et al. 2014). Dopamine receptor agonists, which directly stimulate predominantly dopamine D2 receptors in the brain, are also effective at relieving motor symptoms of PD. Monoamine oxidase B inhibitors (MAOB-I) are used to reduce the catabolism of dopamine, and have a modest symptomatic effect as monotherapy as well as adjunctive therapy in PD (Stern et al. 2004). Catechol-*O*-methyltransferase (COMT) inhibitors such as entacapone are used as adjunctive therapies to levodopa, and improve 'on' time in PwPD (Rinne et al. 1998).

Although PwPD typically show a good therapeutic response to levodopa, fluctuations in the motor response complicate treatment in the majority of cases. The most common manifestation is known as 'wearing-off': the re-emergence of parkinsonian motor symptoms, but also non-motor features such as anxiety, pain and cognitive slowing at the end of an inter-dose interval (Jankovic 2005).

Bradykinesia and rigidity have been proposed as causes of dysphagia in PD. However, dopaminergic medications producing a good effect on motor symptoms have little effect on symptomatic dysphagia in PD (Hunter et al. 1997). A study of non-motor fluctuations in 100 patients with PD showed that dysphagia is one of the few NMS not occurring more commonly in the 'off'-medication state, although it is more severe in the 'off' state when measured objectively (Storch et al. 2013). A meta-analysis of five studies, but only two studies with formal assessments, found

no effect of levodopa on any swallowing parameters (Menezes and Melo 2009). These findings suggest that the involvement of extrastriatal and non-dopaminergic systems linked to the basal ganglia may have a critical role in swallowing dysfunction in PD.

Recently, Michou and colleagues (Michou et al. 2014) performed corticobulbar projection mapping with a neurostimulation technique called transcranial magnetic stimulation (TMS mapping) and formal imaging swallowing assessments, videofluoroscopy (VFS), on a group of PwPD with and without swallowing impairments both ‘on’- and ‘off’-dopaminergic medication. TMS is a safe and non-invasive technique, where a magnetic pulse is delivered through a coil of wire, and when delivered in the form of single pulses over an area of scalp

and the cortical areas representing specific musculature from the periphery, information regarding the activation of the cortico-bulbar-muscular tracts can be obtained. Detailed analysis of the swallowing function revealed that there is marked variability in the responses of PwPD, with some patients showing impairments both ‘on’- and ‘off’-dopaminergic medication and another group experiencing impairments only ‘on’ medication. Marked differences in cortical maps of the three groups (Fig. 2) were observed. Repletion of dopaminergic medication also had an effect in reflexes from the brainstem in the patients studied. Patients with swallowing impairments only ‘on’ medication showed a decrease in brainstem reflexes compared to the ‘off’ state while on medication, implying a similarity to a dyskinetic effect of levodopa to the

