Oropharyngeal Swallowing Disorders in Parkinson's Disease: Revisited

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Abstract: Swallowing impairments in Parkinson's Disease (PD) affect patients' nutritional status, the oral administration of medication, and of course quality-of-life, even in the earlier stages of the disease. Here, we provide a synopsis of the current state of neurological diagnosis and the clinical value of the assessment for nutritional status and swallowing impairments in patients with PD. The recent position statement by European Society for Swallowing Disorders (ESSD) on the clinical assessment of dysphagic PD patients is also reviewed and discussed. Here, we also attempt to summarize and explain the recent findings from neurophysiological studies attempting to underpin the underlying mechanisms of the disease, preceding a short review of the therapeutic approaches. With this review, we aim to increase awareness for the deliberating consequences of swallowing impairments and provide a range of unanswered questions on different levels (physiological, neurophysiological, assessment and therapeutic procedures). Further investigations and collaborative large-scale research studies together with neurophysiological studies seem to be warranted in order to shape more effective clinical practice in the future.

Keywords: Parkinson's disease, oropharyngeal dysphagia, nutrition, neurophysiology.

INTRODUCTION

Parkinson's disease (PD) is the second most frequent neurodegenerative disease with prevalence among general population reaching 100-1000/100000, and an incidence between 13.4-20.5/100000 [1]. The mean age at diagnosis of PD is 55 and most patients are between 50 and 80 years old [2].

Dysphagia, as we will discuss, is a frequent symptom in parkinsonian patients and a frequent cause of comorbidity and death in Parkinson's patients. Dysphagia can affect nutritional status and may result in endotracheal aspiration. Several different oropharyngeal symptoms are usually observed in a PD patient and different assessment methods can provide us with required information.

During the recent years, there has been an increase in the number of research studies on neurophysiological mechanisms underpinning swallowing disorders in PD. By reviewing the evidence below, we aim to assist the clinicians understand these recent findings.

The structure of our paper attempts to discuss the pathophysiology of PD and the approach by the neurologists, the phenotypes of the oropharyngeal symptoms in PD and the clinical practice with regards to assessment. Rather than providing a systematic review, here we discuss the European Society for Swallowing Disorders (ESSD) position statement for oropharyngeal dysphagia and attempt to increase awareness. Lastly, the recent therapeutic studies are discussed briefly below, and we will provide an up-to-date summary of the literature.

1. PATHOPHYSIOLOGY OF PD

Even though PD is considered a sporadic condition, almost a 10% of cases have a genetic implication [3]; most of them with mutations in Parkin or alpha-synuclein-related genes. Several loci have been related with autosomal recessive Parkinsonism, with the PARK2 considered as responsible for 50% of the autosomal recessive cases. In most of the genetic cases, both autosomal dominant and recessive genetic

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cases have an earlier onset of symptoms between the fourth and sixth decades [4]. Exposure to some environmental factors has been associated with PD, including transition metals, such as manganese, iron or pesticide exposure, likely due to neuro-oxidative mechanisms [5]. Probably, most cases are the result of genetic vulnerability plus environmental factors, most of them unknown at this moment.

In the pathological mechanisms of PD, apart from the selective loss of midbrain dopamine neurons in substantia nigra pars compacta, wearing to striatal dener-vation, Lewy-bodies and α-synucleinopathy have been vastly investigated [6]. Lewy-bodies appear as special masses of abnormal aggregates of protein that develop inside nerve cells, displace other components, and are suspected as the pathological bases of PD [7]. Alpha-synuclein (α-Syn), a protein which is the primary component in Lewy-bodies, act normally to maintain proper synaptic processes; however, certain changes in these proteins structure initiate a cascade of pathological events commonly referred to as α-synucleinopathy, which is believed to be the cause of PD [8].

Recently, Braak and colleagues established the predictable topographic sequence of progression for the intracerebral deposition of Lewy-bodies and Lewy-neurites in PD [9]. Stage I [10] involves extra-nigral structures such as autonomic nervous system, olfactory bulb and dorsal motor vagus nucleus, progressing in Stage II to the brainstem sensory relay centers [11]. Only in Stage III, synucleinopathy reaches the nigral substance and, years after that, motor symptoms can be detected. Thus, hyposmia, autonomic dysfunction, pain, mood or sleep disturbances and executive dysfunction can be explained by this pathologic progression, years before any motor symptoms become evident or even before dopaminergic neuronal loss is evident with the use of imaging techniques (i.e. Positron Emission Tomography PET or Single-photon emission computed tomography). The use of radio-ligands for the dopamine transporter allows detection of neuronal loss 4 to 6 years before clinical diagnosis [12] and, during this time, more than 50% of nigrostriatal projections will be lost [13]. Braak stages III and IV are related to progressive cognitive and motivational disorders, while in stages V and VI synucleinopathy reaches the neocortex with evident symptoms of dementia.

