Drooling and dysphagia in Parkinson's disease

Parkinsonia parkinsoni
(Middle Jurassic: 172-168 Ma)

J.G. Kalf

Drooling and dysphagia in Parkinson's disease

Speekselverlies en slikstoornissen bij de ziekte van Parkinson

Johanna Gezina Kalf

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Drooling and dysphagia in Parkinson's disease

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Drooling and dysphagia in Parkinson's disease

An academic essay in the Medical Sciences

Doctoral Thesis

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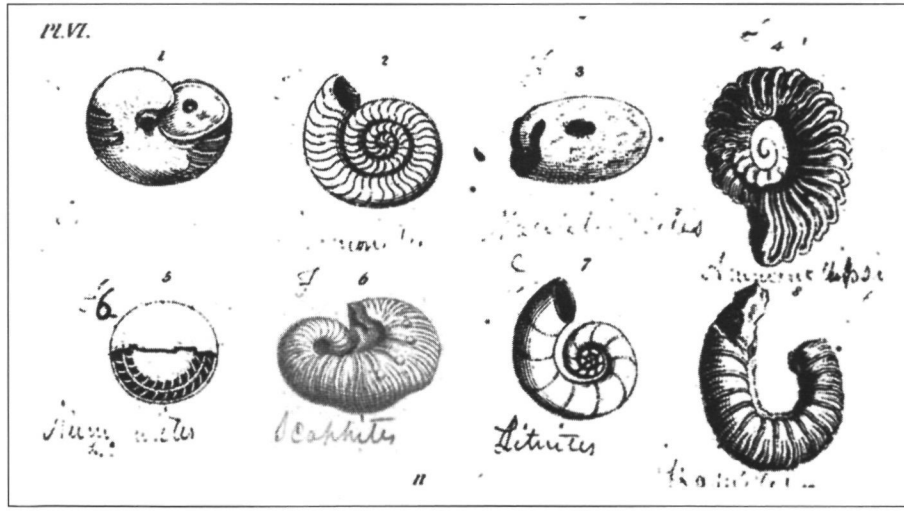
Voor Chelsea, Devon, Sebastiaan en Gustaaf,
the next generation

Over de omslag

Exemplaar van een Parkinsonia parkinsoni (J. Sowerby, 1821) uit de privécollectie van de auteur: een ammoniet (uitgestorven inktvissoort) die leefden tussen 172 en 168 miljoen jaar geleden (Midden Jura).[1] Het is één van de fossielen die naar James Parkinson (1755 – 1824) is genoemd en tevens de enige eponiem zijn waarvan hij geweten heeft.[2] Behalve zijn beroemde *An Essay on the Shaking Palsy* uit 1817, waarin hij voor het eerst het ziektebeeld beschreef dat later zijn naam kreeg, heeft Parkinson zoals zoveel artsen in zijn tijd, ook belangrijke bijdragen geleverd aan de geologie en paleontologie aan het begin van de 19de eeuw, ook wel de 'Heroic Age of Geology' genoemd.[3,4] Hij was een van de oprichters van de Geological Society of London publiceerde onder andere in 1822 *Outlines of Oryctology. An Introduction to the Study of Fossil Organic Remains*, waarvan hieronder enkele illustraties.[5]

About the cover

Specimen of a Parkinsonia parkinsoni (J. Sowerby, 1821) from the private collection of the author: an ammonite (extinct group of marine invertebrate animals) that lived between 172 and 168 million years ago (Middle Jura).).[1] It is one of the fossils named after James Parkinson (1755 – 1824) and the only eponym he could enjoy a few years before his death.[2] Except for his famous *An Essay on the Shaking Palsy* from 1817, in which he described the disease that was named after him much later, Parkinson, as many physicians in his time, contributed to the development of geology and palaeontology at the beginning of the 19th century, known as the de 'Heroic Age of Geology'.[3,4] He was one of the founders of the Geological Society of London and published in 1822 *Outlines of Oryctology. An Introduction to the Study of Fossil Organic Remains*, from which some illustrations are shown below.[5]



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Chapter 1

General introduction and outline of the thesis

Parkinson's disease (PD) is a common neurodegenerative disease The clinical features include a wide range of motor and non-motor difficulties This includes oral motor disorders, i e difficulty with speech and swallowing [6 7] Although in the past speech therapy for PD patients was considered "well-known to be unproductive",[8] today speech therapists can base their treatment on a guideline with 60 recommendations which are based not just on expert opinion, but are increasingly evidence-based [9] For example, it is now generally accepted that reduced intelligibility – caused by hypokinetic speech – can be treated successfully with an evidence-based treatment approach [9] At the same time, many questions remain unanswered As a speech therapist, with clinical experience in the assessment and management of oropharyngeal dysphagia, I became interested in the scientific basis of swallowing problems of patients with PD (hypokinetic dysphagia) One specific symptom which is likely a consequence of this hypokinetic dysphagia includes drooling or dribbling of saliva Drooling has thus far rarely been studied This thesis is devoted to improve our understanding of drooling in PD

This general introduction is aimed at a multidisciplinary audience and briefly reviews basic knowledge about PD, oropharyngeal dysphagia and saliva control, as a vital basis for understanding the chapters of this thesis This introduction concludes with the aims and outline of the thesis

Parkinson's disease

Parkinsonism is an umbrella term for a series of progressive neurodegenerative diseases, with PD as the most common cause [6 10 11] The characteristics of the disease were first described by the English apothecary and surgeon James Parkinson in 'An Essay on the Shaking Palsy' [12] He described the course of this disease (which he termed 'paralysis agitans') based on the observation of six men, three of whom he only casually met in the street Later in the nineteenth century, the French neurologist Jean-Marie Charcot distinguished bradykinesia from rigidity as key clinical features He also observed that patients with PD are not markedly weak, and that tremor is not present in all cases In 1876, he coined the name Parkinson's disease as an eponym for paralysis agitans [2 13 14] It was not until the beginning of the twentieth century that Greenfield and Bosanquet described the nigral degeneration with Lewy bodies in the remaining neurons, as the structural basis of the disease [14] Other historical keystones are the clinical stages described by Hoehn and Yahr in 1967[15] to score the progression of the disease (see Box 1 1) and the discovery of levodopa as a dopamine-replacement therapy in the 1960s [16]

Box 1.1. Diagnosis and staging of Parkinson's disease.

Parkinson's disease is generally diagnosed by the UKPDS Brain Bank criteria [17] The critical feature is akinesia, which is an umbrella term for a symptom complex that can include bradykinesia (slowness of initiation of voluntary movement) and hypokinesia (poverty of movement and movements that are smaller than intended), but also progressive fatiguing and decrement of repetitive alternating movements Akinesia should be accompanied by at least one of the following signs

- Muscular rigidity (increased muscle tone that can be felt during passive movement)
- 4–6 Hz rest tremor
- Postural instability which is not caused by primary visual, vestibular or cerebellar dysfunction (and which is often absent at onset)

The Hoehn & Yahr scale is commonly used to rate disease progression and for demographical presentation of patient groups [15,18]

1 0 Unilateral involvement only
1 5 Unilateral and axial involvement
2 0 Bilateral involvement without impairment of balance
2 5 Mild bilateral disease with recovery on pull test
3 0 Mild to moderate bilateral disease, some postural instability, physically independent
4 0 Severe disability, still able to walk or stand unassisted
5 0 Wheelchair bound or bedridden unless aided

Although the original five-point scale is recommended by the Movement Disorders Society Task Force on rating scales for PD,[18] the modified HY scale with 0 5 increments is widely used, also in this thesis

Phenomenology

PD is a complex multisystem degenerative process The motor signs related to degeneration of the dopaminergic nigrostriatal system are "just the tip of the iceberg" [19] The diagnosis of PD is currently based on the key motor signs (resting tremor, rigidity, bradykinesia and postural instability) The criteria of the United Kingdom Parkinson's Disease Society (UKPDS) Brain Bank are most commonly used to diagnose PD (see Box 1 1) [17,20] These motor signs are usually asymmetric and are generally clearly responsive to dopaminergic treatment, although the 'axial' (or midline) disorders – such as postural instability, and to some extent also speech and swallowing – can be dopa-resistant [6,7,21]

Below the surface, the body of the iceberg contains a wide range of non-motor complaints [6,7,19,22]

- autonomic dysfunction, e g gastro-intestinal disorders, urogenital problems,
- sensory symptoms, e g pain, reduced smell (hyposmia),
- cognitive disorders (dementia), e g reduced memory function, language disorders,
- neuropsychiatric changes e g depression, anxiety, apathy, psychosis,
- fatigue and excessive daytime sleepiness,
- sleep disturbances, REM sleep behavior disorders

Many of these complaints, like hyposmia, pain, depression or REM sleep behaviour disorder, may even preceed the onset of overt parkinsonian motor signs This is supported by the Braak staging hypothesis, which suggest that PD-related Lewy body pathology (with α-synuclein) develops in a predictable stage-like fashion, starting in the olfactory bulb and lower brain stem, and subsequently spreading into the cerebral cortex which is reached the final stage [7 23] Importantly, these non-motor complaints have a major influence on the patients' health-related quality of life, and also form the source of considerable burden for the informal caregivers [24 26]

Parkinsonian syndromes that do not meet the UKPDS criteria are known as atypical parkinsonisms (AP) [27] These are characterized by a more rapid disease progression, a poor or even absent response to dopaminergic treatment, the presence of additional clinical symptoms such as spasticity, cerebellar dysfunction or pronounced cognitive disorders, and by a shorter life expectancy [7] In addition, the various subforms of AP can cause specific symptoms that are not or much less commonly seen in PD, such as nocturnal stridor in patients with multiple system atrophy or motor recklessness in patients with progressive supranuclear palsy Many of these specific complications are bundled under the term 'red flags', as their presence serves as a warning signal that the patient may not have PD, but rather a form of AP [28] The term AP encompasses various disorders multiple system atrophy (MSA-P and MSA-C), progressive supranuclear palsy (PSP), dementia with Lewy bodies (DLB), corticobasal degeneration (CBD), vascular parkinsonism and drug-induced parkinsonism Table 1 1 lists the key clinical features of these disorders (from *Handbook of Atypical Parkinsonism*[29])

Table 1.1. Frequent clinical features in PD and AP with diagnosis confirmed by postmortem examination (Adapted from *Handbook of Atypical Parkinsonism* Colosimo et al , 2011 [29])

	PD	MSA-P	DLB	PSP	CBD
Akinesia	+	+	+	+	+
Rigidity	+	+	+	+	+
Tremor	+	+			
L-dopa response	++				
Gait unsteadiness		+	+	+	+
Falls			+	+	+
Dysarthria		+	+	+	+
Dysphagia			+	+	
Gaze palsy				++	
Autonomic failure		++			
Dementia			+	++	
Apraxia					++

+ reflects >70% of cases, ++ reflects a discriminating feature

The differential diagnosis is mainly based on clinical features Movement disorder special-

ists are able to accurately diagnose five out of six patients referred with a neurodegenerative parkinsonian syndrome [17 27 30 31] Allied health professionals can support the diagnosis process by confirming or refuting the presence of 'red flags' such as frequent falls, apraxia, cerebellar signs in gait or speech, or early presence of dysphagia [32]

Epidemiology

PD is present in 0 3% of the general population and in 1% of the population over 60 years of age, and afflicts approximately 50 000 to 70 000 people in the Netherlands These numbers are increasing due to ageing of the population, and will have doubled by the year 2020 [33] Most people with PD are community-dwelling, with of without the support of informal and formal caregivers Hospitalization in a nursing home is mainly predicted by old age, functional impairment, dementia and hallucinations [34]

Management of PD

For detailed clinical assessment, the Unified Parkinson's Disease Rating Scale (UPDRS) is a commonly used This globally accepted scale for the clinical evaluation of PD patients consists of four domains part I, Mentation, behaviour and mood, part II, Activities of daily living, part III, Motor examination, and part IV, Complications [35] The UPDRS includes subscales for speech (parts II and III), salivation (II), swallowing (II), and facial expression (III) The summarized score of the UPDRS III is generally used to express overall disease severity, because it is responsive to changes over time (disease progression or improvement by therapy) [36] In 2008, the Movement Disorder Society published a revision, the MDS-UPDRS,[37] but an approved and validated Dutch version is not yet available In this thesis, disease severity is expressed by UPDRS III scores measured with the initial version

To investigate non-motor complaints in more detail, patient-rated instruments are available, of which the Scales for Outcomes in Parkinson's disease (SCOPA-AUT and SCOPA-COG)[38 39] and the Parkinson's Disease Nonmotor Symptoms Questionnaire (PD NMSQuest) are most commonly used Also, disease-specific quality of life instruments have been developed, such as the PDQ-39[40] and the PDQL [41]

Medical treatment options for PD include pharmacological approaches or neurosurgery (deep brain stimulation, DBS) [42] The motor symptoms of PD, such as rigidity and bradykinesia, are usually alleviated by dopaminergic stimulation with levodopa or dopamine agonists [6 7 17 42] In some cases where drug treatment is complicated by incapacitating response fluctuations, DBS is required a surgical approach where electrodes are placed in the basal ganglia, most often the subthalamic nucleus (STN), although the globus pallidus pars interna is making somewhat of a comeback [7 43 44] The thalamus is a good target to relieve tremor Evidence-based and consensus-based recommendations for medical treatment of PD are summarised in the new

Dutch multidisciplinary guideline for PD.[17]

Non-pharmacological treatment includes allied health treatment such as occupational therapy, physiotherapy and speech therapy. [32;45-48] These allied health interventions have been developed mainly in patients with PD, but the approaches used also apply to patients with AP. Currently, all these allied health professionals can base their management of PD patients on an evidence-based guideline.[9;49;50] In addition, optimal management of PD also involves a variety of other experts like dieticians, social workers, sexologists, neuropsychiatrists and psychologists. Awareness is growing that these disciplines can also offer useful support for PD patients, especially to better cope with the non-motor and psychosocial consequences of the disease. Speech-language therapy is therefore only one of the many disciplines involved with PD (no less than 19 different disciplines contributed to the Dutch multidisciplinary guideline). The challenge is to coordinate this multidisciplinary care, including the provision of support to the informal caregivers. In the Netherlands, health care for patients with PD or AP is available in regional networks of trained professionals throughout the whole country, known as ParkinsonNet, see Box 1.2.[51;52]

Box 1.2 ParkinsonNet

From 2004 to 2010 ParkinsonNet has been developed throughout the Netherlands in 65 regions to (1) improve PD-specific expertise among allied health personnel, by training a selected number of therapists according to evidence-based guidelines; (2) enhance the accuracy of referrals by neurologists; (3) boost patient volumes per therapist, by stimulating preferred referral to ParkinsonNet therapists; and (4) stimulate collaboration between therapists, neurologists, and patients.[53]
Studies have shown a steady rise in the patient volume of individual therapists,[53;54] and a reduction of health-care costs compared to usual care.[55]

In addition, 1700 participants of ParkinsonNet are actively involved in continued education (www.parkinsonnet.nl) and in online communties at MijnZorgnet (www.mijnzorgnet.nl).

Swallowing and dysphagia

Deglutition of food and liquid is needed for adequate nutrition and hydration, but we generally eat and drink because this is one of the great pleasures in life. Normal chewing and swallowing is generally effortless and although the food transport crossed the airway with every swallow, this process is safe without exception, as long as the oropharyngeal anatomy and innervation is intact. See Box 1.3 for a brief description of normal swallowing.