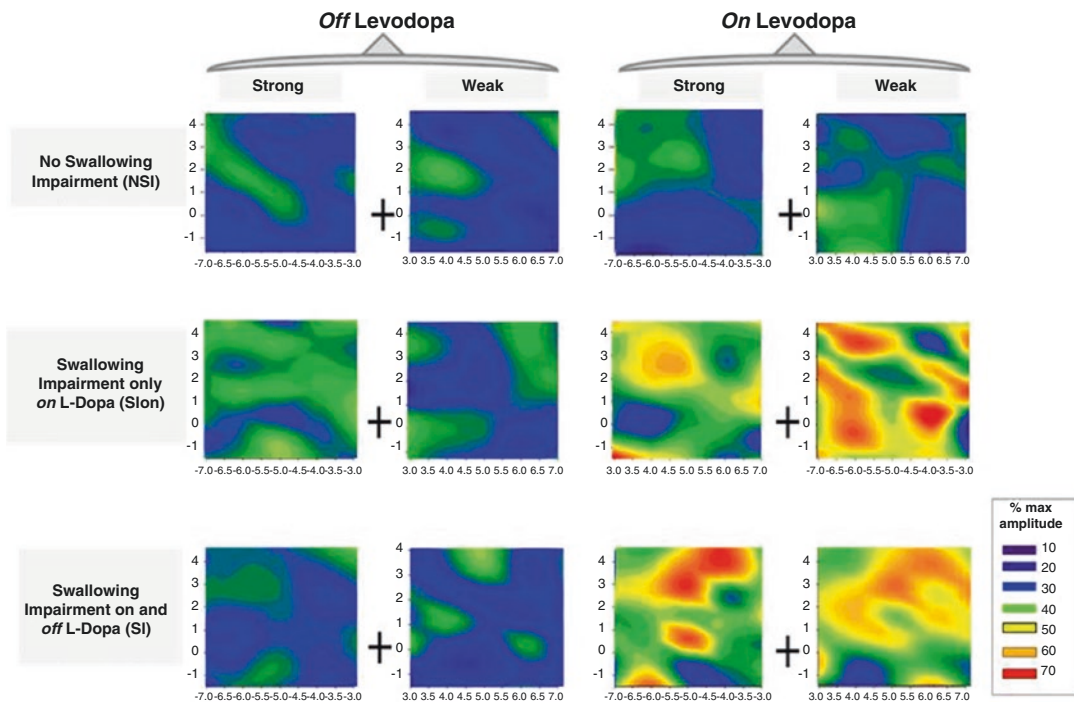


Fig. 2 Topographical maps of cortical representation of the pharynx in the three groups of patients studied with single-pulse TMS when ‘off’ and ‘on’ levodopa. The group of patients with no swallowing impairments had a minor reduction in cortical excitability of the stronger cortico-pharyngeal motor map with levodopa and the group with stable swallowing impairment, irrespective of medication (*third row*), had a bilateral increase in cortical

excitability with medication. The group with swallowing impairments only on levodopa showed an increase in the stronger representation only. The vertex of each plot is marked by a “+”. The intensity scale shown on the right is colour coded as a percentage of the amplitude of the maximum response for each group. With permission Michou et al. (2014)

swallowing pathway or a potential reduction in the ability to compensate for swallowing impairments after dopaminergic repletion.

7.2 Non-oral Medical Therapy

The development of motor complications of PD often triggers the use of non-oral therapies such as apomorphine, levodopa-carbidopa intestinal gel and deep brain stimulation surgery (DBS). Apomorphine is a potent dopamine D1 and D2 receptor agonist which is administered subcutaneously via intermittent injection or continuous infusion, and improves 'on' time and motor fluctuations in PD. A small study using videofluoroscopy showed improvement in some pharyngeal transit time and other aspects of dysfunctional swallowing in PwPD following apomorphine (Tison et al. 1996). The transdermal dopamine receptor agonist rotigotine has also been shown to improve pharyngeal transit time and videofluoroscopy scores in a small open-label study (Hirano et al. 2015).

7.3 Role of Non-oral Dopamine Receptor Agonists in Dysphagia (Acute, Surgery)

Deep brain stimulation surgery involves implantation of stimulating electrodes in basal ganglia nuclei, predominantly the internal globus pallidus (GPi) and subthalamic nucleus (STN). DBS of both nuclei has been shown to improve 'on' time and motor fluctuations in PD, as well as reduce levodopa-induced dyskinesia (Rodriguez-Oroz et al. 2012). A recent clinical trial of GPi versus STN DBS in PwPD showed a rate of dysphagia of up to 15% in those receiving STN-DBS in the first year following surgery, but the long-term rate of dysphagia in both groups after 3-year follow-up was much lower (Odekerken et al. 2016). A systematic review of all studies investigating the effect of DBS on swallowing found no clinically significant effects, although the authors identified that the pharyngeal phase of swallowing appeared sensitive to the effects of STN DBS (Troche et al. 2013).

8 Clinical Assessment of Dysphagia in PD

Swallowing impairments in PwPD should be diagnosed early given the severity of the consequences of dysphagia in PD. Although there is a high risk of aspiration and pneumonia associated with dysphagia in PwPD, swallowing impairments are often overlooked until the patient experiences choking or pneumonia incidences. Amongst the usual symptoms that the patients report are difficulties with swallowing their tablets; therefore a cautionary approach is advisable. Another argument for cautionary approach with dysphagia in PwPD is the fact that the extent and frequency of silent aspiration in PwPD have not been estimated yet.