Parkinsonism is a clinical syndrome characterized by tremor, bradykinesia, rigidity and postural instability. During the past years, it has been recognized that motor symptoms in PD can be accompanied and even preceded by non-motor symptoms with a great variability in its presentation [14]. Hyposmia, pain, autonomic dysfunction as constipation, fatigue, sleep disorders, mood disorders or cognitive deficits, most of them non-dopaminergic symptoms, can precede motor presentation [15], providing weight to the evidence that PD is a multisystem degenerative disorder comprising not only dopaminergic, but also noradrenergic, serotoninergic, cholinergic and probably other neurotransmitter systems [16].

Clinical diagnostic criteria from the UK Parkinson's Disease Society Brain Bank [17], include the diagnosis of parkinsonism symptoms, such as bradykinesia and at least one of the following: muscular rigidity, 4-6 Hz rest tremor, postural instability without any other possible cause. The exclusion criteria currently used in neurology clinics include familial parkinsonism, persisting strictly unilateral features after 3 years, sustained remission, negative response to large doses of levodopa, history of repeated stroke and stepwise progressive parkinsonism, history of repeated head injury or neuroleptic treatment, early severe autonomic, pyramidal or cerebellar signs, and others. The third stage towards the clinical diagnosis of PD is the supportive prospective positive criteria, for which the clinician should gather information from the longer-term course of movement disorders, and provide the definite diagnosis of PD, in combination to the aforementioned. Using these clinical criteria, the diagnostic accuracy reaches 80% [18], indicating that improvement of the diagnostic accuracy should be sought. At this moment, only autopsy can confirm PD in some cases [19].

Clinical progression of PD can be rated with the Hoehn and Yahr Scale [20]: Stage One, with mild unilateral symptoms, Stage Two with bilateral symptoms, Stage Three with early impairment of balance on walking or standing, Stage Four when patient can still walk to a limited extent, to Stage Five with complete invalidism. The Unified Parkinson's Disease Rating Scale (UPDRS) [21], although time-consuming is a very good and generalized 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.

2. COMPLICATIONS IN PD: OROPHARYNGEAL DYSPHAGIA

Oropharyngeal dysphagia (OD) causes specific complications in PD patients that can lead to death [22-

24]. In a recent meta-analysis, the prevalence of PD patients who perceive difficulty in swallowing was estimated at 35% (95% CI:28-41) but when an objective swallowing assessment was performed, the estimated prevalence of OD reached 82% (95% CI:77-87) [25]. Up to 80% of PD patients will have OD, in a very mild form, during the early stages, while in the advanced stages, almost 95% will have dysphagia [26-28]. In the early stages, the swallowing function is relatively well preserved [23, 26], however, this finding is refuted by some authors, who have found no correlation between the presence or severity of OD and overall disease severity [29, 30]. As patients often use compensatory mechanisms in the early stages of PD, OD may be benign [26], but complications like aspiration pneumonia (AP) may occur, especially in the advanced stage [27, 29].

OD may give rise to two groups of clinically relevant complications in these patients: a) malnutrition and/or dehydration caused by a decrease in the efficacy of deglutition; and b) choking and tracheobronchial aspiration caused by the decrease in deglutition safety and which results in respiratory infections and AP with high mortality rates [31]. Despite this, OD is underestimated and underdiagnosed as a cause of major nutritional and respiratory complication in these patients.

The true prevalence of malnutrition in PD has yet to be accurately quantified. A systematic review found that the prevalence of malnutrition is ranging from 0% to 24% in PD patients, while 3-60% of PD patients were reported to be at risk of malnutrition [32]. Progressive weight loss is a major feature in PD starting 2-4 years prior to diagnosis and prevalence of malnutrition and sarcopenia is significantly increased with increasing disease duration, advanced stage and severity of disease. Dysphagia is one of the main factors contributing to malnutrition in PD along neuropsychiatric symptoms contributing to reduced food intake, increased catabolism and energy expenditure, and the effect of drug therapies [25].