Box 1.3. Normal swallowing. (Illustration with permission from *Slikstoornissen bij volwassenen.*

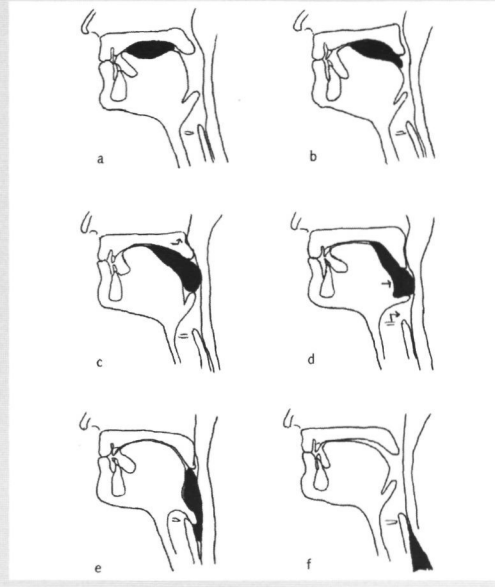
Houten, Bohn Stafleu Van Loghum, 2008.[56])

A. Solid food is usually chewed, mixed with saliva and masticated in order to prepare the food bolus for swallowing; breathing is still possible.

B. Only when chewing is stopped, swallowing can be initiated, transporting the food bolus from the mouth to the phraynx (oral phase).

C-E. Food is transported from the pharynx into the oesophagus (pharyngal phase), while:
the nasal cavity is closed by the velum;
the larynx is closed by glottal closure and folding of the epiglottis over de larynx entrance;
the bolus is pushed down by tongue base retraction and pharyngeal constriction;
the oesophagus is opened because the sphincter relaxes and is being pulled open by the hyolaryngeal excursion.

F. The bolus passes through the oesophagus to the stomach (oesophageal phase).



Swallowing is controlled by multiple areas in the brain, including the primary sensory/motor cortex, the medullary central pattern generator and the basal ganglia.[57;58] Swallowing is both voluntary and reflexive. Manipulating food in the mouth and initiation of swallowing is voluntary, but also based on automated patterns which make it possible to eat and drink while participating in conversation during dinner. When food or liquid enters the pharynx, swallowing becomes irrepressible, the bulbar central pattern generator in the medulla oblongata takes over the swallowing control, making every swallow safe and efficient, independent of consistency or volume.[59;60]

Phenomenology of dysphagia in PD

Dysphagia in PD can be separated into three types: oral; pharyngeal; and esophageal. The influence of rigidity and akinesia is reflected by slowness of chewing, poor bolus formation and delayed onset of swallowing.[61-63] Also lingual festination and repetitive tongue elevation are typical features of (severe) *oral dysphagia* associated with PD.

Pharyngeal dysphagia in PD is characterized by delayed pharyngeal food transport, resulting in choking on food or liquid.[63;64] Also residu of food in the valleculae and pyriform sinuses, described by patients as "food getting stuck in their throat", is a common symptom resulting from slow pharyngeal transit. In addition, decreased oesophageal transit, aperistalsis and reduced pressure of the lower esophageal spincter causing gastro-oesophageal reflux, are common disorders (*esophageal dysphagia*).[62;65]

Dysphagia can give rise to longer mealtimes and eventually adapted food consistencies (softer food) may be needed Enteral feeding to replace oral intake is relatively uncommon in home-living PD patients Unlike in AP, dysphagia is not considered an early symptom in PD,[66] see table 1 2 Aspiration pneumonia is a serious risk when coughing intensity is also reduced, and up to 10% of PD patients with confirmed aspiration risk may develop aspiration pneumonia [67 68]

Management of dysphagia in PD

Oropharyngeal dysphagia is assessed by investigating subjective swallowing complaints, by performing swallowing tests, by observation of eating and drinking, and by instrumental assessment with videofluoroscopy or direct observation of pharyngeal swallowing with a flexible endoscope [68] According to the guideline *Speech-language therapy in Parkinson's disease*, instrumental assessment is only needed when the characteristics and severity of the dysphagia remain unclear [9] When the patient confirms or suggests having difficulty with swallowing, the guideline proposes the following order of assessment [9] first observation of spontaneous drinking (water, coffee, tea), then evaluating the stimulability of drinking using a maximum performance test (maximum swallowing volume or swallowing speed) Typically PD patients will swallow better, quicker and safer if they are stimulated to overcome their hypokinesia, as in other motor tasks like walking or talking [69] Examples of such stimulations include the instruction to take large amounts or to swallow with more speed [70 71] In cases with more severe swallowing complaints, observing the patient during a meal while evaluating the effect of instructions and cues can be helpful

Behavioral treatment in PD as delivered by allied health professionals has evolved during the last decade thanks to an improved understanding of the disease Morris & Iansek have described a theoretical model which has been met with positive experiences in large Parkinson's centres abroad, see Box 1 4 [72]

Box 1.4. General recommendations as the basis of rehabilitation in PD.[72]

1 "Normal movement is possible in Parkinson's disease, what is required is appropriate activation The skilled therapist is able to determine the most effective methods to activate normal movement
2 Complex movements need to be broken down into smaller components This is to avoid motor instability and to take advantage of increased amplitude at the beginning of movement sequences
3 Each component of a task needs to be performed at a conscious level Conscious attention appears to bypass the basal ganglia and restore movement towards normal
4 External cues may be used to initiate and maintain movement and cognitive processes Visual, auditory or proprioceptive cues may be used Cues indicate the appropriate movement size and appear to activate attentional motor control mechanisms
5 Simultaneous motor or cognitive tasks are to be avoided This is because the more automatic task is not executed properly and only the task demanding attention is satisfactorily completed "

As part of the assessment, treatment usually starts with stimulation techniques and cues (see above) In mild cases compensations – such as more efficient head and body positioning – may prevent choking In other cases double tasking (in particular conversation during coffee breaks or meals) should be avoided to prevent choking [9 68] In more severe cases individually adapted cues of conscious strategies are needed, but also training exercises are promising to improve swallowing and reduce choking like the expiratory muscle strength training (EMST) [73 74] Finally, when food consistencies need to be adapted, professional support by a dietician to guarantee optimal nutritional intake is recommended [9]

Saliva and drooling

Drooling is involuntary dribbling of saliva Involuntary, because saliva can also be spitted out The physiology of drooling can actually be demonstrated by anyone who keeps his mouth open and head bent forward, while refraining from swallowing for several minutes James Parkinson already observed this drooling in his report of the course of the disease, when he describes the advanced stages of PD [12] See Box 1 5

Box 1.5. The description of dysphagia and drooling by James Parkinson in 'An Essay on the Shaking Palsy' (1817).[12]

"His words are now scarcely intelligible, and he is not only no longer able to feed himself, but when the food is conveyed to his mouth, so much are the actions of the muscles of the tongue, pharynx &c impeded by impaired action and perpetual agitation, that the food is with difficulty retained in the mouth until masticated, and then as difficultly swallowed Now also, from the same cause, another very unpleasant circumstance occurs the saliva fails of being directed to the back part of the fauces, and hence is continually draining from the mouth, mixed with the particles of food, which he is no longer able to clear from the inside of the mouth " (p 8)

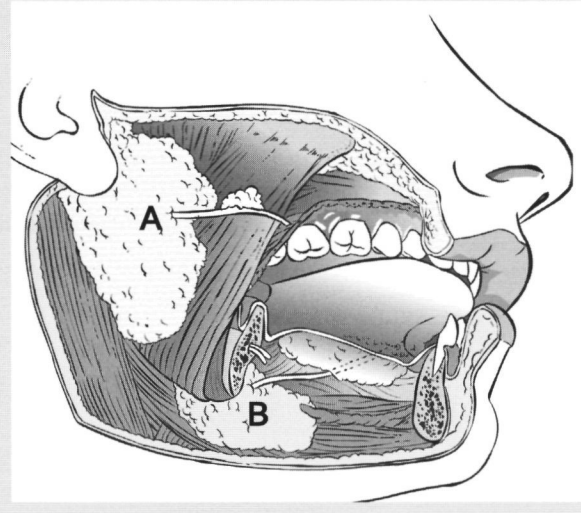
"The chin is now almost immoveably bent down upon the sternum The slops with which he is attempted to be fed, with the saliva, are continually trickling from the mouth The power of articulation is lost " (p 9)

Hypersecretion of the skin occurs in PD as a sign of autonomic dysfunction, as reflected by hyperhidrosis (increased sweating) and seborrhea (greasy skin) [75] However, hypersecretion of the salivary glands was not considered to be the origin of drooling in PD from early on In 1958, Schwab & England, providing an extensive description of the signs and symptoms in PD including seborrhea and hyperhidrosis, stated that "This drooling of saliva is not due to excessive production, but to loss of automatic swallowing" [76] Eadie & Tyler also questioned the presence of hypersalivation, based on their own measurements of salivary secretions [77] and their finding that drooling was present in 86% of patients with dysphagia, but in only 44% of patients without dysphagia [78] It took another few decades before investigators, using rigorous sialometry, were able to demonstrate that saliva secretion in patients with PD is not increased, but is in fact even reduced, and that it is a misunderstanding that drooling in PD would result from primary hypersalivation [79 82] This is similar to other neurological diseases associated with drool-

ing, like motor neuron disease or cerebral palsy, where saliva secretion is generally normal.[83;84] Recent studies in PD, using autopsy or biopsy, have even suggested that hyposalivation is an early manifestation of premotor symptoms in PD.[85-87] Nevertheless, within the framework of this topic, some understanding of saliva production is useful. See Box 1.6.

Box 1.6. Saliva production.

Saliva is produced in numerous minor glands in the oral cavity, but about 90% is produced by the three major glands: the parotid glands (A), submandibular glands (B) and sublingual glands. Only the parotid and submandibular glands are shown here, because these are the focus of medical intervention (botulinum toxin or radiotherapy) to reduce saliva production.



The parotid salivary gland and associated structures. The parotid glands produce serous or watery saliva and are responsible for 60% of the stimulated saliva. The submandibular salivary gland and associated structures. The submandibular glands produce seromuceus saliva and are responsible for 70% of the resting saliva.

Normal saliva production

Saliva production is influenced by several factors, like smell, taste, chewing, anxiety or medication. Individual salivation varies between less than 0.1 ml per minute during rest or sleep to 6 ml/min at maximum stimulation (during a short period) and between 0.5 to 1.0 liter per day.[88-91] The mean production of resting saliva is 0.3 to 0.4 ml/min, but varies between individuals. Total saliva production rises during the day to an afternoon peak and decreases to a minimal during the sleep.[92]

The frequency of spontaneous saliva swallowing in healthy individuals without thirst or hunger for all age groups up to 70 years and older is on average 0.44 times per minute (range 0.28 to 0.75).[93]

The function of saliva

Saliva is of principal importance for the maintenace of oral health.[94;95] It is composed of 99% water and less than 1% of solds, mostly proteins and salts.[96] Saliva firstly protects the teeth by diluting sugars and acids and clearing the mouth. Secondly, it has anti-viral, anti-bacterial and anti-fungal capacities, to protect the oral cavitiy from infections. Thirdly, it has a function in the

digestive system, because saliva is needed to taste, to moist and soften solid food (activated by mastication) and to break down carbohydrates with α-amylase [94 95 97] In addition, adequate lubrication of the mouth is also required during speaking and intimate kissing

Saliva swallowing

Saliva is produced to maintain oral health (see Box 1 4) and is ment to be swallowed, but not to leave the mouth We know from own unpublished experiments with healthy volunteers (SLTs at swallowing courses) that for most people, it is very difficult to resist the urge to swallow for more than 5 minutes One simply has to swallow when it becomes unpleasant to bear the saliva accumulation or to prevent loosing saliva when opening the mouth to speak

The physiology of saliva swallowing is not fully understood Studies using fMRI have shown that the lateral primary motor cortex is involved in spontaneous saliva swallowing but also in reflexive and voluntary swallowing [60 98 99] Saliva swallowing is mostly spontaneous or automatic, because saliva is generally swallowed in small quantities hundreds of times throughout the day without conscious control Volitional saliva swallowing is processed in the cerebral cortex,[99] but automatic swallowing likely requires basal ganglia input, similar to other automated movements [100]

Drooling

In clinical practice, speech-language therapists mainly see struggle with saliva retention and inadequate removal resulting in drooling in patients with severe oropharyngeal dysphagia or patients who are incapable of swallowing at all (aphagia) In these cases, patients have to spit their saliva out or have it mechanically suctioned away This happens, for example, in patients with Wallenberg's syndrome caused by lateral medullary infarction,[101] or in patients with severe bulbar amyotrophic lateral sclerosis [102 103] When oral or pharyngeal suctioning is insufficient, placement of a cuffed canula via tracheostomy is needed to prevent chronic saliva aspiration and recurrent pneumonia [104] Aspiration of saliva is also known as "posterior drooling" [105] Only in few PD cases drooling can be observed, usually in patients with profuse saliva loss, who need to wear a napkin or towel to protect their clothes from staining

Current management of drooling

Unlike dysarthria or dysphagia, drooling is difficult to examine clinically Saliva production can be measured with saliva collecting techniques (e g the swab method), but this is only used when changes of salivation must be evaluated, for example after botulinum toxin injections to objectively document the treatment response Clinical observation of drooling in children with cerebral palsy is done using the drooling quotient (DQ) the ratio of observed drooling episodes and the total number of observations during 15 minutes [106] But for use in PD patients this is typically insufficient, because dribbling of saliva during professional consultation is only visible

in very severely affected cases Consequently, the assessment of drooling in PD is currently based entirely on the subjective response of patients (or caregivers) to questions, but objective instruments are lacking or unsatisfactory [9 107]

Treatment of drooling is presently almost entirely medical, and all available approaches are aimed at reduction of salivation Botulinum toxin injections in the salivary glands is the most studied treatment,[108 110] but other treatments such as (systemic or topical) anticholinergics and radiotherapy over the saliva glands essentially aim to achieve the same goal This is unsatisfactory, because as pointed out earlier, excess saliva production is not the core problem, so reducing saliva production is only 'cosmetic' and not aimed at the primary pathophysiology Moreover, suppressing saliva production can have unpleasant adverse effects, such as a dry mouth

Outline of this thesis

This introduction underscores that drooling is much more than an ordinary problem for patients with PD At the same time, there is still a serious lack of understanding about drooling in PD, and this hampers development of more effective treatment strategies Drooling is considered to be a normal phenomenon in children under three years of age, but it can be highly embarrassing for older children and adults If saliva production is not increased, then why do PD patients loose saliva? And what is the impact of drooling on daily functioning? How common is this complaint in PD? If prevalence rates are as high as is sometimes reported (namely up to 74%),[108] then why is there so little evidence to support the clinical assessment and tailored management in PD, compared to e g dysarthria and dysphagia?[9] All current medical treatment options aim to reduce saliva secretion, but salivation is not increased [108] So what other treatment options could be developed if we begin to better understand the underlying pathophysiology?

In this thesis, we will describe the **phenomenology** and **epidemiology** of drooling in PD, in order to improve **assessment and treatment**, aiming to answer the following questions

1 What causes drooling in Parkinson's disease?
2 What is the impact of drooling in Parkinson's disease?
3 How prevalent are drooling and dysphagia in Parkinson's disease?
4 How can drooling in Parkinson's disease and its severity be assessed?
5 What are the treatment options for drooling in Parkinson's disease?

We first try to explain which factors can cause drooling in PD in Chapter 2 1 Except from dysphagia, there are several characteristics in PD that could contribute to drooling In Chapters 2 2 and 2 3 we describe the impact of drooling in PD The prevalence of drooling and also the prevalence of dysphagia in PD is reported in Chapters 3 1, 3 2 and 3 3 Because PD-specific measures are currently limited, we undertook to develop and validate a new questionnaire in

the three oral motor domains: speech, swallowing and saliva control. The results of the clinimetric evaluation are reported in Chapter 4.1. Treatment with botulinum neurotoxin injections is investigated further in Chapter 4.2.
Finally, Chapter 5 summarizes and discusses all outcomes, and describes future perspectives.