Screening approaches in the clinical setting sometimes rely on a single question in UPDRS (Movement Disorder Society Task Force on Rating Scales for Parkinson's D 2003) and lately the Non-Motor Symptoms Questionnaire (Chaudhuri et al. 2006) from PD UK has offered a single yes/no question regarding coughing and choking of PwPD. Swallowing-specific questionnaires designed to be completed by PwPD have been developed (Manor et al. 2007; Simons et al. 2014), but there is not currently a specified screening tool for dysphagia in parkinsonism to be administered in the clinic. However, there is emerging evidence that some dysphagia screening tools (i.e. 100 ml (Belo et al. 2014) or 150 ml timed water test) or wet voice testing (Sampaio et al. 2014) could be potentially useful in screening for PwPD.

Evidence from studies of swallowing-breathing coordination has shown that inspiratory events after a swallow and a shorter apnoeic interval could indicate PwPD who are at risk of swallowing impairments (Troche et al. 2011; Gross et al. 2008). In addition, rigorous research is underway for delineating those indicators for potential risk of aspiration in PD patients based on reflexive cough and other indicators, such as the urge to cough (Hegland et al. 2016).

Thorough clinical assessment is required by the dysphagia specialists, which usually takes into consideration information from the medical notes regarding medication and in particular

dosage concomitant conditions and overall motor symptomatology. Understanding the role that confounding factors such as cognition and fatigue play is also an important part of the assessment. Formal assessments with imaging should be performed and dysphagia specialists can utilise techniques such as fibre-optic endoscopic evaluation of swallowing (FEES), VFS or (video) manometry. FEES is well tolerated and easily repeatable, and attempts have been made to standardise the assessment in parkinsonism (Warnecke et al. 2010). On the one hand FEES and VFS can provide the clinician with information about the occurrence and the cause of aspiration, while multichannel manometric or even more synchronous multichannel intraluminal impedance and manometry assessment, demonstrating the motility patterns of the oesophageal phase, can provide information of bolus propagation and the potential overlapping symptomatology of pharyngeal and oesophageal phase. The use of any formal imaging technique should take place not only for the visualisation of any potential risk of aspiration and further respiratory complications, but also to inform the clinician whether functional swallowing is intact enough so as the patient can remain nourished and hydrated, in addition to informing the treatment and management options (including compensatory manoeuvres). Oral and pharyngeal phase problems, as presented in Table 1, should be carefully evaluated. Post-swallow residue could be multifactorial in nature (reduced sensory and motor functions) (Michou et al. 2014) and it is very important to investigate the severity and the effect on swallowing safety. Also, perhaps of importance in building the most appropriate management plan, there may be loads to learn from supplementing the bedside assessment with lingual strength and reserve, airway somatosensory thresholds and/or cough strength; however more research is needed prior to clinical implementation of these techniques.

In the current clinical practice, the diagnostic examinations (and treatment, below) are conducted during the 'on'-levodopa (medication) phase, which starts roughly 90–120 min after the intake of antiparkinsonian medication. However,

given the recent evidence regarding the different responses to dopaminergic therapy from early- to mid-stage PD (Michou et al. 2014) and late-stage PD (Warnecke et al. 2016), there might be important information to be gained from reviewing how efficient is the swallow both 'on' and 'off' pharmacological treatment. More research in this field will provide evidence on the utility of this binary approach.

Lastly, it is important to note that the different forms of clinical assessments are seen to be sensitive enough to investigate subtle and overt differences in dysphagic profiles of PwPD and atypical parkinsonian syndromes. Warnecke and colleagues compared FEES evaluation in 18 patients with PSP to 15 PwPD; despite the much shorter disease duration of 3.4 years in PSP compared to 13.5 years in PD, there were no significant differences in the severity of FEES impairments between groups (Warnecke et al. 2010). All endoscopic variables were affected in PSP, most frequently: bolus leakage, delayed swallow reflex and residues in vallecular spaces and pyriform sinuses. Disease severity and duration correlated with swallow impairment, with only a minority of PSP patients showing any levodopa responsiveness of dysphagia (Warnecke et al. 2010). Higo and colleagues evaluated swallow function in 29 patients with MSA (22 MSA-C, 7 MSA-P, median H&Y stage IV) using VF and manometry: the most common fluoroscopic findings were delayed bolus transport (73%), insufficient tongue movement (55%) and disturbance of intra-oral bolus holding (49%), while aspiration was seen in 21% of patients (Higo et al. 2003). Oropharyngeal and hypopharyngeal pressures were also reduced compared to controls, with frequent incomplete relaxation of the upper oesophageal sphincter in patients with >5 years' disease duration (Higo et al. 2003). A further study by the same group in 21 patients with MSA-C examined progression of VF findings over the disease course: delayed bolus transport was seen in 50% of patients <3 years' disease duration, and 85% of those >7 years' duration, while pharyngeal swallowing disturbance was minimal in early disease but progressed with time (Higo et al. 2005). It seems that further work is

needed, and will increase our knowledge for the profiling of swallowing disorders in different patient groups.