The position statements by the European Society for Swallowing Disorders (ESSD) unify several criteria and provide best clinical practices among the different healthcare centers and professionals working with patients with OD [33]. These statements defined that patients with OD associated to neurodegenerative diseases are at risk of malnutrition and dehydration. Therefore, the nutritional status should be screened and monitored regularly. The minimum data to be monitored are weight changes over time together with validated and reliable nutritional risk screening tools as these are recommended by the European Council [34]. Screening for malnutrition can be performed using simple tools such as the Mini Nutritional Assessment Short Form (MNA-SF) [35], which latter requires minimal training, and is widely available. If following screening, a person is found to be at risk of malnutrition, appropriate referrals should be made to nutrition healthcare professionals for a full assessment and specialized nutritional support.

Aspiration Pneumonia is a serious complication of OD and the leading cause of death in PD [36]. The pathogenesis of AP presumes the contribution of risk factors that alter swallowing function, causing oropharyngeal aspiration, predisposing the oropharynx to bacterial colonization and impairing the host's resistance to infections [37, 38]. It is important to state that although pneumonia is a very common cause of hospitalization and the commonest cause of death among patients with PD [39] in the clinical setting; OD and aspiration are not usually considered etiologic factors for the incidence of pneumonia in PD.

The ESSD statement concluded that the diagnosis and treatment of AP can be improved by early identification of patients who are at risk of aspiration using easy and reliable screening tools, by applying a standardized oral healthcare program in hospitals and nursing homes to reduce colonization and an appropriate diet adaptation of fluids and solids to avoid aspirations [33].

3. PHYSIOLOGICAL CHARACTERISTICS OF SWALLOWING IN PD

In PD, any stage of the swallowing process (oral, pharyngeal or oesophageal) may be affected. Moreover, the impairment of some complementary systems such as the respiratory, olfactory or salivary, can also contribute to swallowing impairment. Below, we summarise the symptomatology of OD in PD.

Oral Phase

Impairments of the oral phase of swallowing are present in many patients with PD, since voluntary movements are predominantly affected in these patients. Jaw tremor and rigidity, lingual and lip tremor, impaired preparatory lingual movements and mastication leading to abnormal bolus formation, pre-swallow spillage, delayed initiation of swallowing, repeated tongue pumping, piecemeal swallows and

increased oral residue are common radiological observations during the oral phase of swallowing of PD patients [29, 30, 40]. Disease-related tremor, bradykinesia and rigidity may be contributing factors to the observed oral motor abnormalities. Moreover, an excess of saliva is reported in up to 78% of PD patients [41]; however, this may not be the result of excessive production, but due to a decrease in frequency of swallowing [42].

Pharyngeal Phase

The pharyngeal phase of swallowing in PD patients is characterized by slow and delayed vertical laryngeal movement, epiglottic dysmotility, reduced pharyngeal motility and peristalsis which may lead to pharyngeal residue. As a result of the pharyngeal dysfunction, laryngeal vestibule penetrations and tracheobronchial aspirations are commonly observed in PD patients [29, 30, 40]. In addition to the abnormal pharyngeal motion, higher hypo-pharyngeal intrabolus pressures and reduced peak pharyngeal pressures can be also reported in PD patients when compared to age-matched controls [29]. Moreover, impaired sensory function has been also hypothesized for PD patients, due to affected pharyngeal sensory nerves with Lewy-body pathology [43], which can contribute to delayed swallowing responses.

Oesophageal Phase

Incomplete Upper Oesophageal Sphincter (UOS) relaxation and/or UOS opening, usually with cricopharyngeal bar formation, are also common findings in PD patients [29]. Weak bolus propulsion, impaired performance of supra-hyoid muscles and hypertonic sphincter contribute to the UOS dysfunction in PD patients. The presence of Zenker's diverticula, probably as a consequence of the impaired UOS function and high hypo-pharyngeal pressures, has also been reported in patients with PD [44].