Chapter 2
Phenomenology

2

2.1

Pathophysiology of diurnal drooling in Parkinson's Disease

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Abstract

Drooling is an incapacitating feature of Parkinson's disease (PD) Better pathophysiological insights are needed to improve treatment Here, we test the hypothesis that the cause of drooling is multifactorial We examined 15 PD patients with distinct diurnal saliva loss ('drooolers') and 15 PD patients without drooling complaints ('non-droolers') We evaluated all factors that could potentially contribute to drooling swallowing capacity (maximum volume), functional swallowing (assessed with the dysphagia subscale of the Therapy Outcome Measures for rehabilitation specialists), unintentional mouth opening due to hypomimia (UPDRS item), posture (quantified from sagittal photographs), and nose-breathing ability We also quantified the frequency of spontaneous swallowing during 45 minutes of quiet sitting, using polygraphy Droolers had more advanced PD than non-droolers (UPDRS motor score 31 versus 22, p=0 014) Droolers also scored significantly worse on all recorded variables, except for nose breathing Swallowing frequency tended to be higher, possibly to compensate for less efficient swallowing Logistic regression with adjustment for age and disease severity showed that hypomimia correlated best with drooling Linear regression with hypomimia as dependent variable identified disease severity, dysphagia and male gender as significant explanatory factors Drooling in PD results from multiple risk factors, with hypomimia being the most prominent one When monitored, patients appear to compensate by increasing their swallowing frequency, much like the increased cadence that is used to compensate for stepping akinesia These findings can provide a rationale for behavioural approaches to treat drooling

Introduction

Drooling (or sialorrhea) is both common and incapacitating in Parkinson's disease (PD) A systematic review showed that dribbling of saliva may be present in more than half of PD patients[111] and has a negative impact on quality of life, especially in advanced PD.[112 114] Most currently available treatment strategies aim to reduce saliva production, including anticholinergics, botulinum-toxin injections in the salivary glands, or radiotherapy over the glands.[115,116] These therapies are not always successful, because salivation itself is probably not the core factor contributing to drooling. Although one of the early publications on PD already stated that "drooling of saliva is not due to excessive production, but to loss of automatic swallowing"[76], studies using rigorous sialometry were published only in the last decade. None of these could confirm hypersalivation, and most demonstrated that salivary flow in PD patients is even lower than in controls.[79 81,87] Several factors have been suggested, e.g. hyposmia, hypogeusia or reduced mastication that may inhibit the salivary reflex, or the presence of Lewy pathology in the submandibular glands and superior cervical ganglia.[87] This may have its own consequences like more viscous saliva that may be more difficult to swallow.[79] Studies on the influence of levodopa on salivation show contradictory results.[79,82] These findings suggest that other factors may cause drooling, including swallowing akinesia.[87,117] However, experimental evidence how motor dysfunctions influence drooling is scarce.

Here, we test the hypothesis that the cause of diurnal drooling in PD is multifactorial, resulting from a combination of the following factors decreased frequency of saliva swallowing, causing pooling of saliva in the mouth, unintentional mouth opening due to hypomimia, making accumulated saliva more likely to drip from the mouth; stooped posture with a dropped head, allowing gravity to aggravate the dripping of saliva; reduced swallowing ability resulting in inefficient saliva collecting and removal by swallowing; and difficulty with nose-breathing ability, because inability to breathe through the nose would force patients to resort to mouth-breathing, which in turn may contribute to lip parting and thereby to drooling

Patients and methods

Patients

We recruited 30 consecutive outpatients with PD (according to the UK Brain Bank criteria). 15 with distinct diurnal saliva loss, defined as saliva loss from the corners of the mouth or chin, or worse saliva loss ('droolers', score ≥ 5 on DSFS-P, see 'Clinical assessments') and 15 without any complaints about saliva control ('non-droolers', score 2 on DSFS-P). To ensure optimal contrast, patients with a mere subjective sensation of saliva pooling, but without actual saliva loss, were excluded from the non-droolers group. Further exclusion criteria included excessive daytime sleepiness or inability to remain seated for one hour because of fatigue or restless legs syndrome In both groups only one patient used no dopaminergic medication Twenty-eight

patients were examined in their subjective *on*-phase, and one drooler and one non-drooler in a subjective *off*-phase (intake of last medication between 30 to 60 min before start of the assessment) None of the patients had severe response fluctuations The local ethical committee approved the study All patients gave written informed consent

Clinical assessments

Baseline assessments included scoring of disease severity (UPDRS part III, Hoehn & Yahr stages) *Drooling severity* was scored according to the Drooling Severity and Frequency Scale (DSFS-P) that has been adapted and validated for use in PD patients [118] Severity was scored as follows 1 = no complaints, 2 = feeling of increased saliva in the mouth, but no drooling, 3 = loss of saliva in the corners of the mouth or the chin, 4 = saliva also on cloths, 5 = saliva on cloths, and also on books or the floor Frequency is scored as follows 1 = never or less than once a day, 2 = once or twice a day, 3 = two to five times a day, 4 = six to ten times a day, 5 = almost constantly The summarized score ranges from 2 to 10

Swallowing capacity was measured by determining the maximum volume of water (in ml) that could be swallowed in a single swallow (dysphagia limit) [119 120] Patients started with a standard amount of water (10 ml) and were instructed to ingest this in one swallow The volume is then gradually increased to find an individual maximum An amount of 20 ml or more in one swallow is considered normal, but usually individual maximum amounts are larger [120]

Functional swallowing was assessed with the dysphagia subscale of the Therapy Outcome Measures (TOM) for rehabilitation specialists, ranging from 5 (normal oral intake) to 0 (complete enteral feeding) [121]

Hypomimia (masked face) was rated with the UPDRS item for facial expression [35] In addition to this clinician-rated scale we scored facial changes according to the impression of the caregiver 1 = closed mouth without effort, 2 = sometimes parted lips when distracted, 3 = frequently open mouth, also in rest, 4 = almost constant open mouth, hardly able to keep the mouth closed Caregivers are usually well aware of involuntary mouth opening, because parted lips create an inattentive and sometimes annoying appearance

Nose-breathing was also scored, because parted lips may lead to (or be aggravated by) mouth-breathing We scored this as follows 1 = can easily breath through the nose for at least one minute, 2 = can breathe through the nose for one minute, but with visible effort, 3 = cannot breath through the nose for one minute, 4 = can hardly breathe through the nose

The level of *stooped posture* was documented by taking lateral photographs of the patients while standing The degree of stooping was scored according to the corresponding UPDRS item

Electrophysiological assessments

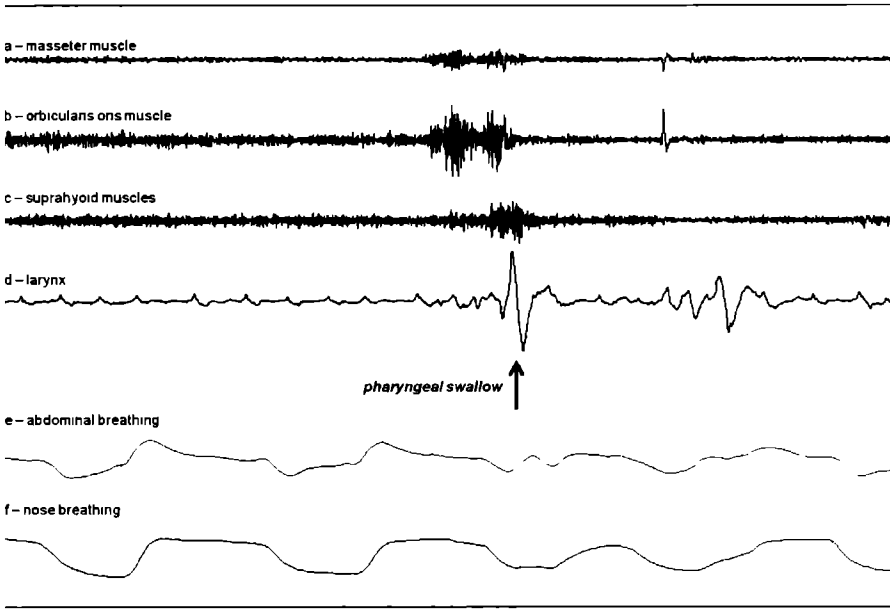
To measure the frequency of naive saliva swallowing, we used polygraphy including surface electromyography (sEMG), motion sensor and video to register every single swallow This is a relatively easy and non-invasive method to study human swallowing [63 93] Before we started testing our patients, the complete procedure was first piloted and optimized in three PD patients, until we were sure to identify every swallow A 45-minute testing period was considered sufficiently long to document swallowing frequency without imposing too much burden on the patients Patients were instructed not to drink or eat anything for half an hour before the assessment, to eliminate variability in saliva production due to stimulation by food intake During the assessment, patients were comfortably positioned in a chair To prevent talking, laughing or dozing off, patients were instructed to watch a documentary

Surface electrodes with a bipolar configuration were taped unilaterally (right-sided) on the skin to record EMG signals from various muscles that are involved in oral and pharyngeal swallowing the orbicularis oris muscle, the masseter muscle, and the suprahyoid muscles group (mylohyoid muscle and anterior belly of the digastric muscle) Also a highly sensitive motion sensor was attached onto the larynx to detect mechanical upward and downward laryngeal motion during every swallow We did not aim to measure the characteristics of the swallows, only to capture every single swallow, as demonstrated in Figure 1 The breathing pattern was monitored with a flexible abdominal band with stretch sensors Also, an airflow sensor was placed directly under the nose to record changes in nose breathing In addition, the patient was filmed laterally (from the left) with a digital camera, allowing us to count after the experiment if and how long unintentional mouth opening had occurred during the recordings All signals were synchronously recorded with a standard neurophysiological system (NicoletOne, CareFusion, Madison WI)

Data acquisition

Experienced speech-language pathologists, who were blinded with respect to the study design, performed all the clinical assessments A single examiner (JGK), assisted by a clinical neurophysiology technician performed the electrophysiological assessments and data were stored for offline analyses Another examiner (LvdE), who was blinded with respect to drooler status, carried out the swallowing frequency counts based on the recordings The photographs of the postures were rated according to the UPDRS subscale for posture by a single examiner (BdS), who was also blinded with respect to the status of the patients

igure 1. Polygraph of swallowing with surface EMG and laryngeal motion sensor.



xample of single swallow demonstrated by activity of the masseter (a) and orbicularis oris (b) muscles, followed by elevation) and descending of the larynx (d) At the same time the traces of eathing (e, f) are shortly flattened representing the swallowing apnea

tatistics

Ve first compared baseline variables between droolers and non-droolers, using t-tests and hi-squared tests Next, we used linear regression to compare the swallowing characteristics, acial characteristics, posture and salivation between both groups, with adjustment for age nd disease severity For a multivariable analysis, the number of variables was high compared o the number of patients in the study, so we constructed composite scores based on factor nalysis (with varimax rotation and eigenvalues >1), by combining the Z-scores of the variables hat each factor was composed of We then performed a logistic regression with the compos- e scores as independent variables and drooling as the dependent variable Results with two- ided *p*-values below 0 05 were considered significant

Results

omparison between droolers and non-droolers

haracteristics of droolers and non-droolers are summarized in Table 1 Droolers were older han non-droolers and had more advanced PD There were significantly more men among roolers compared to non-droolers Droolers also demonstrated significantly lower swallow- ng capacity, worse functional swallowing, more severe facial hypokinesia, and more severe

involuntary mouth opening. These differences remained significant when adjusted for age, UPDRS III score and gender. The mean frequency of saliva swallowing was 30% higher among droolers than non-droolers (difference not significant). During the electrophysiological swallowing assessment, droolers more commonly demonstrated unintentional mouth opening than non-droolers (difference not significant after correction for age, disease severity and gender). Difficulty with nose breathing was rare in both groups and did not differ between droolers and non-droolers. Finally, posture of droolers was significantly more stooped. Overall, drooling was absent during the electrophysiological swallowing assessment, except for one patient (with unintentional mouth opening for 24% of the time) who lost some saliva once at the end of the observation.

Multivariable analysis

The factor analysis revealed the following: facial expression and mouth opening could be considered the same factor ('hypomimia'; see Figure 2 for a typical example of distinct hypomimia with parted lips); UPDRS III and posture were one factor ('disease severity'); capacity and functional swallowing represented one factor ('dysphagia'); gender represented one factor; and age represented one factor. We then constructed hypomimia, disease severity and dysphagia composite scores. Logistic regression showed that hypomimia was a perfect predictor of drooling (i.e. from a statistical point of view, the two were indistinguishable). Consequently, we assumed that hypomimia was an intermediate factor. We then continued with forward linear regression and hypomimia as the dependent factor. This resulted in a model with disease severity, dysphagia and gender as significant explanatory variables.

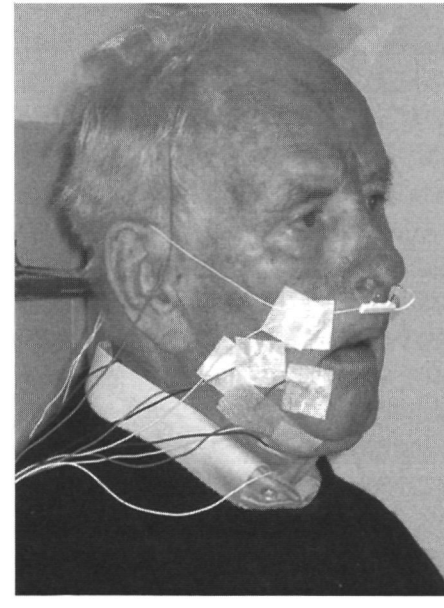


Figure 2. Example of hypomimia with parted lips.

An 80 year old patient with PD since 12 years (Hoehn & Yahr stage 3, UPDRS motor score = 37) and drooling complaints (DSFS-P = 7). The picture is taken about 5 minutes after the start of the observation.

Table 1. Differences between droolers and non-droolers.

Patient characteristics								
Drooling severity (2 – 10)	7	(5-10)	2	(2)	-		-	<0 001
Number of men (%)	14	(93%)	7	(47%)	-		-	0 019
Age (years, SD)	71	(7 2)	61	(10 1)	10 3	(3 7 – 16 9)	-	0 003
UPDRS (section III, SD)	31	(6 0)	22	(11 7)	8 9	(1 9 –15 8)	-	0 014
Hoehn & Yahr stages mild (1 – 2 5)	8		14					0 007
- moderate (3)	6		1					
- severe (4)	1		0					
Disease duration (years)	9	(5 9)	6	(3 6)	2 4	(1 3 – 6 1)	-	0 193
Medication dopamine agonists	2		4		-		-	
- levodopa	10		7					
- levodopa + dopamine agonists	2		2					
Swallowing characteristics								
Swallowing frequency (events / 45 min)	23	(17 4)	18	(11 8)	5 2	(-5 9 – 16 3)	-	0 346
Swallowing capacity (ml)	36	(10 7)	54	(19 3)	-18 1	(-29 8 – -6 5)	-29 8	(-44 3 – -14 3) 0 004
Functional swallowing (5 – 0)	4	(4-5)	5	(4-5)	-0 5	(-0 8 – -0 1)	-0 5	(-1 0 – -0 1) 0 029
Facial characteristics								
Facial expression (0 – 4)	3	(2-4)	1	(0-2)	1 7	(1 4 – 2 1)	1 7	(1 1 – 2 3) <0 001
Mouth opening (1– 4)	2	(1-3)	1	(1-2)	1 3	(0 9 – 1 6)	1 1	(0 6 – 1 6) <0 001
Mouth opening during EMG assessment								0 005
- < 10% of the time	2		1					
- 10% - 50% of the time	4		0					
- > 50% of the time	2		0					
Nose breathing (1 – 4)	1	(1-3)	1	(1-2)	0 3	(-0 1 – 0 7)		0 217
Other characteristics								
Posture (0 – 4)	2	(0-4)	0	(0-2)	1 5	(0 9– 2 1)	1 3	(0 6 – 2 0) <0 001

[a] *Adjusted for age, UPDRS section III and gender*

Discussion

We systematically evaluated a series of factors that could possibly contribute to drooling in PD Our results suggest that drooling in PD results mainly from facial and oropharyngeal akinesia, which is partially compensated for by an increased swallowing frequency

Out of all contributing factors, hypomimia was linked most strongly to drooling It was more likely to occur in men with advanced PD and with dysphagia Hypomimia in PD is considered a manifestation of akinesia [122] Severe hypomimia – score 3 and 4 on the UPDRS item for facial expression – is characterized by involuntary mouth opening, allowing accumulated saliva to drip from the mouth Hypomimia may thus represent a risk factor for drooling in PD However, habitual mouth breathers (generally healthy people with long-term blockage of nasal passage) have parted lips day and night, but they are not known to be droolers, so parted lips are unlikely to be the only cause