9 Early- vs. Late-Stage Dysphagia in PD

Although dysphagic symptoms are estimated to be experienced around 130 months post-diagnosis (Muller et al. 2001), there is not enough evidence regarding the onset of the symptomatology in the disease progression. As a consequence, there is not enough information regarding the optimal time window for clinical assessments of dysphagia, given that silent aspiration is a common phenomenon. Formally assessing PwPD for dysphagia when this is clinically severe manifested with incidences of choking and pneumonia may not be optimal since the patient may no longer benefit from active treatments.

Early-onset dysphagia in PD is atypical and usually alerts the clinician to an alternate diagnosis such as PSP or MSA. It is clinically important to understand when swallowing impairments appear in the course of the disease and how dysphagia symptomatology develops over the years. Even in early stages of the disease, dysphagia can be observed in a very mild form, while in the advanced stages almost 95% will have dysphagia (Nagaya et al. 1998; Ertekin et al. 2002; Wintzen et al. 1994).

One of the current debates is whether severity of PD is associated with dysphagia. While some clinicians showed that swallowing function is relatively well preserved earlier in the disease, when disease is not as severe, and worsens with disease severity (Umemoto et al. 2011; Leopold 1996; Baijens et al. 2011), others have shown that disease severity does not predict swallowing impairments (Bushman et al. 1989; Fuh et al. 1997; Ali et al. 1996; Troche et al. 2016; Ertekin et al. 2002). Impaired mastication and orofacial functions are frequent in moderate-advanced PD and there is a trend for progressive difficulties in mastication and orofacial functions with disease progression (Bakke et al. 2011).

From a clinical perspective, disease duration and frequency of swallowing problems, which

could be higher in the later stages, may account for the more clinically significant dysphagia problems in PD. Based on the neurophysiological overview provided in this chapter, one can postulate that the changes at the different areas of the CNS of the PwPD could account for the differences in swallowing impairments in PD. Also, it is important to state that there is currently no definition for the swallowing impairments accompanied with changes in swallowing efficiency but no overt risk in swallowing safety as opposed to the clinically significant dysphagia resulting in overt aspiration, which could be the reason behind the differences in clinical opinions.

10 Therapeutic Approaches in PD

Therapeutic approaches in the clinical setting and outpatient clinics are usually prescribed to those who show clinical severe dysphagia problems only. One of the main unanswered question is when should therapy start and longitudinal studies are needed to show that early therapy will have an effect in the long term and will delay the debilitating consequences of dysphagia.

Nevertheless, there are various approaches for dysphagia in PD including surgical interventions, oromotor exercises (Argolo et al. 2013; South et al. 2010), bolus modification for enhanced sensory awareness as well as swallow safety (Robbins et al. 2008; Rofes et al. 2013), biofeedback (Manor et al. 2013), electrical stimulation (Baijens et al. 2013; Heijnen et al. 2012), postural changes and compensatory airway protective manoeuvres, expiratory muscle strength training (EMST) (Pitts et al. 2009; Troche et al. 2010), thermal stimulation applied to the faucial pillars (Regan et al. 2010) as well as pharmacological interventions (for reviews Wood et al. 2010, Baijens and Speyer 2009, Deane et al. 2001, van Hooren et al. 2014).