Even though the site of reported dysphagia in the majority of patients with PD is oropharyngeal, abnormalities in the oesophageal stage, such as oesophageal dysmotility, loss of peristaltic waves and appearance of simultaneous non-progressive contractions in the oesophageal body and incomplete relaxation of the lower oesophageal sphincter, have frequently been found in PD patients, even in the early stages of the disease [45]. The accumulation of abnormal alpha-synuclein in the enteric nervous system and dorsal motor nucleus of the vagus, has been related to the development of the upper gastrointestinal abnormalities in PD [46].

4. ASSESSMENT OF SWALLOWING IMPAIRMENT IN PD: CURRENT SCOPE

Assessment of OD in PD is an essential step in the clinical management of these patients and the recommendations by the ESSD [33] are:

a) patients who during clinical assessment are found to likely suffer from OD or poor airway protection should undergo an instrumental examination, either Videofluoroscopy (VFS) or Fiberoptic Endoscopic Evaluation of Swallowing (FEES);

b) VFS and FEES should be performed in a standardized way, preferable in an upright position. In particular, VFS should always include lateral projection of the oral cavity, pharynx, and oesophagus;

c) a standardized protocol is essential for both VFS and FEES;

d) the diagnostic test should focus on the patient's worst swallow, to reveal dysfunction or morphologic abnormalities that can explain the patient's symptoms;

e) the instrumental test should include the assessments of the impaired physiology and assess methods by which the impairment might be best remediated; and

e) the procedure should include manoeuvres and postures where necessary as well as the use of different viscosities and textures including, if deemed safe, thin liquid, puree and soft solid.

FEES offers the dysphagia professional a reliable tool to investigate the pharyngeal phase of swallowing [47]. FEES is well-tolerated, easily repeatable, and can be performed at the bedside [48]. However, various protocols exist, and there is no consensus on the number of swallow trials, bolus consistencies, and bolus volumes to include in a FEES. With FEES, the clinician is able to visualize manifestations such as residue in the valleculae and pyriform sinuses, uncontrolled bolus or premature loss of liquid, penetration and aspiration, and piecemeal deglutition in PD [49, 50]. Currently, clinical practice diagnostic examinations and dysphagia treatment are conducted

during the “on” Levodopa (medication) phase, which starts roughly 90 to 120 minutes after the intake of antiparkinsonian medication [51], while L-dopa levels are high in the brain. Long-term use of L-dopa preparations may provoke motor complications, notably the involuntary movements called dyskinesia, and cause fluctuations in the response to medication. Parkinson patients may experience phase fluctuations ranging from a good response to medication and few motor limb symptoms (“on”-phase) to no response and significant symptoms (“off”-phase) [52]. Research studies for the effects of medication on swallowing system and the optimal time for treatment and assessment are still on-going.

The aim of the VFS study in PD patients is: a) to evaluate the safety and efficacy of deglutition, b) to characterize the alterations of deglutition in terms of videofluoroscopic signs, c) to help select and assess the effect of treatments; and d) to make accurate measurements of oropharyngeal swallow response. For instance, the Volume-Viscosity Swallowing test (VVST) [53] can be performed on every patient with PD with a positive screening for OD. VFS can assess a) several signs related to the function of swallowing, b) the efficacy of deglutition, which is the patient’s ability to ingest all the calories and water he or she needs to remain adequately nourished and hydrated; and c) safety, which is the patient’s ability to ingest all needed calories and water with no respiratory complications.

With standardised VFS protocols, the clinical pathological manifestations of OD in PD, as described above, can be observed in detail, as well as any potential glossopalatal (tongue-soft palate) seal insufficiency during the oral stage, which is a serious dysfunction that results in the bolus falling into the hypopharynx before the triggering of the oropharyngeal swallow response and while the airway is still open, which causes pre-deglutitive aspiration.

For the pharyngeal phase, the main sign of efficacy is pharyngeal residue. Post-deglutitive residue is an important VFS sign as aspiration after the pharyngeal swallow is the result of ineffective pharyngeal clearance. Mechanisms of aspiration are classified as pre-deglutitive (before activation of pharyngeal phase), intra-deglutitive or post-deglutitive according VFS. The VFS signs of reduced safety of the pharyngeal phase are penetrations and aspirations into the airway.