As predicted, dysphagia was a significant factor in the multifactorial model explaining drooling Indeed, recent studies seem to confirm that tongue bradykinesia is associated with both oropharyngeal dysphagia and drooling [123,124] On the other hand, none of our participants scored worse than 4 ("may avoid certain foods or drinks, may eat slower than previously") on the dysphagia scale So, although the droolers in our cohort had less efficient swallowing than the non-droolers, they did not have prominent dysphagia, unlike patients with drooling resulting from severe bulbar amyotrophic lateral sclerosis [102]

We also predicted that the frequency of naive saliva swallowing would be lower among droolers, but we actually found the opposite droolers tended to swallow more often than non-droolers This contradictory result is most likely related to the fact that only one of the droolers actually lost any saliva during the experiment This observer's paradox corresponds with everyday professional consultation Patients try to prevent the embarrassment of dribbling saliva in front of others Overt drooling is merely visible in severe PD cases, especially in an *off*-phase or under specific circumstances, e g when being distracted during dual tasking [114] Covert monitoring with portable equipment is therefore required to measure the patients' actual swallowing frequency [125] The same is observed in gait studies where freezing of gait is typically less prominent during clinical examination, but worsens when patients are unobserved or when attention is distracted [126] Swallowing frequency might bear another similarity with gait the walking pattern in PD is characterized primarily by a reduction in stride length, which is compensated by a higher stepping cadence [127] As such, the tendency for increased saliva swallowing frequency in droolers could be interpreted as a compensation for the less efficient swallowing

To further demonstrate that drooling results from reduced swallowing and decreased frequency, future work should also include patients with almost constant and visible drooling

Our data confirm that drooling mainly develops in more advanced stages of PD [66 111] Male gender was another explanatory factor for drooling In fact, all droolers except one were men, while gender was equally divided among non-droolers Although this is probably an overestimation, other studies also showed higher proportions of men among droolers [128 130] Why men should have more severe drooling may be related to the finding that women with PD do seem to have a more benign phenotype than men [131] In our study there was no age difference between men and women but men tended to have more severe PD (UPDRS III 29 for men vs 22 for women, p = 0 06), and this may have contributed to the gender difference in our study

This study had several limitations First it was designed as an enriched cohort study, excluding PD patients with mild complaints (only subjective accumulation of saliva, without actual loss) Consequently, the strength of the relationships may have been overestimated Also, we cannot be certain about causality, because droolers with clear hypomimia could be a subtype of PD with more axial or bulbar pathology Furthermore, some of the observed correlations may be explained by associations with e g disease severity However, most relevant factors (e g hypomimia and dysphagia) remained significantly worse in droolers even after adjustment for age and disease severity Future research, in particular intervention studies that systematically tackle the 'risk factors' identified here, remain needed to further underpin a possible causal relationship Second, levodopa or dopamine-agonists may have influenced salivation [82] However, we have examined patients in their *on*-phase, because withholding medication overnight can be uncomfortable and endangered patient cooperation Consequently, we cannot control for medication effects Third, the sample size was relatively small, which was necessitated by our labour-intensive assessments However, this only limits the multivariable analysis, but not the main finding that droolers and non-droolers differ with respect to disease severity, facial expression, swallowing and posture

Considering therapy, dopaminergic drug treatment is not always effective in reducing dysphagia,[132] this underscores the need to examine alternative treatment approaches It will be interesting to evaluate whether behavioural approaches are effective in reducing drooling Such treatment strategies also need to consider the possible contribution of perceptual disorders, as well as the influence of cognitive deterioration on drooling Pending the outcome, our present findings would suggest that behavioural treatment strategies should be offered to patients first, before choosing options that only reduce saliva production

2.2

Impact of drooling in Parkinson's Disease

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Kalf JG, Smit AM, Bloem BR, Zwarts MJ, Munneke M. Impact of drooling in Parkinson's Disease. Journal of Neurology 2007; 254:1227-1232.

Abstract

Drooling is a well-known problem in patients with Parkinson's disease (PD). The aim of this study was to investigate the severity and consequences of drooling in PD. A comprehensive drooling questionnaire was sent to 105 PD outpatients, who had volunteered drooling during a previous questionnaire (n = 216). Among 63 patients who responded and confirmed drooling, 27% experienced severe saliva loss. Social and emotional consequences were reported by 17% to 77% of patients, and significantly more often by those with severe drooling. We conclude that drooling is a frequent, disabling and apparently undertreated symptom of PD. History taking ought to be detailed and specific to understand the full impact of drooling for an individual patient. Therapeutic options should be evaluated more intensively.

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disease, best known for its motor symptoms tremor, bradykinesia and rigidity In addition, PD is commonly associated with non-motor symptoms, such as cognitive decline, autonomic dysfunction or sensory disturbances Symptoms and signs occur not only in the extremities or trunk, but frequently also involve the orofacial area One example is excessive loss of saliva (drooling), which is well recognized in PD Epidemiological studies showed a high drooling prevalence in PD (clearly exceeding that of controls), with frequencies ranging from 30% to 74% [78 128 133] However, information on the severity and impact on everyday life has never been explicitly obtained Therefore, we examined the clinical impact of drooling in PD on daily and social functioning

Patients and methods

Patients

All 260 consecutive PD patients who visited the movement disorders outpatient clinic of both hospitals in the city of Nijmegen (one university clinic and one large general teaching hospital) were sent a Global Screening Questionnaire on PD symptoms This questionnaire contained questions concerning disabling consequences of PD experienced in the preceding year [134] The questionnaire contained one specific question about drooling "Do you suffer from involuntary loss of saliva (drooling)?" Of the 260 patients, 216 responded (mean age 66 4 years, SD 10 2, mean duration of PD 6 7 years, SD 6 1) In total, 105 patients answered "Yes" to this question These patients were sent an "Extensive Drooling Questionnaire" (see below) A reminder was sent after two weeks The study was approved by the medical ethical committee

Extensive Drooling Questionnaire

The Extensive Drooling Questionnaire (available from the corresponding author) is based on questions from the Drool Rating Scale (DRS),[135] describing the characteristics and consequences of drooling, using a 5-point scale The severity of drooling and frequency of occurrence were both rated on a 4-point scale, adapted from the Drooling Severity and Frequency Scale (DSFS) [136] We added some questions about current treatment

Statistical analysis

For data analyses, we used SPSS 12 0 1 (SPSS, Chicago IL, USA) Differences between groups were calculated with independent t-tests for continuous data and the Mann-Whitney U test for comparing scale responses Odds ratio of factors associated with drooling were calculated with backward stepwise logistic regression A p-value of 0 05 was used to determine significance

Results

Patient characteristics

Ninety-two of the 105 patients responded. Among these subjects, 11 were unable to complete the questionnaire because of decreased cognition or inability to write, and 15 denied drooling problems when asked this second time round. Three patients had not answered the questions about the severity of drooling, leaving 63 records for analyses (29% of 216) , being 50 (76%) from male subjects. The mean age was 68.5 years (SD 9.4) and the mean duration of PD was 6.7 years (SD 5.6). Drooling had been present for about 2.4 years. Six patients even experienced drooling one or two years before they were diagnosed with PD (Table 1).

Table 2. Characteristics and consequences of drooling

	[redacted]	[redacted]	[redacted]
N (total 63)	46	17	
Characteristics of drooling:			
- when relaxed	33 (75)	17 (100)	0.00
- when tired	33 (75)	16 (94)	0.00
- during activities	31 (70)	15 (88)	0.00
- while eating	25 (57)	11 (65)	0.15
Physical consequences of drooling:			
- changing a handkerchief or napkin [3] 1/day	25 (57)	14 (82)	0.00
- noisy breathing or gurgling	9 (20)	8 (47)	0.03
- halitosis (bad breath)	9 (20)	6 (35)	0.33
- skin irritation (face, neck)	8 (18)	2 (12)	0.54
Social and emotional consequences:			
- Overall, how bothered are you as a result of your drooling?	33 (75)	15 (88)	0.00
- Does your drooling effect your self-confidence?	13 (30)	15 (88)	0.00
- How limiting is your drooling on doing activities outside the home?	6 (14)	8 (47)	0.00
- Are people reluctant to have contact with you?	4 (9)	7 (41)	0.00
Summarized score (median, range)	5 (4 – 11)	8 (4 – 14)	0.00

[1] *The 5-point scales were dichotomized into 'No' or 'Yes' (= minimal, mild, moderate or severe).*
[2] *The total number of responses ranged from 43 to 46, percentages are calculated with n = 44.*

Severity of drooling

The severity of drooling is summarized in Table 1. Mild to moderate drooling was present in 73% of patients, and severe or profuse drooling in 27%. Infrequent or occasional drooling was most common (78%), but 22% drooled frequently or continuously. Severity and frequency of drooling were interrelated (Spearman's rho = 0.51; p = 0.01). Drooling was equally common during the day or night. The mild and severe drooling patients had equal duration of PD (p = 0.34) and duration of drooling (p = 0.69), but they differed significantly in age (p = 0.03), the severe drooling patients being on average 5.8 years older.

Characteristics and consequences of drooling

Drooling was reported most frequent (Table 2) when patients are relaxing (75% -100%) or tired (75% -94%) or during concurrent activities like walking (70% - 88%) and significantly more among severe drooling patients (p = 0.00). Drooling during eating was reported less frequent (57% - 65%) and not significant between mild and severe drooling patients (p = 0.15). The most frequent physical consequences were the need of changing a handkerchief at least once a day (57% -82%) and noisy breathing or gurgling (20% - 47%), both aspects occurring significantly more often in the severely drooling patients (p = 0.00 and 0.03 respectively).

Table 1. Patient characteristics

	total	range/%
N	63	
Mean age (y)	68.6	(42 – 85)
Mean duration PD (y)	6.8	(1 – 24)
Mean duration drooling (y)	2.3	(0 – 14)
Mean time drooling after PD onset (y)	4.6	(-2 – 21)
Severity:		
- mild or moderate: only lips wet or lips and chin wet	46	(73)
- severe to profuse: clothing soiled or clothing, hands etc. moist and wet	17	(27)
Frequency:		
- not frequently or occasional drooling: less than once a day	49	(78)
- frequent drooling: daily, frequently or continuous	14	(22)
Moments of drooling:		
- only or mainly during day	24	(38)
- only or mainly during night	19	(30)
- equal day and night	20	(32)

The social and emotional consequences were all reported considerably more often (p = 0 00) by the severe drooling patients, ranging from 41% to 88% Also, the sum score of these four questions (internal consistency a = 0 77), describing the drooling-related quality of life, was significantly higher in severely than in mildly drooling patients

In our group only 5% of patients had received dedicated drooling treatment, while 40% wanted some form of treatment for drooling

Factors associated with drooling

Thirteen variables from the database of all patients that had returned the first questionnaire (n = 216) correlated significantly with the variable 'drooling y/n' Backward stepwise logistic regression revealed that aging (OR 1 03, 95% CI 1 00 –1 07), difficulty with posture (OR 2 29, 95% CI 1 03 –5 13), difficulty with speech (OR 2 47, 95% CI 1 21 – 5 05) and difficulty with arm/hand mobility (OR 2 54, CI 95% 1 20 – 5 34) are independently associated with drooling

Discussion

Our results underscore that drooling is a considerable problem in PD, not only in terms of its high prevalence, but also because of the significant clinical impact Drooling was scored by most subjects (73%) as mild or moderate, but as severe and incapacitating by a quarter of the patients Furthermore, the results show that drooling has serious physical and emotional consequences and a negative impact on social functioning in a substantial number of drooling patients This demonstrates that history taking should be detailed and specific to grasp the full impact of drooling for an individual patient Our findings also emphasise that many patients are currently being undertreated, because 40% of our respondents expressed a wish to be treated, but only a minority of them had actually received dedicated treatment to decrease drooling

Several factors may cause or increase drooling in PD Mounting evidence suggests that hypersalivation is unlikely to induce drooling [81 82 137] In fact, it is more likely to result from pooling of saliva in the mouth, due to decreased frequency of swallowing and antecollis Pehlivan et al [125] found significant differences in the frequency of spontaneous saliva swallowing between PD patients and controls Accordingly, our results demonstrate that drooling is most prevalent during rest or while performing distracting activities and less common during eating, suggesting that in some patients oral activity makes it easier to remove saliva by swallowing In addition, we demonstrated significant associations between drooling and difficulty with posture or difficulty with speech

Treatment of drooling can be achieved by either decreasing saliva secretion or by improving swallowing frequency Saliva secretion can be diminished using anticholinergics, radiotherapy over the salivary glands or botulinum toxin A or B injections in the submandibular or parotid glands [109] Improving swallowing frequency and efficiency could be accomplished with behavioural techniques, including cueing strategies [138] However, the effectiveness of all these treatments needs to be evaluated more thoroughly Likewise, efforts must be undertaken to

implement treatments with proven efficacy into everyday clinical practice Indeed, our study suggests that even patients in a movement disorders clinic of a university hospital were often withheld treatment, partially due to underreport by patients, but perhaps also because of insufficient medical attention for drooling and its treatment

In general a survey study has limitations, especially when cognitive problems are prevalent in the population In the present study, 11 patients were unable to complete the questionnaire and 15 patients denied drooling problems, although they were selected because they reported drooling in the first screening questionnaire However, our survey included a comprehensive questionnaire which provided, for the first time, a detailed perspective of the clinical impact of drooling in a large cohort of PD patients, representing all PD-patients known in the outpatient clinics in Nijmegen at that time

We conclude that drooling is a frequent, disabling and apparently undertreated symptom of PD New therapy options such as botulinum toxin therapy or 'cueing' strategies to improve swallowing should be investigated more thoroughly to diminish and alleviate this incapacitating problem for affected patients

Appendix

Extensive drooling questionnaire

Derived from the Drooling Severity and Frequency Scale (DSFS)[139] and the Drooling Rating Scale (DRS).[135]

Do you currently experience drooling? Yes / No

In what year was your PD diagnosed?

In what year did you experience the first symptoms of drooling?

What is the severity of your drooling?

1. mild: only lips wet
2. moderate: lips and chin wet
3. severe: clothing soiled
4. profuse. clothing, hands etc. moist and wet

What is the frequency of your drooling?

1. not frequent less than once a day
2. occasional drooling: daily, now and then
3. frequent drooling: daily, frequently
4. constant drooling: daily, continual

When do you experience drooling?

1. Only or mainly during the day
2. Only of mainly during the night
3. Both during the day and during the night.

Do you experience drooling when you are relaxed and resting?

1. No
2. Minimal (does not disturb)
3. Moderate (does disturb a little)
4. Moderate-severe (does disturb moderately)
5. Severe (does disturb severely)

Do you experience drooling when you are tired?

1. No
2. Minimal (does not disturb)
3. Moderate (does disturb a little)
4. Moderate-severe (does disturb moderately)
5. Severe (does disturb severely)

Do you experience drooling during activities (walking, sporting, housekeeping etc.)?

1. No
2. Minimal (does not disturb)
3 Moderate (does disturb a little)
4 Moderate-severe (does disturb moderately)
5. Severe (does disturb severely)

Do you experience drooling when you are eating or drinking?

1. No
2. Minimal (does not disturb)
3. Moderate (does disturb a little)
4 Moderate-severe (does disturb moderately)
5. Severe (does disturb severely)

How many times a day to you need to change a handkerchief or napkin?

1 Never
2. Once a day
3. 2 or 3 times a day
4. 4 or 5 times a day
5. More than 6 times a day

Do you experience noisy breathing or 'gurgling' caused by saliva?

1. Never
2. Seldom. once a week
3 Occasional. once a day
4. Frequent· > twice a day
5. Constant

Do you suffer from halitosis (bad breath) because of dr ooling?