Most of the clinical studies designed to investigate the effects of the aforementioned treatments on swallowing in PwPD have been performed in a small number of patients. Nevertheless, it seems that improvements in swallowing measurements

(changes in aspiration of material, reduction in residue in the oropharynx) as viewed with formal imaging assessments and changes in QOL have been observed with several of these approaches (Pitts et al. 2009; Argolo et al. 2013; Manor et al. 2013; Heijnen et al. 2012). In addition, as we mentioned previously, therapy is applied during the 'on'-medication state and most of the therapeutic protocols have been applied for about 4–5 weeks (Argolo et al. 2013; Manor et al. 2013; Heijnen et al. 2012; Troche et al. 2014b; Baijens et al. 2012). It is interesting to say that most of the therapeutic approaches have been applied to patients of mild to severe PD severity (H&Y stage II–IV). Further research, however, is needed to allow us to understand whether some of the techniques may have a beneficial effect or not. Some placebo effects have been already observed in the trials with neuromuscular electrical stimulation applied through electrodes on the neck (Baijens et al. 2012). Traditional swallowing therapy seems to be working as good as the recent proposed stimulation techniques (head-to-head comparison: (Baijens et al. 2013, Heijnen et al. 2012); direct application of traditional therapy only (Argolo et al. 2013; Regan et al. 2010), while gum chewing seemed to increase swallowing frequency in a case-control study (South et al. 2010).

The clinicians' toolbox of swallowing therapies includes biofeedback, thermal tactile stimulation (Regan et al. 2010), compensatory head postures, modification of the bolus, etc. Biofeedback with the use of videos of normal swallowing process, videos obtained with FEES showing the individual's swallowing impairments and the effects of compensatory techniques in a paradigm called video-assisted swallowing therapy (VAST) showed that it can reduce the post-swallow residue in PwPD (Manor et al. 2013). Another interesting approach is the EMST, which is received as individual training and can be performed at home. Four weeks of EMST had a direct effect on measurements of cough (increase in cough volume acceleration) (Pitts et al. 2009) and reduced penetration in PwPD (Troche et al. 2010). The sustainability of the effects of this non-specific treatment (Laciuga et al. 2014) has to be examined in details, as a

study investigated the 3-month post-training period and showed that maintenance protocols are needed to sustain the effects (Troche et al. 2014b). Especially for drooling, botulinum toxin (BT-A) injection in the parotid gland has been effective for reducing sialorrhea (Truong et al. 2008) but may not have specific beneficial results on swallowing measurements (Nobrega et al. 2009). Evidence also exists that supplementation of the bolus with piperine could speed swallow response and improve safety of swallow (Rofes et al. 2013), but further studies should take place to elucidate the mechanisms and the medium of supplementation.

Importantly, there is missing evidence as to which patients and what type of swallowing impairments can be targeted with which therapeutic approach, given the marked heterogeneity in PwPD.

In the more severe swallowing problems, PwPD are not able to receive adequate oral nutrition due to severe aspiration or reduced oral intake as a result of food modification and oral-stage symptoms for instance. Alternative options should be considered for the PwPD. The decision for percutaneous endoscopic gastroscopy (PEG) insertion is important to be made after careful consideration and discussion between the multidisciplinary team, the patient and carers. The complication rate of PEG insertion in PwPD and atypical parkinsonian syndromes is increased, as is the 30-day mortality rate (Sarkar et al. 2017). In the retrospective study by Sarkar et al. (2017) aspiration pneumonia was the main cause of early mortality in PwPD with PEG feeding tubes, indicating that PEG is not a direct solution to aspiration and dysphagia.

One of the important complications of a PwPD experiencing dysphagia or being nil by mouth is the loss of medication administration, which can lead to neuroleptic malignant-like syndrome when dopamine levels drop dramatically in the brain. Even though specific medications such as carbidopa/levodopa/entacapone among others are not manufactured to be crushed, this is usually the case in the current practice. However, different approaches to medication should be considered at this stage (Alty et al. 2016). Evidence also

shows that a specialist inpatient Parkinson's disease Unit could tackle the multifactorial patients' outcomes when PwPD required hospitalisation (Skelly et al. 2014), but further work might be needed to see how dysphagia and aspiration pneumonia can be readily managed in such units.

11 Health Outcomes of Dysphagia in PD

The health outcomes of dysphagia in PD and atypical syndromes include malnutrition and dehydration, aspiration pneumonia and a reduced overall QOL, as well as depression and anxiety.