Pathophysiology of impaired safety and aspirations in patients with PD can be assessed by VFS as it is mainly associated with delayed airway protection and late laryngeal vestibule closure caused by both central neurological impairment and increased sensory loss in the pharynx and larynx [54]. Impaired efficacy is associated with weak tongue squeeze, weak bolus propulsion forces and incomplete UES relaxation and reduced UES compliance found in up to 21% patients with PD and caused by bradykinesia, weakness, and extrapyramidal rigidity [29, 55]. Silent aspirations are frequently observed during VFS in patients with PD as cough reflex sensitivity and cough intensity deteriorates in advanced PD, but also in asymptomatic patients during the early stages of the disease [56].

5. NEUROPHYSIOLOGICAL EVIDENCE: UNDERSTANDING THE MECHANISMS FOR SWALLOWING IMPAIRMENTS IN PD

The number of neurophysiological studies to describe and delineate the swallowing neural network in health is increasing due to advances in neuroimaging, neurostimulation, and electrophysiology [57]. The sensorimotor act of a healthy and safe swallow depends on the functional network of several brain areas, and the intact networks of neurons in areas of interest for swallowing i.e. brainstem central pattern generator and fiber tracts along the projection from cortical to brainstem levels. The brain areas activated mostly during swallowing in functional magnetic resonance studies (fMRI) and PET include: the primary sensorimotor cortex, sensorimotor integration areas, the insula and frontal operculum, the anterior cingulate cortex, brainstem, and supplementary motor areas (SMAs).

For the interest of this review in PD, we discuss below the regions that attract most of the interest of this ‘*multidimensional* [58] in nature’ swallowing network, being within the medullary area housing motoneurons whose firing patterns allow the timely execution of swallowing, namely: (1) a dorsal region consisting of the neurons within and around the nucleus tractussolitarius (NTS) and (2) a ventral region corresponding to the reticular formation surrounding the nucleus ambiguus (NA) [59, 60]. These two regions are represented on both sides of the brainstem and are interconnected extensively so that either side can coordinate the pharyngeal and oesophageal phases of swallowing [61, 62]. The medullary swallow pattern generator receives descending inputs from cerebral cortex and subcortical structures.

Of interest for understanding the PD literature, a summary of the functions and the connections of the

basal ganglia circuitry is warranted. Basal ganglia are a sub-cortical nuclei group composed of the striatum, subthalamic nucleus and substantia nigra (for review [63]). This group of nuclei receives information from cortical areas, which is processed with two proposed processing hypotheses (the parallel and the information convergence hypothesis). It seems that both processes are important and are taking place at the striatal regions where the cortical projections terminate. Disorganization of the basal ganglia and abnormal firing rates and patterns in the motor areas may result in movement disorders, such as PD. Acute and localized lesions in the basal ganglia area (i.e. stroke) have been reported to cause swallowing disorders [64].

i. Evidence from Tissue Preparations Studies Related to Swallowing Function

Histochemical and histological studies are important for the understanding of the muscle physiology. In the past, autopsied PD patients' skeletal muscles, such as the tibialis anterior muscle, have shown alterations in muscle fiber morphology and size [65] when studied with electrically induced contractions.

Recently, Mu *et al*. [43, 66] conducted two studies to characterize the histological and histochemical characteristics of pharyngeal musculature in tissue preparations of 4 dysphagic and 4 non-dysphagic PD patients and controlled with aged-matched healthy groups' tissues. Pharyngeal muscles in PD patients showed more atrophied myofibers compared to PD patients without dysphagia, the latter estimated according to the UPDRS subscale question for swallowing disorders before death. Moreover, in PD patients the fiber type grouping and atrophied myofibers were mainly fiber type I. This might have been a result of hypomobilisation if the PD patients had modifications in oral consumption of food due to swallowing difficulties. However, the findings of this study [66] showed that changes are mainly due to chronic denervation and innervation. This would suggest that this atrophy is pathogenic in nature.

In the follow-up study by Mu *et al*. [43] the research team investigated whether these pathological findings in dysphagic PD patients' tissue preparations were caused by neurodegeneration of the motor branches of the pharyngeal nerve (X). Synucleinopathy has been already observed in cervical nerve X fibers [67, 68], which fibers are mainly afferent in nature. The findings showed that tissue preparations of dysphagic PD patients had higher density of α-synuclein aggregates in the motor fibers compared to non-dysphagic patients, implicating that axonal degeneration in the pharyngeal motor nerve could be responsible for the atrophy observed earlier [66] and therefore swallowing impairments. However, from these results, there is an implication that the motoneurons in NA would also show Lewy-body pathology.