1. No
2. Slight halitosis
3. Moderate halitosis
4 Moderate-severe halitosis
5. Severe halitosis

Do you suffer from skin irritation because of drooling?

1. No
2. Slight redness, occasionally
3. Slight redness, always
4. Moderate redness, always
5. Severe redness

Overall, how bothered are you as a result of your drooling?

1. Not bothered at all
2. Bothered a little
3. Bothered a lot
4. Extremely bothered

Does your drooling effect your self-confidence?

1. No
2. Yes, slightly
3. Yes, moderately
4. Yes, severely

How limiting is your drooling on doing activities outside the home?

1. Never
2. Very mild
3. Mild
4. Moderate
5. Severe

Are people reluctant to have contact with you?

1. No
2. Minimal, people sometimes avoid physical contact with me
3. Moderate, people regularly avoid physical contact with me
4. Severe, people often avoid physical contact with me

Have you been / are you being treated for your drooling?
If so, which treatment did you receive / are you receiving?

Would you currently like to be treated for your drooling?

2.3

Debilitating consequences of drooling

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Bloem BR, Kalf JG, van de Kerkhof PC, Zwarts MJ Debilitating consequences of drooling. Journal of Neurology 2009; 256(8) 1382-1383.

Abstract

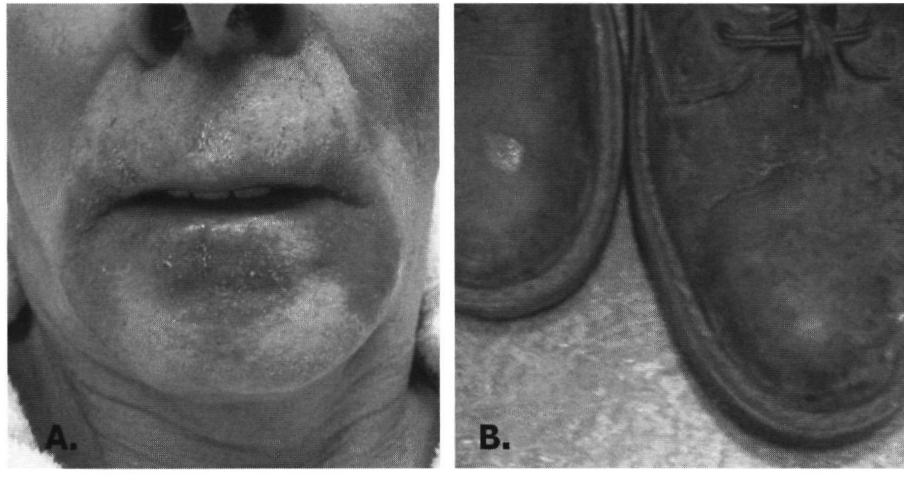
Loss of saliva in patients with Parkinson's disease is reported by patients, but only visible for observers in severe cases. This case demonstrates some debilitating and unique consequences of very severe drooling

Debilitating consequences of drooling

A 71-year-old man with a thirteen year history of idiopathic Parkinson's disease (PD) was referred to us because of severe and intractable drooling. His complaints started four years earlier with nocturnal drooling, but this had progressed to profuse drooling throughout the day. By that time he also suffered from severely impaired swallowing and severe hypokinetic dysarthria. The corners of his mouth were persistently wet, and this had produced a debilitating dermatitis in the perioral region, which is illustrated in Figure 1A. At investigation we observed erythematous plaques, in part sharply demarcated. The lesions showed some rhagades and mild scaling. Moreover, despite use of handkerchiefs, saliva was constantly dripping onto the patient's clothes and feet, destroying the leather of his shoes and necessitating him to purchase new shoes every other three months (Figure 1B). Symptomatic treatment with anticholinergics had been tried, but this was stopped because of systemic side effects. Injection of botulinum toxin into the submandibular and parotid glands effectively suppressed saliva production, and the perioral skin lesions improved considerably.

This case history underscores that drooling can have a tremendous impact on the quality of life of affected patients.[114]. The exact pathophysiology remains to be determined, but is more likely related to dysphagia (reduced automatic swallowing frequency) than to increased production of saliva.[79]. Various symptomatic treatments are available, aiming either to reduce saliva production (botulinum toxin, anticholinergics, or radiotherapy over the salivary glands) or to improve the quality and frequency of swallowing.[108;140]

Figure 1. A: prior to botulinum toxin injections into the salivary glands, there was a marked perioral dermatitis. B: detail of the patient's shoes, showing leather erosion on the dorsal side.



Chapter 3
Epidemiology

3.1

Prevalence and definition of drooling in Parkinson's disease: a systematic review

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Kalf JG, de Swart BJM, Borm GF, Bloem BR, Munneke M Prevalence and definition of drooling in Parkinson's disease: a systematic review. Journal of Neurology 2009; 256(9):1391-1396

3

Abstract

Drooling (saliva loss) is a frequently reported symptom in patients with Parkinson's disease (PD), but an accurate estimate of the prevalence of drooling is lacking The aim of this study was to systematically review the prevalence of drooling in published research papers. A systematic PubMed and CINAHL search was done including studies published until January 2009 Eight studies were found, presenting prevalence rates of drooling based on responses of PD patients to questionnaires. The statistical heterogeneity was highly significant ($p < 0.0001$), with prevalence rates ranging from 32% to 74%. The pooled prevalence estimate with random effect analysis was of 56% (95% CI 44-67) for PD patients and 14% (95% CI 3-25) for healthy controls; the pooled relative risk (RR) with random effect analysis was 5.5 (95% CI 2.1-14 4). All studies reported data of community-dwelling idiopathic PD patients, with a mean age around 65 years and mild PD in 50% to 60% of the cases Heterogeneity was mainly caused by differences in definition or frequency of drooling. The highest prevalence rates included nocturnal drooling where others noted only diurnal drooling. Analysis of the data of two studies showed that drooling is reported frequently by 22% to 26% of the patients. Prevalence rates were lower in milder PD patients The summarized findings demonstrate that drooling can be present in half of all PD patients. In about a quarter of PD patients drooling appears to be a frequently occurring problem We recommend to report drooling in future studies more detailed considering severity, frequency and nocturnal versus diurnal complaints

Introduction

Parkinson's disease (PD) is present in about 0 3% of the population and is characterized by both motor and non-motor symptoms [6 141] Speech-language therapists are involved with the oral-motor disorders in PD, such as speech impairments, swallowing disorders and increasingly also the issue of drooling Drooling, defined as an involuntary loss of saliva, is an embarrassing problem with a serious impact on social functioning [114] However, it is unclear how many PD patients experience drooling and to what extent Published estimates of the prevalence of drooling vary considerably, from 30% up to 74%,[78 128] the highest estimate would be comparable with the frequency of speech impairments, which is estimated at about 70% [142 143] A more accurate approximation of the prevalence of drooling is currently missing, including clarity about the definition of drooling and association with disease duration and severity The aim of this study is to systematically review studies reporting the prevalence and severity of drooling in PD

Methods

A literature search was conducted by the first author in PubMed and Cinahl in January 2009 with the following search terms ("Parkinson Disease"[Mesh] OR "Parkinsonian Disorders"[Mesh]) and ("Sialorrhea"[Mesh] or "Salivation"[MESH] or "Drooling" [tw] or "Saliva"[tw] OR) A second search was done to find eligible studies concerning the investigation of more general PD complaints possibly including drooling, using ("Parkinson Disease"[Mesh] OR "Parkinsonian Disorders"[Mesh]) and ("Gastrointestinal Diseases" [MESH] or ["Autonomic Nervous System Diseases" [MESH] or "Nonmotor" [tw] as search terms

Articles were considered eligible when (a) the results provided an estimate of the prevalence of drooling in a population-based study of patients with PD or atypical parkinsonism (only if clearly stated), (b) the results were published as an article, not as an abstract, and (c) the definition or method to ascertain drooling was described No language limitations were used Study selection was done independently by the first author (JGK) and second author (BdS) In addition, the first author checked references in review articles and studies on the treatment of drooling that were published between 2000 and 2008

The following data were extracted from the included studies

- patient recruitment and study sample (patients and controls)
- patient and disease characteristics age, disease duration, disease severity and specific diagnosis (idiopathic PD or atypical parkinsonism)
- definition and identification of drooling
- drooling rate in the studied patients (and controls)
- correlation between drooling and disease severity

All data were summarized in one table to study clinical heterogeneity

Statistics

Statistical heterogeneity was evaluated and an estimate of the pooled prevalence for patients and controls and the overall risk ratio were computed with a random effect model to account for between-studies variation [144]

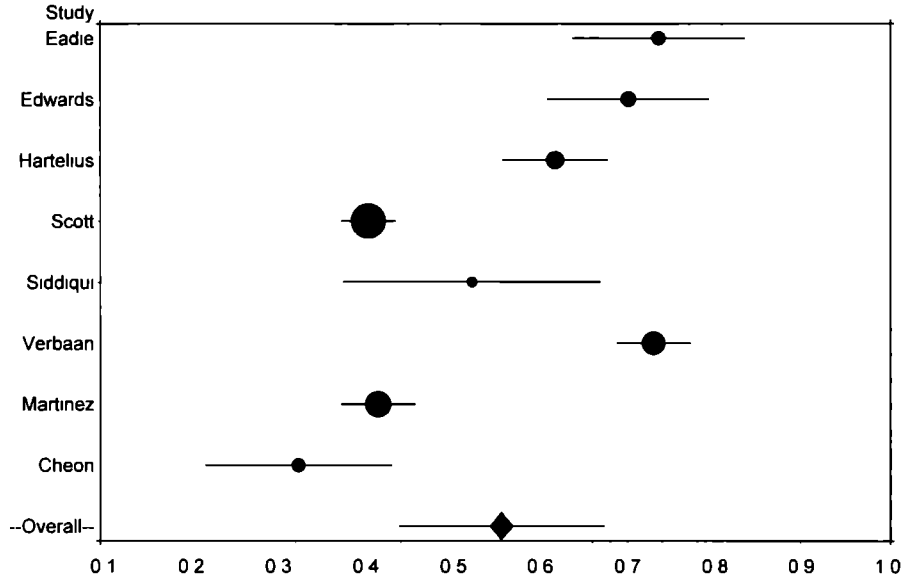
Results

The initial search strategies revealed 111 articles, of which only one met the selection criteria [128] The second search revealed 1624 articles of which 6 met the inclusion criteria [129 133 142 145 147] Reference tracing exposed a further study [78] Two other studies that were also found via reference tracing [148 149] were excluded because they were only published as an abstract, therefore the available data were incomplete for this review A comparable search in CINAHL did not reveal additional studies

Hence, eight studies met all inclusion criteria All relevant data are summarized in Table 1 In all studies the data on drooling were extracted from the results of questionnaires two studies investigated drooling as part of gastrointestinal symptoms in PD,[78 147] two other studies as part of autonomic dysfunction – although the authors acknowledge that drooling is not a sign of autonomic dysfunction – [133 146] and two further studies as part of non-motor symptoms in PD [129 145] One study had speech and swallowing in PD as the main focus [142] and one study reported gender differences for the most frequent PD symptoms [128] We found no studies that merely and specifically addressed the prevalence of drooling in PD None of the studies included patients with atypical parkinsonism

The eight studies reported the prevalence of drooling in clinically approximately comparable populations of consecutive community-dwelling PD patients, with a mean age around 65 years and mild PD in 50% to 60% of the cases (Table 1) However, statistical heterogeneity was highly significant ($p < 0.0001$), with prevalence rates ranging from 32% to 74% (Figure 1) The pooled prevalence estimate with random effect analysis was of 56% (95% CI 44-67) for PD patients and 14% (95% CI 3-25) for healthy controls The pooled relative risk (RR) with random effect analysis was 5 5 (95% CI 2 1-14 4) (Figure 1)

Figure 1. Forest plot demonstrating the prevalence rates of drooling with the 95% confidence intervals of eight studies.



The circle size represents the sample size The overall rate, calculated with random effect analysis is 56% (95% CI 44 67)

The definitions of drooling vary widely, ranging from the broad description of "ever dribbling of saliva" to more precise characterizations such as "dribbling of saliva during the daytime, experienced during the last month" The methods used to obtain responses to the questionnaires also varied One study used different severities to scale the answers[133], four studies used a 'yes/no' response [78 128 129 145] and three studies used an adjective frequency scale, but only two (partly) reported percentages per scale item [142 146] The percentages per frequency item in the latter studies revealed that 36%[142] and 51%[146] experience loss of saliva 'seldom' or 'sometimes' while a quarter of patients (26% and 22%) reported drooling 'often' or 'frequent' (Table 1)

Correlation of drooling with disease severity was reported in four studies Three of them found a positive and significant correlation with drooling as single complaint[78 146] or drooling as part of the digestive complaints [145] One study found that gastrointestinal complaints (including drooling) did not increase with disease duration or severity, but a correlations with single items were not reported [133] Gender differences were investigated in three studies Two reported significant higher drooling rates in men than in women[128 129] and one did not find a gender difference in digestive complaints, but single items were not reported [145]

Discussion

The results of this systematic review reveal that in a community-based population of PD patients, about half of the patients experiences drooling, while in a quarter of patients drooling occurs often The relative risk of drooling problems is more than five times higher in comparison with healthy controls Despite an intensive search strategy, only eight studies were found with useful data, but we acknowledge that additional relevant reports on prevalence rates might have been missed because this kind of studies is poorly indexed However, since the search did not reveal any studies focusing primarily on drooling in PD, publication bias seems unlikely, and this corroborates the internal validity of this present review

The large differences between the studies (heterogeneity) may be explained as follows The three studies with the highest prevalence rates (70% and more) may have overestimated the prevalence of drooling The study reporting the highest rate of 74%[78] was also the oldest (1965) It could be argued that this high prevalence might be caused by the fact that PD patients in those days were not yet receiving adequate anti-parkinson medication, because treatment with levodopa only started to become accustomed after 1967 [16] However, in the other two studies reporting high prevalence rates, 80% to 90% of patients used anti-parkinson medication, emphasizing that the prevalence is also considerable in patients using medication, although 'levodopa phobia' might keep many PD patients unjustly on low dosages [150 151] The high rate in the Verbaan-study consists of 51% of patients who reported to have this complaints only 'sometimes' The 73% prevalence rate may be further clarified by having included nocturnal drooling Verbaan et al [146] and also Martinez-Martin et al [145] and Cheon et al [129] asked for "dribbling of saliva during the last month", but the latter two studies used the PD NMSQuest in which "during the daytime" is added This might explain the lower prevalence rates of 32% to 42% The 70% rate in the Edwards-study might be clarified likewise, but data on frequency of saliva complaints or diurnal versus nocturnal drooling were not reported

A positive correlation between drooling complaints and disease severity was reported in three studies, suggesting that drooling is more commonly present in more severely affected patients This is in agreement with the finding that the two studies reporting the lowest prevalence rates (42% and 32%) had the smallest number of severely affected PD patients (0% to 9%), hence these figures might represent an underestimation Additionally, none of the studies included PD patients in nursing homes, leaving out the severely advanced Hoehn & Yahr stage 5 patients, with probably the highest prevalence of severe drooling Taken together, the prevalence in the total PD population might be higher than 56%

Unlike dysarthria or dysphagia, drooling is difficult to examine Saliva production can be measured, but clinical experience dictates that dribbling of saliva in PD patients during professional consultation is only visible in very severe cases, so observation is typically insufficient Consequently, this finding is fully based on the subjective response of patients (or caregivers)

Table 1. Prevalence of drooling in PD.