Malnutrition and dehydration in PwPD are highly prevalent, yet there is no accurate quantification of prevalence as yet. There are different factors such as dysautonomia, disease severity and dopaminergic repletion medication dosage (Barichella et al. 2013) for malnutrition in PwPD. A systematic review found that the prevalence of malnutrition ranges from 0 to 24% in PwPD, while 3–60% of patients were reported to be at risk of malnutrition (Sheard et al. 2011). Progressive weight loss, and especially fat mass loss (Markus et al. 1993), is a major feature in PD starting 2–4 years prior to diagnosis (Chen et al. 2003) and prevalence of malnutrition and sarcopenia is significantly increased with increasing disease duration, advanced stage and severity of disease (Kashihara 2006; Montaurier et al. 2007; Lorefalt et al. 2004). Additionally, it has also been observed that decreased skeletal muscle mass could be a risk factor for dysphagia in long-term care (Murakami et al. 2015). Dysphagia is one of the main factors contributing to malnutrition in PD along neuropsychiatric symptoms contributing to reduced food intake, increased catabolism and resting energy expenditure—in both untreated and optimal treated PwPD. Therefore, screening for malnutrition should be performed and weight changes should be monitored over time with validated and reliable nutritional risk screening tools.

In PwPD, aspiration pneumonia is the leading cause of death (Fernandez and Lapane 2002; Lo et al. 2009; D'Amelio et al. 2006), with dysphagia

being associated with a reduction in survival time. Aspiration pneumonia events in hospitalised PwPD can reach 2.4% (Martinez-Ramirez et al. 2015). Death seems to occur within 15 to 24 months post-confirmed swallowing disorders in PD patients (Muller et al. 2001); however further longitudinal studies are warranted to understand the natural history of dysphagia in PwPD. In the Sydney Multicenter Study (Hely et al. 2005), which investigated the effects of low-dose levodopa compared with low-dose bromocriptine, half of the population followed up was reported to 'choke', indicative of dysphagia that may lead to consequent pneumonia; the latter was the most common cause of death in the study. Impaired resistance to infections and bacterial colonisation could be an additional factor for aspiration pneumonia (Ortega et al. 2014), although significant different oral bacterial load has not been found between PwPD and same-age control group (Pereira et al. 2017).

Quality of life is reduced in PwPD and dysphagia may reduce QOL even further. In studies where QOL questionnaires specifically designed for the effects of swallowing disorders were used, such as SWAL-QOL (McHorney et al. 2000), it is demonstrated that PwPD have clearly reduced QOL (Michou et al. 2014; Carneiro 2014; Leow et al. 2010). There is also a potential link between dysphagia and depression and/or QOL (Carneiro 2014; Leow et al. 2010; Manor et al. 2009; Perez-Lloret et al. 2012; Plowman-Prine et al. 2009; Walker et al. 2011). It is now accepted that depression is commonly experienced NMS by PwPD and that such psychosocial factors have a significant impact on QOL (Maass and Reichmann 2013). Importantly, cognitive impairments could have a significant negative impact on QOL (Chagas et al. 2014). McKinlay et al. (McKinlay et al. 2008) reported that PwPD-related dementia is more likely to have psychosocial illnesses such as anxiety and depression. Nevertheless, most of the studies that described a relationship between reduction in QOL and dysphagia (above) rigorously excluded patients with cognitive problems, which indicates the factual correlation of dysphagia and reduction in QOL. Being able to eat and drink safely is not only of importance to

a person's health, they are also social activities around which society places a lot of emphasis through ritual and custom. Ekberg et al. (Ekberg et al. 2002) argue that dysphagia has a significant impact on an individual's confidence and desire to participate in social activities.

Conclusions

This chapter focused on the current clinical status and research directions on swallowing impairments (dysphagia) in PwPD. The increased incidence of dysphagia in PwPD leads to increased risk of mortality, secondary to aspiration pneumonia. Although studies show that aspiration pneumonia is a common cause of death in this group of patients, therapeutic approaches for dysphagia lack a strong evidence base and there is an increased need for large randomised clinical trials that will allow us to understand how early and what swallowing impairments can be treated as well as the compliance and sustainability of the effects of treatments in this neurodegenerative disease. Importantly, the underlying mechanisms accounting for the progression of dysphagia in PD are still unclear. It is noteworthy to state that investigating changes in physiology alone as an outcome measure for the effects of treatment, without observing the underlying neurophysiological basis for such changes, is likely to give an incomplete picture of the aetiology, the volume of therapy required and how to use even compensatory techniques in the management of dysphagia in PD (Michou and Hamdy 2010). Future research in the field is warranted and may result in improved management of dysphagia in patients with PD.

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