These findings are important since we already observed some evidence that NA could be free from Lewy-bodies during PD course [69]. We also know that neurologically normal aged population may show signs of α-synuclein pathology distributed throughout the brain [70-72] and these pathologies would in theory be enough to produce motor symptoms similar to those of PD, yet such symptoms are not overt. Therefore, these results pose the question whether the possible degeneration seen in the pharyngeal motor branches follows or precedes neurodegeneration at the level of the motoneurons in NA.

ii. Evidence from Animal Studies in Relation to Swallowing Function

With respect to swallowing and pharmacological agents in PD, research studies in animals have shed some light into the mechanisms and the effects of different chemical stimulation in swallowing mechanism. Research in earlier years has shown that injection of catecholamine in the lateral solitary complex of the medulla oblongata (which includes the nucleus tractus solitarius and the adjacent reticular formation) in the rat, can have an inhibitory effect on swallowing reflex (as this is elicited from the electrical stimulation of the superior laryngeal nerve [73]). One additional study in the late 1970s used catecholamine injections in the amygdala and basal forebrain and showed enhanced reflex swallowing [74] and postulated that there are forebrain dopamine-sensitive mechanisms to modulate swallowing and probably these areas coincide with the areas responsible for converging olfactory, gustatory and interoceptive inputs.

On the other hand, animal disease models generated mainly through chemical or neurotoxin lesioning or even genetic manipulation, have contributed vastly in the quest for the mechanisms underlying several contributors of disease. There is a wide spectrum of animal disease models. The animal modelling is challenging, as it has to represent a wide range and spectrum of clinical symptomatology. It has been shown that when striatal dopamine depletion

reaches 80% and when nigrostriatal dopaminergic neurons are degenerated up to 40%, then clinical manifestations of the symptoms are evident [75].

One of the animal models used to recreate the behavioural abnormalities of the cranial nerves (and forelimbs) closely linked to feeding and oral preparatory phase of swallowing behaviour (licking) is the 6-Hydroxydopamine (6-OHDA), a neurotoxin induced model of PD. With this technique, we can induce a unilateral lesion at the substantia nigra and /or medial forebrain bundle [76], serving us as a model of dopamine dysfunction.

Lately we observed a variety of testing protocols and batteries that allow us to understand the exact effect of lesioning, resembling the PD disease discoordination (review [77]). Interestingly, we also observed the inclusion of video fluoroscopic (VFS) swallow study in rats [78]. A specific protocol was compiled to show how specific motor aspects in the animal VFS could represent the motor behavior in humans [78]. Lastly, a lingual training protocol for the animal model has been previously documented to induce changes in the lingual force in healthy animals (aging rats [79-81]).

During the last 5 years, two areas have been targeted for the use of catecholamine neurotoxin 6-OHDA injection in PD animal model by different research groups.

A unilateral lesion to the *medial forebrain bundle with 6-OHDA* had shown to impair the force (reduce) and the timing of a complex licking task (longer) [82], reflecting the sings of hypokinesia and bradykinesia in PD. This year, the same group [83] reported the effects of a 4-week tongue force rehabilitation regime (licking behaviour) on animals with unilateral lesions (to the dominant hemisphere for forelimb use) *vs.* a control. The results following the training were compared towards baseline and control (animal responses: press force for licking and press rate). Physiological measurements of tongue contractions were also measured following stimulation of the hypoglossal nerve. PD-induced animals that underwent training showed to perform as well as the control rats (with no PD). Interestingly, PD animals with no exercise showed signs of worsening during the 4-week follow-up period. However, the animals undergoing rehabilitation did not show any change in the stimulated tetanic forces and the authors were led to the conclusion that central mechanism could rescue the force in PD animals.

A different group induced intrastratial *6-OHDA* infusion lesions which has been shown to produce significant forelimb impairments, correlated to a reduction in cortical forelimb representation (motor map loss) [84], but at the same time the induced cranial motor impairments did not correlate to the cortical maps. This year, this second animal model was used to review the effects of the same lingual resistance training as in the previous study [79] and compared the results to a forelimb training regime. Baseline and post-training measurements were acquired with the use of a lick-force recording apparatus to test the cranial motor dynamics during licking and reaching (retrieval) forelimb movements, together with intracortical microstimulation and near-infrared densitometry. While initially, the intrastriatal dopamine depletion impaired both limb and cranial motor function, it has been shown that in the early stage of PD (rats where assigned to rehabilitation of limb and cranial motor training immediately following the lesions), limb-targeted rehabilitation resulted in an increase in reaching accuracy, but lingual resistance training protocol did not result in increase in lingual force compared to control.