Eadie & Tyler, 1965 [78]	consecutive idiopathic PD patients with rigidity and tremor seen at hospital (Australia)	76 / 96	median approx 65 (controls same distribution)	grade I to IV (most severe) I 24% II 40% III 29% IV 7%	-	None	Questions on alimentary disorders (interview)			Yes, for saliva amount and drooling
							any change in the amount of saliva since disease onset?	50*	5	
							ever dribbling of saliva?	63*	17	
							ever wet pillow beside mouth when awake from sleep?	53*	25	
							Total manifestation of drooling	74*	32	
Edwards et al , 1991 [147]	consecutive PD patients from MDC (USA)	94 / 50	66 3 / 63 3	mild 69% mod 19% severe 12%[5]	-	80%	GI questionnaire (interview)			NR
							'abnormal salivation' (excess saliva in mouth or drooling)	70*	6	
Hartelius & Svensson, 1994 [141]	members of PD society, 69% response (Sweden)	249	15% < 60 41% 60-70 44% > 70	-	< 3 12% 3-10 51% >10 37%	major-ity	Postal survey speech & swallowing			NR
							drink or saliva escaping between lips (seldom/fairly often/very frequently/always)	62 36% seldom, 18% often, 8% frequent/always	-	
Scott et al , 2000 [128]	members of PD society with PD diagnose by a physician, 53% response (Sweden)	948	9% < 55 25% 55-65 66% > 66	-	9 3	major-ity	Postal survey on PD complaints			NR
							problems with salivary flow	40 females 30%, males 47%*	-	

Siddiqui et al , 2002 [133]	PD patients from MDC without consideration of symptoms (USA)	44 / 24	65 6 ± 9 / 63 5	HY 2 1 ± 1-4	8 3 ± 6 5	NR	GI symptom severity (interview) salivation			No, for total GI score
							mild (= nocturnal)	30	13	
							moderate (= excess)	20	0	
							severe (= active)	0	0	
							constant (= hankie)	2	0	
							Total	52*	13	
Verbaan et al , 2007 [146]	community-based PD patients, recruitment on age at onset (≤/> 50 years) and disease duration (≤/> 10 years) (Netherlands)	420/ 150	61 1 ± 11 5 / 60 9 ± 9 9	mild 53% mod 27% severe 20%[§]	10 5 ± 6 5	90%	SCOPA-AUT, GI domain (self-rated on 4-point frequency scale)			Yes, mild/ mod vs severe
							dribbling of saliva out of mouth in past month (sometimes/regularly/ often)	73*	7	
								51% sometimes, 22% regular/often		
Martinez-Martin et al , 2007 [145]	consecutive nondemented PD patients from MDC's (multicentre, international)	525	67 7 ± 10 5	mild 57 7% moderate 33 5% severe 8 8%[§]	7 ± 5 3	majority	PD NMSQuest, GI domain (self-rated, yes/no)			Yes, for domain 'Digestive'
							dribbling of saliva during the daytime ('yes' if experienced during the last month)	42	-	
Cheon et al , 2008 [129]	consecutive PD patients (Korea)	74	64 9 ± 8 6	HY 1 5–3	6 4 ± 6 1	NR	PD NMSQuest (translated)			NR
							dribbling of saliva during the daytime ('yes' if experienced during the last month)	32		
								females 22% males 50% *		

*NR = not reported GI = gastrointestinal MDC = movement disorders clinic [§] PD severity mild = H&Y 1 2 5, moderate = H&Y 3, severe = H&Y 4 5 * p < 0 05 APM = anti-parkinson medication, SCOPA AUT = Scales for Outcomes in Parkinson's disease (Autonomic) PD NMSQuest = Parkinson's Disease Nonmotor Symptoms Questionnaire*

to questions and therefore highly dependent on how patients are interviewed This notion underlines the problem of how to investigate a drooling complaint what do patients really mean when they score the frequency of their drooling problem as 'sometimes', 'regularly', 'often' or 'frequent'? It is a well known psychometric problem that adjective scaling leads to high variability in responses, because meanings of adjectives differ depending on the context [152]

The results of the current review demonstrate that research is required examining the prevalence and severity of drooling in PD in more detail We therefore suggest that for future studies on drooling it is needed

- to report when drooling occurs nocturnal or diurnal, and if diurnal while busy, or during daytime sleep etcetera,
- to differentiate between feeling of accumulation of saliva in the mouth and actual loss of saliva from the mouth,
- to express the frequency in a countable manner, as in times per day, less than once a day etcetera

These recommendations might also be used by clinicians in order to evaluate possible worsening of drooling over time, or to decide about the need for pharmacological or non-pharmacological treatment For example, when is a PD patient eligible for treatment with botulinum toxin, or when is behavioural treatment by a speech-language therapist worth trying first? Although supportive evidence is lacking, in our experience mild drooling complaints can be diminished by practicing the usefulness of swallowing saliva before starting to speak of before standing up Unless a patient only looses saliva during sleep or dozing off, which obviously cannot be treated with voluntary adaptations In many cases thorough questioning is required to make this clear

3.2

Diurnal and nocturnal drooling in Parkinson's disease

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3

Abstract

Drooling as symptom of Parkinson's disease (PD) has thus far been poorly defined. This uncertainty is reflected by high variations in published prevalence rates. The aim of this study was to investigate the prevalence of saliva loss versus accumulation of saliva as a possible preliminary stage; and diurnal drooling versus nocturnal drooling In addition, we evaluated the association between drooling severity and the severity of facial and oral motor disorders. We collected age, disease duration, UPDRS III and Hoehn & Yahr stage from 104 consecutive outpatients with PD. Diurnal and nocturnal drooling was evaluated with a validated questionnaire (ROMP-saliva). A speech pathologist, blinded for drooling severity, rated facial expression, involuntary mouth opening and difficulty with nose breathing and also interviewed patients about sleeping position and nose-breathing during the night.

Thirty patients (29%) had no complaints with saliva control ('non-droolers'), 45 patients (43%) experienced accumulation of saliva or only nocturnal drooling ('pre-droolers'), and 29 (28%) had diurnal drooling (24 of which also drooled during the night; 'droolers'). The droolers had longer disease duration (10 vs. 7 years, p = 0.01) and drooling was independently associated with involuntary mouth opening (OR = 2.0, 95% CI 1.02-3.99) and swallowing complaints (OR = 1.2; 95% CI 1.03-1.31). Diurnal drooling – defined as dribbling of saliva while awake – is present in about 28% of PD patients. This is less than usually reported Diurnal drooling typically appeared later in the disease course. The association with oral motor behaviour should encourage the development of behavioural treatment approaches.

Introduction

Parkinson's disease (PD) is a common movement disorder characterized by motor and non-motor symptoms [6 11 153] Oral motor problems such as dysarthria and dysphagia are frequently reported by PD patients Drooling (or dribbling of saliva) is considered a related problem In a meta-analysis based on 10 studies, we found that prevalence rates of drooling varied between 32% en 74%, depending on disease severity and definition [111] The pooled prevalence in community-dwelling PD patients was 56% However, many clinicians would feel that the prevalence rate is lower, because overt dribbling of saliva is relatively rarely seen in clinical practice Complaints about saliva or drooling can be assessed subjectively, but questionnaires that include drooling such as SCOPA-AUT[146] and PD NMSQuest[145] rarely make a distinction between diurnal and nocturnal drooling Moreover, little distinction is being made between awareness of saliva accumulating in the mouth versus actual loss of saliva from the mouth These inconsistencies in how drooling was defined might explain why published prevalence rates vary so much

There are no data on the prevalence of accumulation of saliva or nocturnal drooling versus diurnal drooling Therefore, our first aim was to investigate the prevalence and distribution of diurnal and nocturnal drooling in a large cohort of community-dwelling PD patients Second, we aimed to test the assumption that accumulation of saliva or mere nocturnal saliva loss is an intermediate phase leading up towards the most severe condition of diurnal drooling, as is expressed in the new MDS-UPDRS (Table 1)[37] and the ROMP-saliva (Table 2) [154] Third, we aimed to extend our pilot observations that drooling is associated with facial and oropharyngeal akinesia and male gender [155]

Table 1. MDS-UPDRS: 2.2 Saliva & drooling.[37]

0	Normal	Not at all (no problems)
1	Slight	I have too much saliva, but do not drool
2	Mild	I have some drooling during sleep, but none when I am awake
3	Moderate	I have some drooling when I am awake, but I usually do not need tissues or an handkerchief
4	Severe	I have so much drooling that I regularly need to use tissues or a handkerchief to protect my clothes

Table 2. Drooling severity scales (2 items from the ROMP-saliva[154]).

Do you experience loss of saliva during the day?

1. I do not experience loss of saliva during the day and I do not feel increased amounts of saliva in my mouth either.
2. I do not experience loss of saliva during the day but I do feel increased amounts of saliva in my mouth.
3. I experience saliva in the corners of my mouth or on my chin.
4. I lose saliva on my clothes.
5. I lose saliva on my clothes, but also on books or on the floor.

Do you experience loss of saliva during the night?

1. I do not experience loss of saliva during the night at all.
2. My pillow sometimes gets wet during the night.
3. My pillow regularly gets wet during the night.
4. My pillow always gets wet during the night.
5. Every night my pillow and other bedclothes get wet.

Patients and methods

A total of 104 consecutive community-dwelling outpatients with PD (according to the UK Brain Bank criteria) were included. Data on age, disease duration, UPDRS III, Hoehn & Yahr stage were collected All patients completed the Radboud Oral Motor inventory for Parkinson's disease (ROMP).[154] This is a validated questionnaire consisting of three domains: seven items with a 5-point scale for the domains 'speech' and 'swallowing' and nine items for the domain 'saliva control'. We used the scores on two items of the latter subscale to identify the presence and severity of diurnal and nocturnal drooling (Table 2). We then constructed three different severity groups following the Saliva & Drooling subscale of the MDS-UPDRS (Table 1) 'non-droolers', i.e. patients without any complaints (score 0); 'pre-droolers', a term we suggest to use for patients who only experience accumulation of saliva or only nocturnal drooling (score1 or 2); and 'droolers', meaning patients with diurnal drooling (loss of saliva from the mouth) with or without nocturnal drooling (score 3 or 4)

To investigate which oral and facial characteristics might be associated with drooling severity, an experienced speech pathologist (who were unaware of the patients' score on the ROMP) scaled three facial characteristics: the UPDRS subscale for facial expression; a scale focused on mouth opening, and a scale to score difficulty with nose breathing, as previously described.[155] In addition, to explore factors possibly related to nocturnal drooling severity, the speech pathologists asked patients and spouses whether the patient slept mainly on their side or mainly in the supine position. And also whether the patient breathed mainly through the nose or mainly through the mouth during sleeping The rationale behind the last variable is that when the mouth is open, gravity directs the saliva flow into the pharynx while supine, but out of the mouth when lying sideways.

Statistical analyses

We used SPSS 16.0 for statistical analyses and p-values of < 0.05 were considered significant. The hypothesis that the three groups differ considering disease characteristics and oral and facial parameters, was tested with one-way Anova for numerical variables and the Kruskal Wallis Test for ordinal and nominal variables. To explore factors that would best predict drooling, we compared the characteristics between the droolers vs. the non-droolers & pre-droolers with independent *t*-tests for continuous variables, Mann–Whitney U test for ordinal variables and chi-square for nominal variables. We then performed a multivariate analysis using forward logistic regression with drooling as the dependent variable and the significant disease characteristics and oral-facial scores (except ROMP-saliva) as independent variables.

Results

Of 104 patients, 30 patients (29%) were non-droolers, 45 patients (43%) pre-droolers, and 29 (28%) were droolers (of which 24 also had drooling during the night) (Table 3). Severe diurnal drooling (scores 4 or 5) was present in four patients (4%), and in only two cases actual drooling was visible during consultation. Nocturnal drooling (with or without diurnal drooling) was present in 58%; in 14 patients (14%) regularly (score 3) and in five (5%) every night and severe (score 4-5).

Table 3. Distribution of diurnal and nocturnal drooling complaints.

Diurnal drooling	No (1)	30[1]	15[2]	3[2]	48
	Only accumulation (2)	11[2]	10[2]	6[2]	27
	Yes (3-5)	5[3]	14[3]	10[3]	29
	Total	46	39	19	104

Interpretation for classification in subgroups:
[1] *Group 1 = no nocturnal or diurnal complaints (non-droolers)*
[2] *Group 2 = accumulation of saliva or only nocturnal drooling (pre-droolers)*
[3] *Group 3 = diurnal drooling with or without nocturnal drooling (droolers)*

The distribution of disease characteristics and oral and facial parameters for the three subgroups is given in Table 4. All disease characteristics and all facial, oral motor and sleeping parameters that may be associated with drooling show a trend of increasing difficulty. Difference between the three groups were significant except for age, difficulty with nose breathing and posture and breathing during sleep.

Table 4. Characteristics of subgroups.

N (%)	30 (29%)	45 (43%)	29 (28%)	
Patient characteristics				
Gender: % of men	37%	82%	69%	0.000
Age (y; SD)	62 (10.2)	62 (10.3)	68 (9.4)	0.069
UPDRS III (SD)	24 (10.7)	28 (9.9)	31 (9.8)	0.019
Hoehn &Yahr :				
- mild (1 – 2)	60%	42%	31%	0.044
- moderate (2.5 – 3)	37%	53%	62%	
- severe (4 – 5)	3%	5%	7%	
Disease duration (y; SD)	6 (4.9)	7 (4.6)	10 (5.4)	0.010
ROMP-saliva control (7 – 35)*	7 (0.0)	9 (3.3)	15 (4.8)	0.000
Facial and oral motor characteristics				
ROMP-speech (7 – 35)	11 (4.2)	15 (5.1)	16 (5.7)	0.002
ROMP-swallowing (7 – 35)	9 (2.6)	10 (3.9)	12 (4.4)	0.006
Facial expression (0 – 4)	1 (0 – 3)	1 (1 – 3)	2 (0 – 3)	0.044
Mouth opening (1 – 4)	1 (1 – 3)	1 (1 – 3)	2 (1 – 3)	0.010
Difficult nose breathing (1– 4)	1 (1 – 2)	1 (1 – 3)	1 (1 – 3)	0.137
Sleeping characteristics				
Sleeping on one side (%)	43%	50%	68%	0.266
Breathing through the mouth (%)	36%	37%	57%	0.291

**ROMP saliva minus items 'day' and 'night' (see Table 2)*

When comparing the non-droolers & pre-droolers (n = 75) with the droolers (n =29), droolers were older (68 vs. 62 years, p = 0.02), had more severe PD (UPDRS III 31 vs. 27 points, p = 0.03), longer disease duration 10 vs. 7 years, p = 0.01), worse scores on dysphagia (ROMP-swallowing 12 vs. 10 points; p = 0.01), worse scores on facial expression (1.85 vs. 1.42, p = 0.01) and more severe involuntary mouth opening (1.74 vs. 1.32; p = 0.01). Men were equally present: 64% of non/pre-droolers and 69% of droolers (p = 0.63).

Forward logistic regression with these variables identified involuntary mouth opening (OR = 2 0, 95% CI 1 02 – 3 99) and dysphagia (OR = 1.2; 95% CI 1 03-1.31) as the factors independently associated with drooling.

Discussion

We investigated the prevalence of diurnal and nocturnal drooling in a large cohort of community-dwelling outpatients with PD Seventy-one percent of patients confirmed problems with saliva or drooling, which is roughly the prevalence that is usually cited in publications [79,116,156,157] However, here we demonstrate that actual diurnal drooling, i.e dribbling of saliva from the mouth while being awake, is reported by only 28% of PD patients. Among these, severe drooling (i.e. saliva loss on clothes or on the floor) was present in only 4 cases

The prevalence rate of 28% seems more in accordance with everyday clinical practice than the overall rate of 56% that we estimated in a meta-analysis [111] Furthermore, the present observations underline the importance of being unambiguous in drooling studies about how drooling is defined [111]. Nevertheless, drooling should not be trivialized as the physical, emotional and social consequences can have a major impact on everyday life [113,114,158]

Our results confirm that saliva complaints increase with disease severity. We also provide new evidence that the experience of saliva accumulation or nocturnal drooling may precede complaints about actual dribbling of saliva, as stated by the Saliva & Drooling subscale of the MDS-UPDRS.[37] Furthermore, our data imply that drooling is generally not an early complaint, and that it takes on average three years to develop diurnal drooling after the patient starts to feel accumulation of saliva or noted a wet pillow when waking up in the morning

Accumulation of saliva suggests hypersalivation, but there is mounting evidence from sialometry studies that saliva production in PD patients is normal or even lower than in controls.[79,80,87]. Experiencing accumulation or loss of saliva might then be caused by a reduced swallowing frequency. However, in our experience this is difficult to demonstrate when patients are overtly observed.[155] Specifically, we compared 15 droolers with 15 non-droolers (with exclusion of pre-droolers), and demonstrated that drooling was independently associated with hypomimia (including parted lips), which was in turn associated with dysphagia, disease severity, and male sex. In the current study, the same facial and oral motor factors were different between non-droolers, pre-droolers and droolers. Moreover, when comparing non-droolers/pre-droolers with droolers, mouth opening and dysphagia were the only factors independently associated with drooling, consistent with previous studies on the pathophysiology of drooling.[117,124,155] But men were similarly represented in both groups, so these results contradict our previous finding that drooling is more common in men than in women [155]

Nocturnal drooling has rarely been studied as a specific problem In our cohort it was reported by 58% of patients, but in only 18% it was present regularly or every night It remains important to evaluate nocturnal drooling, mainly in relation to concurrent diurnal complaints, or as a prelude to more severe diurnal drooling several years later Five patients in group 3 lost saliva exclusively during the day, having no complaints during the night One explanation may be their sleeping positioning, as one of these patients with most severe diurnal drooling (score 5) always slept on his back This reduces the risk of nocturnal saliva loss, but at the same time may increase the risk of nocturnal aspiration of saliva, especially in severely affected patients with respiratory problems Our results show a trend that sleeping on one side and with an open mouth facilitates nocturnal drooling However, the reliability of these responses is doubtful Obviously, only objective documentation with polysomnography would provide reliable data about position, breathing and saliva swallowing during sleep [159]

An overall limitation of this study is the reliability of several measures The speech pathologist who assessed the patients was blinded with respect to drooling status, but was expected to do a full exam, so observation bias cannot be ruled out Second, our centre is a dedicated referral centre for patients with PD, and this may have caused referral bias However, the basic characteristics of our study population are comparable with other studies on home-living PD patients with respect to age (mean 64 years), disease severity (mean UPDRS III score, median Hoehn & Yahr stage 2 5, range 1-5) and disease duration (8 years) This is probably because our centre also attracts large numbers of uncomplicated patients, not just patients with advanced PD

In conclusion, diurnal drooling defined as dribbling of saliva while awake is present in about 28% of community-dwelling PD patients Drooling may be preceded by the awareness of saliva accumulation and nocturnal drooling, and is associated with involuntary mouth opening and swallowing complaints These findings should encourage the development of behavioural treatment approaches for drooling in PD

3.3

Prevalence of oropharyngeal dysphagia in Parkinson's disease: a meta-analysis

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Abstract

Dysphagia is a potentially harmful feature, also in Parkinson's disease (PD). Published prevalence rates vary widely, so we aimed to estimate the prevalence of oropharyngeal dysphagia in PD in a meta-analysis. We conducted a systematic literature search in February 2011 and two independent reviewers selected the papers. Estimates of the pooled prevalence weighted by sample size were computed. Twelve studies were available to calculate prevalence rates. Ten studies provided an estimate based on subjective outcomes, which proved statistically heterogeneous (p<0.001), with a pooled prevalence estimate with random effect analysis of 35% (95% CI 28 – 41). Four studies provided an estimate based on objective measurements, which were statistically homogeneous (p=0.23), with a pooled prevalence estimate of 82% (95% CI 77 – 87). In controls the pooled subjective prevalence was 9% (95% CI 2 – 17), while the pooled objective prevalence was 23% (95% CI 13 – 32) The pooled relative risk was 3.2 for both subjective outcomes (95% CI 2.32 – 4.41) and objective outcomes (95% CI 2.08 – 4.98). Clinical heterogeneity between studies was mainly explained by differences in disease severity. Subjective dysphagia occurs in one third of community-dwelling PD patients. Objectively measured dysphagia rates were much higher, with 4 out of 5 patients being affected This suggests that dysphagia is common in PD, but patients do not always volunteer swallowing difficulties. This underreporting calls for a proactive clinical approach to dysphagia, particularly in light serious clinical consequences

Introduction

Dysphagia is an inconvenient and sometimes hazardous feature of Parkinson's disease (PD) Oropharyngeal dysphagia can have a negative impact on the quality of life,[160 161] and increases the risk of aspiration pneumonia, which is one of the main causes of death in PD [162 163] It would be helpful to know the actual prevalence of dysphagia as a function of disease severity, because this would inform clinicians with respect to timely assessment and treatment Such prevalence rates are available for hypokinetic dysarthria (70%) and drooling (56%),[111 164 165] which like dysphagia are reckoned among the oral-motor disorders in PD Unfortunately, prevalence rates for dysphagia are less clear, with widely varying estimates [166] We therefore performed a meta-analysis to estimate the prevalence of oropharyngeal dysphagia in PD

Method

Search strategy

We conducted a systematic PubMed literature search in February 2011 with the following search strategy ("parkinson disease" [MeSH Terms] OR ("parkinson" [All Fields] AND "disease" [All Fields]) OR "parkinson disease" [All Fields] OR ("parkinson's" [All Fields] AND "disease" [All Fields]) OR "parkinson's disease" [All Fields]) AND ("deglutition disorders" [MeSH Terms] OR ("deglutition" [All Fields] AND "disorders" [All Fields]) OR "deglutition disorders" [All Fields] OR "dysphagia" [All Fields]) Since dysphagia is generally considered to be part of gastrointestinal problems and therefore regarded as a non-motor disorder, we ran a second search using ("parkinson disease" [MeSH Terms] OR ("parkinson" [All Fields] AND "disease" [All Fields]) OR "parkinson disease" [All Fields] OR ("parkinson's" [All Fields] AND "disease" [All Fields]) OR "parkinson's disease" [All Fields]) AND nonmotor [All Fields]

Study selection

Articles were considered eligible when (a) the results provided an estimate of the prevalence of dysphagia in a population-based study of patients with PD (only if clearly stated), (b) the definition or method to ascertain dysphagia was described, and (c) the results were published as a full paper Initially no language limitations were used In order to get the best estimate for the average population, we decided to exclude articles in which patients with only early PD (Hoehn & Yahr stage 1 to 2) or only advanced PD (stage 4 to 5) had been studied

The first two authors (JK, BdS) independently performed the study selection The first reviewer checked the eligibility of articles found by the second reviewer and vice versa Disagreements were resolved by discussion The following data were extracted from the included studies patient recruitment patient characteristics age, disease duration, disease severity and use of anti-parkinson medication assessment and diagnosis of dysphagia prevalence rate of dysphagia in patients (and controls)

All data were summarized in a table to study clinical homogeneity. Papers were divided into two subgroups: studies using subjective assessments (patient-rated questionnaires or interviews); or studies using objective assessments (clinician-rated observations or swallowing tests).

Statistical analysis

Statistical homogeneity of the studies was evaluated per subgroup Estimates of the pooled prevalence weighted by sample size were computed. A fixed effects model was used when the studies were statistically homogeneous and a random effects model when studies were statistically heterogeneous to account for between-studies variation.[144] When applicable the overall risk ratio between patients and controls was also estimated.

Results

The first search strategy revealed 350 articles, of which seven met the selection criteria.[71,133,142,167 171] The second search revealed 274 articles, of which four could be included [25,129,145,146] Five studies were excluded, four because the diagnostic assessment or diagnosis of dysphagia was not clearly described [66,172 174] and one because inclusion of patients was limited to Hoehn & Yahr stage 4 to 5.[175] All eligible studies were published in English In total twelve studies were thus available to estimate prevalence rates of dysphagia. All included studies dealt with community-dwelling patients with idiopathic PD. Two studies provided both subjective and objective outcomes (Tables 1 and 2).

The 10 studies with subjective outcomes were statistically heterogeneous ($p < 0.001$), with prevalence rates ranging from 16% to 55%, giving a pooled prevalence estimate with random effect analysis of 35% (95% CI 28 – 41). The four studies with objective measurements were statistically homogeneous ($p = 0.23$), with prevalence rates between 72% and 87%, giving a pooled prevalence estimate of 82% (95% CI 77 – 87).

In controls (healthy, age-matched volunteers) the pooled dysphagia prevalence was 9% (95% CI 2 – 17) when based on subjective outcomes, and 23% (95% CI 13 – 32) when based on objective outcomes The pooled relative risk (RR) with random analysis for the subjective outcome was 3 2 (95% CI 2.32 – 4.41) and for the objective outcome 3.2 (95% CI 2.08 – 4.98) Overall, subjective dysphagia was significantly correlated with disease severity according to five studies[25,71,145,146,167 169] and objective dysphagia was correlated with disease severity according to three studies.[71,168,171]

Table 1. Prevalence of dysphagia in PD, based on subjective or patient-rated measures.

Edwards et al., 1992 [10]	Consecutive patients from MDC (USA)	94/ 50	mean 66.3 / 63.3	H&Y stage: 1-2: 69% 3: 19% 4-5: 12%	NR	75	GI symptom questionnaire by interview - dysphagia (difficulty with swallowing food, respiratory symtoms etc.)	52*	6
Hartelius & Svensson, 1994 [11]	Members of Swedish PD society: 69% response (Sweden)	249/-	< 60: 15% > 70: 44%		< 3 y: 12% 3 – 10 : 51% >10 y: 37%	majority	Postal survey speech & swallowing - ability to chew and swallow worse than prior to onset	41	-
Clarke et al., 1998 [14]	Consecutive series of idiopathic PD patients attending MDC (UK)	64/ 80	mean 66.7 / 67.1	H&Y median 3 (1.5-5)	9 (1 – 43)	NR	Questions on swallowing difficulties by interview - any difficulty swallowing food - any difficulty swallowing liquids - any difficulty swallowing tablets - cough after meals or drinks	 30* 10* 22* 25*	 4 1 8 5
Siddiqui et al., 2002 [15]	From MDC without consideration of symptoms (USA)	44/ 24	mean P: 65.6 (SD 9); C: 63.5 (SD 10)	H&Y mean 2.1 ± (1-6)	8.3 (SD 6.5)	NR	GI questionnaire by interview Total amount - rare choke - occasional choke - soft food - tube feeding	 30* 18 7 5 0	 8 4 4 0 0
Verbaan et al., 2007 [18]	Community-based; recruitment on age at onset (≤/> 50 years) and disease duration (≤/> 10 years) (Netherlands)	420/ 150	mean 61.1 (SD 11.5) (controls age-matched)	H&Y stage: 1-2: 53% 3: 27% 4-5: 20%	10.5 (SD 6.5)	all in ON state	SCOPA-AUT (GI domain) - difficulty swallowing or choked in past month - food ever become stuck in throat (dysphagia) in past month	 55* 38*	 19 9
Martinez-Martin et al., 2007 [19]	Consecutive nondemented PD patients from MDC's (multicentre, international)	525/ -	67.7 (SD 10.5)	H&Y stage: 1-2: 58% 3: 33% 4-5: 9%[5]	7 (SD 5.3)	majority	PD NMSQuest, GI domain (self-rated; yes/no) - difficulty with swallowing food or drink or problems with choking ('yes' if experienced during the last month)	28	-

Cheon et al., 2008 [20]	Consecutive PD patients (Korea)	74/ -	64.9 (SD 8.6)	H&Y: 1.5 – 3	6.4 (SD 6.1)	NR	PD NMSQuest (translated) - difficulty with swallowing food or drink or problems with choking ('yes' if experienced during the last month)	32	-
Miller et al., 2009 [16]	Community-based and hospital-based cohort (UK)	137/ -	median 73 (IQR 68-77)	H&Y median 2 (IQR 2 – 3)	5 (IQR 3.5-11)	all in Off state	Question by interview: - Do you have a problem swallowing food or drink?	37	-
Barone et al., 2009 [21]	Consecutive patients with PD from multiple centers (Italy)	1,072 /-	67 (SD 9.4)	H&Y stage: 1-2: 64% 2.5-3: 31% 4-5: 5%	5.1 (IQR 2.8 – 9.1)	all in ON state	Semi-structured interview (GI domain as one of 12 NMS domains): - difficulty with swallowing (yes/no)	16	-
Walker et al., 2010 [17]	PD patients in area of North Northumberland (UK)	75/-	75 (SD 9.7)	H&Y stage: 1-3: 80% 4-5: 20%	4.8 (0-18)	all in ON state	Interview: - Do you have difficulty swallowing food or liquid or tablets? - Do you cough after eating/drinking?	32	-

Abbreviations: P/C = patients/controls, NR = not reported; GI = gastrointestinal; MDC = movement disorders clinic, APM = anti-parkinson medication; SCOPA-AUT = Scales for Outcomes in Parkinson's disease (Autonomic), PD NMSQuest = Parkinson's Disease Nonmotor Symptoms Questionnaire

** $p < 0.05$*

† for total GI domain

Table 2. Prevalence of dysphagia in PD, based on objective or clinician-rated measures.

Nilsson et al., 1996 [12]	Regularly attending depart. of neurology; excluding dementia (Sweden)	75/-	mean 71 (43-85)	H&Y stage: 1-2: 34% 3: 43% 4-5: 23%	9	optimally treated	ROSS test: – any abnormality in single swallow or forced repetitive swallow	87	-
Coates & Bakheit, 1997 [13]	IPD patients diagnosed by neurologist (UK)	53/-	mean 69.9 (52-87)	-	6.7 (1-24)	all but 2; state NR	CAS (10 swallow items on 5-point scale): – score < 5 on at least one item	81	-
Clarke et al., 1998 [14]	Consecutive series of idiopathic PD patients attending MDC (UK)	58/ 80	mean 66.7 (controls: 67.1)	H&Y median 3 (1.5-5)	9 (1 – 43)	all in Off state	Swallowing speed (ml/s): – < 10 ml/s	72*	23
Miller et al., 2009 [16]	Community-based and hospital-based cohort (UK)	137/-	Median 73 (IQR 68-77)	H&Y median 2 (IQR 2-3)	5 (IQR 3.5-11)	all in Off state	Swallowing speed (ml/s) - > 1 SD below norm	84	-

Abbreviations P/C = patients/controls, NR = not reported, GI = gastrointestinal, APM = anti-parkinson medication, CAS = Chicago Assessment Scale, ROSS-test = Repetitive Oral Suction Swallow
** p < 0.05*

Discussion

This meta-analysis shows that oropharyngeal dysphagia is prevalent in at least a third of PD patients, with prevalence rates depending on disease severity and assessment technique Overall, PD patients are three times more likely to have swallowing disorders than healthy controls This estimate seems robust, as the observed risk ratio was identical for both the subjective and objective assessments We will next discuss these findings in further detail

The studies using subjective judgments were clinically and statistically heterogeneous One explanation is the lack of consistency in the definition and preferred assessment of oropharyngeal dysphagia in PD, demonstrated by the differences in questions by interview or survey (Table 1)

Another explanation is the difference in disease severity For example, when focusing on the three largest studies (> 400 patients), the study with the lowest dysphagia prevalence included only 5% of patients with late stage PD (Hoehn & Yahr stage 4 or 5)[25] whereas the study with the highest dysphagia prevalence (55%) included 20% of patients with late stage PD [146] This is further corroborated by one study with solely late stage PD patients (which we excluded from the meta-analysis), where subjective dysphagia was reported to be present in no less than 68% of patients[175]

In that perspective it is important to notice that all studies that were available for this review had included home-living PD patients only This implies that the prevalence is likely to be higher for the total population, including hospitalized PD patients Futhermore, when clinical dysphagia is not an early stage symptom in PD, it may add to distinguising idiopathic PD from atypical parkinsonism In a retrospective study of 83 postmortem confirmed cases, subjective dysphagia was reported to be much higher in multiple system atrophy (MSA 73%) or progressive supranuclear palsy (PSP 83%), because of additional neuropathology [66] Hence, subjective dysphagia (especially when it is confirmed by endoscopic or radiologic examination of swallowing) in the early stage of the disease may be a red flag for MSA of PSP [27] In addition, dysphagia in PD is generally mild,[154 176] therefore severe dysphagia should always be evaluated by a swallowing expert, also to check for other causes than PD