iii. Evidence from Whole-Human Studies

Studies investigating the pathophysiology of the underlying OD in PD are starting to appear and our knowledge is still evolving. Unlike other motor-related symptoms, OD responds to dopaminergic treatment only in a small portion of patients [85-88]. It has been postulated that persistence of OD in the “on” levodopa motor phase is likely to result from disturbances in the medullary swallowing central pattern generator [11] and especially the pedunclunopontine area [46]. Nevertheless, there has been an increasing number of evidence in the literature from different motor function models that there can be cases of PD patients that anatomical deficits due to neurodegeneration in ‘sensorimotor connections’ are more marked [89, 90]; however more evidence for the effects of medication on swallowing neural system is required.

Recently, two whole-human studies have shown interesting results. First, the longitudinal and cross-sectional 3-year imaging study of PD patients by Kikuchi *et al*. [91], where PD patients with and without dysphagia and an aged-matched group were enrolled in a comparative study measuring changes in a) brain glucose metabolism ([18] F-fluorodeoxyglucose –PET) and b) the time needed to swallow initiation by reviewing laryngeal elevation visually and measuring

with a stop-watch. There were marked increase of hypometabolism in the SMA and anterior cingulate area in the dysphagic PD patients compared to healthy controls and over the period of the 3 years, the patients with dysphagia showed marked increase of hypometabolism in other areas as well, including thalamus and frontal gyri. This was not seen in the PD patients without dysphagia.

Suntrup *et al*. [92] performed a study with MEG in a similar number of dysphagic patients with and without dysphagia and an age-matched control group and found a strong decrease of overall task-related cortical activation in patients. Additionally, non-dysphagic patients with PD showed a shift of peak activation towards lateral motor, premotor and parietal cortices starting at swallowing initiation (tongue musculature), whereas activity in the supplementary motor area was markedly reduced. This distinct pattern was not found in dysphagic patients. These results are not immediately in keeping with the results seen in the previous study. The 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.

iv. Evidence from Neurostimulation Studies with the Focus on Swallowing

Troche *et al*. [93] published a systematic review on deep brain stimulation (DBS) and swallowing function in PD. The nine experimental studies included in this review did not find clinically significant improvement or decline in swallowing function with DBS. Despite these findings, several common methodological threads were identified across experimental studies. Additionally, available data demonstrated that, although subthalamic nucleus (STN) stimulation has been considered to cause more impairment to swallowing function than globus pallidus internus (GPi) stimulation, there are no experimental studies directly comparing swallowing function in STN *vs*. GPi. Moreover, there has been no comparison of unilateral *vs*. bilateral DBS surgery and the coincident effects on swallowing function.

6. TREATMENTS AND RESEARCH INTO THERAPEUTICS FOR OD IN PD

Few reports have been published on the effect of therapies for OD in PD [94]. Physicians usually start with antiparkinsonian medication like L-dopa. According to several studies, as noted above, OD responds to dopaminergic treatment only in a small proportion of patients, whereas other studies showed improved swallowing function after the intake of L-dopa [95-99]. In case of persistent dysphagic symptoms despite pharmacological treatment, alternative approaches such as logopedic or surgical treatment can be considered [27, 100, 101]. However, the literature on the effects of surgical therapy for dysphagia in PD is extremely limited [100, 101]. Several studies to determine the effects of swallowing training in PD have been performed. Several – including bolus modification, cueing (e.g. visual, auditory, tactile), behavioural exercises such as Lee Silverman Voice Treatment (LSVT) or expiratory muscle strength training (EMST), and video-assisted swallowing therapy (VAST) -- have shown beneficial results [102-106]. A randomized, blinded, sham-controlled trial for the effects of EMST showed promising results, however it was performed in PD patients with mild OD (mean AP score 2.5). Interestingly, the sham group showed deterioration over the 4-week period, which is one of the first studies showing that PD patients can deteriorate that rapidly. The underlying mechanism for the improvement following EMST is considered to be the effects on the hyolaryngeal complex movement using the EMST device (calibrated, one-way, spring-loaded valve to overload the expiratory muscles mechanically) [105].

VAST is an interesting technique for the Parkinson population. In cognitively intact patients with PD and swallowing disturbances VAST was associated with improved swallowing related quality-of-life and less food residues in the pharynx. VAST was investigated in a randomized controlled trial and this technique is similar to asynchronous FEES biofeedback or visual cueing [106].

Thermal–tactile stimulation (TTS) is a sensory technique whereby stimulation is provided to the anterior faucial pillars to speed up the pharyngeal swallow [107]. TTS significantly reduced temporal measures of swallowing in Parkinson patients. However, we need further evidence to validate whether these findings will translate into a clinically beneficial effect for PD.

Furthermore, studies using surface electrical stimulation of the neck in PD did not find a positive therapy effect of this technique [108, 109]. Surface electrical stimulation combined with traditional logopedic dysphagia treatment (exercises, bolus modification etc.) in a randomized controlled trial did improve the swallowing physiology and quality-of-life of these patients although groups differences were not

observed suggesting a therapy effect of traditional logopedic dysphagia treatment without any additional influence of surface electrical stimulation [110].

According to some studies, subjects with advanced PD who underwent deep brain stimulation (DBS) have made significant improvement in swallowing ability (self-assessment of patients) [111-113].

Where is the Void? How to Shape the Future

Here, we summarized the current evidence about current clinical practice within several different levels (neurological, physiological, and neurophysiological) and attempted to cover the important information that a clinician should take into consideration when working with PD patients with OD.

From the various levels of evidence that we covered, it seems that we need to increase the awareness among health care providers on the relevance of OD in PD. There is also missing information about the natural course of OD in PD. Our clinical assessments, as well as our treatment procedures will benefit if we increase and improve our understanding of the natural history of OD in PD.

With the new evidence from histological studies, it is now clear that investigating swallowing disorders in PD can provide further information to the neuroscience community. Major steps have also been made with PD animal models for cranial nerve dysfunction. As a point of fact, the use of animal models to recreate and measure with accurate batteries the speech, vocal, oral and cranial motor impairments and of course swallowing, seems challenging. However, these models may not represent all the neurochemical and pathological features of PD in humans, especially since it targets specific areas in the animal brain (for stereotaxic injections). Nevertheless, it is a very rich source of information especially for the understanding of several parameters and pharmacological treatment modalities. Neurophysiological studies in human coupled with accurate assessment of swallowing are important for the understanding of the factors and the parameters that may play a role in training and neurorehabilitation protocols for swallowing problems in PD.

In the clinical setting, it seems that it would be beneficial if combined strategies are used for the PD patients with OD. These strategies should include: a) evaluating and treating the swallowing dysfunction, b) improving the oral health programs, c) capturing, and managing nutritional status of the patients. The aforementioned approach seems that it will enable us to reduce morbidity and mortality rates in PD and of course minimize the adverse effects of AP. Clinical trials in the near future will show the extent of the benefits following this approach.

Patients with PD often suffer from several physical and psychological dysfunctions, cognitive impairments, and clinically relevant symptoms of depression, prompting many visits to medical specialists or allied health professionals. In that light, a dysphagia rehabilitation program should take treatments for other Parkinson-related symptoms into consideration.

However, there is not enough evidence for the optimal time of the application of therapeutic approaches (early vs. late), for the stability of the effects of therapeutic approaches (for how long do the benefits last), which is the optimal approach to treat which symptoms etc. We need more information about the effects of medication on symptomatology and this has to be reviewed in a manner that will allow the clinicians to assess and understand the underlying symptoms and manage these properly in the best appropriate way. The potential treatment therapies should be reviewed both for the short-term effects on physiology and the longer-term effects, in other words, the clinical effects. Therefore, it seems that we currently need additional large randomized controlled trials to assess the effectiveness of different treatments for dysphagia in PD.

Lastly, the uncertainty about the underlying mechanisms of the pathophysiology of PD in relation to OD does not permit concrete understanding of the symptomatology. This is, consequently, depicted onthe limited efficacy of therapeutic studies. This is also the case about the direct effects of pharmacological manipulation of the disease and the effects of the medical clinical management on swallowing neural mechanisms. We therefore, need to formulate hypotheses based on neurophysiological properties of swallowing neural network. We also need to take into consideration the changes that are taking place in this neurodegenerative model if we wish to allow effective treatments to assist patients throughout the course the disease.

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