The studies based on objective clinician-rated measurements showed a high overall prevalence rate of 82%, twice as much as when self-reported by patients Here, disease severity was not an explaining factor We even included two studies that reported both subjective and objective judgments within the same patient population, both studies identified much higher prevalence rates for objective ratings compared to subjective ratings (30% vs 72% in one study, and 37% vs 84% in the other study) [71 168] Besides, the relative risks were the same (3 2) for subjective and objective judgments of dysphagia This shows that the two assessment approaches measure essentially different elements of swallowing At the one end of the spectrum there are the early signs of oropharyngeal changes that can be detected objectively, but which need

not necessarily lead to complaints At the other end there are functional swallowing difficulties with a negative impact on quality of life,[160] which are easily detected with a single question
The fact that dysphagia can remain subclinical or asymptomatic is plausible when patients gradually adapt as a consequence of the slow progression of PD For example, patients may have adjusted in daily life by swallowing carefully with small bolus sizes, but dysphagia may come to light when such subjects are tested with a formal swallowing speed test [71,168] At the same time, a slow but safe swallowing speed is a useful compensation for mild dysphagia and even found common in healthy volunteers [168] Likewise, taking more time for drinking or dining can be a compensation for mild dysphagia or just a well-appreciated change of life style On the other hand, PD patients might be more at risk for underestimation, because of cognitive deterioration or sensory problems, e g reduced cough reflex sensibility [177] Moreover, elderly subjects generally tend to accept even severe swallowing problems as a normal and almost inevitable accompaniment of aging, even when their dysphagia is actually caused by serious underlying pathology [178] This underreporting emphasizes the need for a proactive clinical approach to dysphagia, particularly in light of the possibility of serious clinical consequences, as we will discuss next
Progressive weight loss is a major feature of PD, and this may even precede the clinical diagnosis [179] Dysphagia is one of the factors contributing to malnutrition or weight loss in PD, along with increased energy expenditure, loss of appetite and intestinal malabsorption [180,181] Malnutrition management should therefore, include a screening for concurrent dysphagia
Dysphagia resulting in aspiration of food or liquids can lead to aspiration pneumonia A large follow-up study of 252 patients with PD and confirmed aspiration risk revealed that 10% developed pneumonia [182] However, aspiration pneumonia is a multifactorial event, and incidental choking on food or saliva alone is insufficient to cause aspiration pneumonia Aspiration pneumonia only develops in the setting of altered bacterial flora in the oropharynx, a reduced resistance of the host and decreased pulmonary clearance [183,184] Cough reflex sensitivity and cough intensity tend to deteriorate in advanced PD, and this predicts silent aspiration [177] This reduced pulmonary clearance explains why pneumonia (although not necessarily aspiration pneumonia) is a main cause of death in PD [185,186] Interestingly, speech-language pathologists have developed a new technique that focuses on expiratory strength, aiming to improve both the strenght of coughing and swallowing efficiency in PD patients [74]
Another result of dysphagia may be difficulty with swallowing tablets Since most PD patients are dependent on taking medication multiple times a day, dysphagia for tablets, especially when severe in the *off*-phase, may have consequences for the effectiveness of medical treatment [187]
Hypokinetic dysphagia itself responds to medical treatment, but usually less compared to other motor disfunctions [132] Behavioral treatment options with documented positive effects are available, but large controlled trials are missing [188] There is currently no evidence to recommend systematic screening and early dysphagia treatment in order to delay symptomatic swal-

lowing disorders However, we feel that symptomatic dysphagia should be a clear indication for further assessment and treatment by a speech-language pathologist, to reduce dyscomfort and to avoid nutritional or pulmonary complications.

This study was not without limitations. In the first place, despite careful search strategies, under- or overestimation of the pooled prevalence rates cannot be excluded, mainly because dysphagia prevalence is poorly indexed in databases. Although from a speech pathologist's point of view, dysphagia is a motor disorder, we were aware that dysphagia is included in non-motor questionnaires used for PD patients. So, we included 'non-motor' as a search term related to Parkinson's disease, which revealed another four large cohort studies.[25,129,145,146] However, while two reviewers independently carried out two extensive searches, it is still possible that eligible studies were missed.

Secondly, oesophageal dysfunction like slowed oesophageal transit or dysfunction of the lower oesophageal sphincter may also be responsible for swallowing complaints in PD patients [166,189,190] Although oesophageal dysphagia has been reported to be present in 60-70% of PD patients,[166] it is unclear how reported rates relate to age-matched controls [190] While most questionnaires included in this review investigate oropharyngeal complaints, others (e g. SCOPA-AUT and PD NMSQuest) do not differentiate between oropharyngeal and oesophageal dysphagia, so it cannot be ruled out that oesophageal complaints have contributed to dysphagia in some PD patients.

Nevertheless, we conclude that subjective oropharyngeal dysphagia is present in over one third of community-dwelling PD patients, with higher numbers in advanced PD When subclinical dysphagia is included, 4 out of 5 PD patients are affected These figures justify an active clinical approach to dysphagia, using structured interviews or patient-rated questionnaires like the SCOPA-AUT or PD-NMSQuest, or a swallowing screening instrument for PD like the Swallowing Disturbance Questionnaire.[145,146,191]

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Chapter 4

Assessment and treatment

4.1

Reproducibility and validity of patient-rated assessment of speech, swallowing and saliva control in Parkinson's disease.

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Abstract

The aim of this study was to report on the development and psychometric evaluation of the Radboud Oral Motor inventory for Parkinson's disease (ROMP), a newly developed patient-rated assessment of speech, swallowing and saliva control in Parkinson's disease We enrolled consecutive community-dwelling patients with Parkinson's disease (n = 129) or atypical parkinsonism (n = 49), mean age 64 years (SD 9.8), mean disease duration of 7 years (SD 5 1) and median Hoehn and Yahr stage of 2.5.

To evaluate reproducibility, 60 patients completed the ROMP twice within 24 days (SD 12 days) To study validity, another cohort of 118 patients who had completed the ROMP was assessed by both a neurologist (Hoehn and Yahr stage, UPDRS III) and speech-language pathologist (severity of dysarthria, dysphagia and drooling), who were blinded for the ROMP scores. Confirmatory factor analysis identified the 3 a priori designed ROMP domains speech, swallowing and saliva control. Internal consistency was 0 95 for the total ROMP and between 0.87 and 0.94 for the 3 domains or subscales. ICC for reproducibility was 0.94 and between 0.83 and 0 92 for the subscales. Construct validity was substantial to good with correlations ranging from 0.36 to 0 82 The ROMP differentiated significantly ($p < 0.001$) between patients who were indicated for speech therapy (based on independent assessment) and those who did not and between mild, moderate and severe PD according to Hoehn and Yahr stage. In conclusion, the ROMP provides a reliable and valid instrument to evaluate patient-perceived problems with speech, swallowing and saliva control in patients with PD or atypical parkinsonism

Introduction

Patients with Parkinson's disease (PD) can experience a wide range of motor and non-motor symptoms [6] Oral motor disorders like dysarthria, dysphagia and drooling are common in PD Dysarthria occurs in around 70% of patients [142 143] Dysphagia is also common, occurring in about 40% to 80% of PD patients,[145 146] whereas drooling complaints are reported by about a quarter to a half of the population, depending on the diagnostic criterion [111]

Presence and severity of oral motor disorders can be accessed through observation by a trained clinician or speech-language pathologist [192] This is however less appropriate for use in clinical trials Another option is to use measures like sound pressure level in relation to speech or oropharyngeal transit time in relation to swallowing, but these measures do not reflect the impact of the problem for the patient Consequently, self-administered questionnaires evaluating the subjective severity, like being unintelligible or feeling limited in social interaction because of drooling, are needed to measure the impact on functioning and social interaction

Only few validated scales or questionnaires can assess subjective dysarthria, dysphagia or drooling for PD [107] Existing questionnaires are either too long (e g the Swal-Qol[193]) or not specific enough to seize the problems that PD patients deal with For example, the influence of cognitive deterioration on conversational skills or the consequence or dysphagia on taking medication multiple times a day is not included in generic questionnaires [194 195] Therefore, we developed a new questionnaire, the Radboud Oral Motor inventory for Parkinson's disease (ROMP), to assess all 3 domains speech, swallowing and saliva control We designed the ROMP in such a way that it would capture complaints at the level of functioning, activities as well as participation in accordance with the International Classification of Functioning (ICF),[196] while limiting the number of items In this article we describe the development of the ROMP and report about its psychometric properties as well as the reproducibility and construct validity

Methods

Scale development

To construct the questionnaire we first searched for existing generic and PD-specific questionnaires assessing difficulty with speaking, swallowing or controlling saliva in adults For dysarthria items we scrutinized the Living with Dysarthria questionnaire,[197] and a scale for communicative participation [198] For dysphagia items we investigated the Dutch version of the Swal-Qol,[199] the Performance Status Scale for Head and Neck Cancer Patients (PSS-HN)[200] and the Swallowing Disturbance Questionnaire (SDQ) [191] And for drooling items we verified an ad hoc questionnaire[114] and the Sialorrhea Clinical Scale for PD (SCS-PD) [201] Relevant items applicable for PD were then identified and 3 subscales were constructed, all consisting of 20 items

with a Likert scale to response When we explored this in 10 PD patients, several of them had difficulties with the interpretation of the scaling responses and some items proved redundant We then chose to construct adjective 5-point scales (1 = normal, 5 = worst score) and to limit the number of items per subscale to seven In addition to the drooling subscale, we decided to include both items of the Drooling Severity and Frequency Scale (DSFS), a scale originally developed to score drooling in children with cerebral palsy [107 139] We modified the Severity item by including the response "I do not lose saliva, but I feel accumulation of saliva in my mouth" which is a typical complaint in PD and also in agreement with the MDS-UPDRS subscale 2 2 Saliva & Drooling [37] And we changed the Frequency item from a 4-point into an adjective 5-point scale as we argued previously [111]

To compensate for cognitive problems we constructed the responses in such a way that the core of every item was repeated in the response possibility (see Appendix) All items were discussed with a group of experienced speech-language pathologists to establish face validity and 3 speech-language pathologists from the Parkinson Centre Nijmegen decided on the final version For the English version the questionnaire was translated by the first author and back-translated and corrected by 2 independent speech-language pathologists [202]

Data gathering

For this study we included 178 consecutive outpatients with Parkinson's disease (PD), including patients with a form of (probable) atypical parkinsonism, because the specific speech and swallowing complaints in these patient groups are almost similar

In the first part of the study we evaluated the test-retest reproducibility by asking 60 consecutive outpatients to complete the ROMP twice Patients first completed the ROMP when they were scheduled for consulting our Parkinson Expert Centre, and the second time on the first day of their visit

In the second part of the study we included 118 consecutive outpatients to evaluate the construct validity including known-groups validity of the ROMP Construct validity was examined by associating the ROMP with measures of disease severity and oral motor functioning A movement disorder neurologist estimated disease severity using Hoehn & Yahr staging (1 = mild, 5 = most severe) and the motor examination of the Unified Parkinson's Disease Rating Scales (UPDRS part III, range 0 to 108) Oral-motor functioning was rated by a neurologist with the UPDRS subscales for 'speech, 'swallowing', 'salivation' and 'facial expression' and by an expert speech-language pathologist with the following rating scales For the evaluation of dysarthria and dysphagia severity, subscales of the Therapy Outcome Measures (TOM) were applied, a commonly used set of disorder-specific clinician-rated scales in speech-language pathology and other rehabilitation professionals, where 1 = most severe and 5 = normal [121] To score drooling severity, the speech-language pathologist used the modified DSFS as part of the interview Both the neurologist and the speech-language pathologist were blinded for the patients' scores on the ROMP

To study known-groups validity, clinical subgroups were made in 3 different ways First, except from their responses on the questionnaire, patients were asked whether they desired professional attention for their oral motor impairment during their visit to our Parkinson Centre. Answers were classified as 'no', 'possibly' or 'definitely'. Second, the outcomes of the assessments were classified into either· (a) no indication for speech-language therapy; (b) no indication for further speech-language therapy, because the patient had been adequately instructed during the visit at the centre on how to optimally compensate for his or her oral motor problem; and (c) indication for further (intensive) speech-language therapy. And third, patients were divided according to disease severity into mild PD (HY stage 1 – 2), moderate PD (HY stage 2.5 – 3) and severe PD (HY stage 4 – 5).

Statistical analyses

We used SPSS 16 0 (SPSS Inc. Chicago, IL) for all calculations and considered *p*-values below 0 05 statistically significant. To analyze the scale characteristics of the questionnaire, we conducted a confirmatory factor analysis with varimax rotation, to evaluate whether items loaded on the factors that corresponded with the *a priori* defined 3 domains We considered item-scale correlations adequate when they exceeded 0.30.[203] To determine the homogeneity of the construct(s), we calculated Cronbach's α for the total questionnaire and for the subscales, accepting values between 0.70 and 0.95.[204] We regarded floor or ceiling effects of the ROMP and subscales acceptable when less than 15% of patients scored the lowest or highest possible score [205]

To evaluate reproducibility, we calculated both test-retest reliability and absolute agreement between 2 measures. We estimated reliability with intraclass correlation coefficients (ICC) taking systematic errors and random errors into account (ICC A,1).[204] Reliability coefficients above 0.90 are generally accepted as a minimum for individual measurements, but when group means are compared reliability coefficients can be lower, accepting 0 70 as a minimum.[206] When the ICC is 0.70, the Pearson correlation coefficient is also at least 0 70, which makes it possible to conduct more efficient clinical trials. The size of a trial that compares mean ROMP scores can be reduced by 49% when the baseline measure is also included as an additional covariate in the analysis.[207]

We also aimed to evaluate the agreement between the test scores and the retest scores according to the method of Bland and Altman, to check whether the measurement errors were independent from the mean of the 2 scores and whether the mean difference was near zero [208] When the differences are normally distributed, 95% or the errors will lie between ± 1.96 standard deviations of the mean difference.

Considering convergent construct validity, we *a priori* judged coefficients of less than 0.30 as weak, between 0.30 and 0.70 substantial and above 0.70 strong.[209,210] We hypothesized that the

ROMP and the subscales would correlate significantly, but probably weakly with disease duration and disease severity (UPDRS motor) We also hypothesized that the scales would correlate substantially with the measures of oral motor function Correlations were calculated with Pearson's correlation coefficient for comparison with continuous data and Spearman's correlation coefficient for comparison with ordinal data Finally, we estimated known groups validity by comparing the subgroups using one-way ANOVA

Results

Patients

Patient characteristics are shown in Table 1 One hundred and twenty-nine (73%) had PD (defined by the UK Brain Bank criteria[211]) and 49 (27%) had a form of atypical parkinsonism (multiple system atrophy, progressive supranuclear palsy , corticobasal degeneration or vascular parkinsonism) The mean time between 2 measurements was 24 days (SD 12 days) On average patients were able to finish the questionnaire within ten minutes The men-women ratio was 1 7 1 and patient characteristics were similar for men and women except for disease severity measures with the UPDRS, on which the mean score of men was 4 points worse compared to women (p = 0 022)

The mean scores on the total ROMP and the subscales are given in Table 2 Men scored on average 42 points (SD 13 9) and women 36 (SD 13 3) After adjustment using multiple linear regression for disease severity according to UPDRS score, men scored 5 points worse (95% CI 0 6 – 8 9, p = 0 025) on the total ROMP and 3 points worse (95% CI 0 8 – 4 8, p = 0 006) on the ROMP-saliva than women

Table 1. Patient characteristics.

N	178
Men / women	63% / 37%
Age (years; SD)	64 (9 8)
Disease duration (years, SD)	7 (5.1)
UPDRS III (0 – 108, SD)	29 (10 9)
Hoehn & Yahr stage	
- mild (1 – 2)	71%
- moderate (2 5 – 3)	24%
- severe (4 – 5)	5%
Diagnosis.	
- idiopathic PD	73%
- atypical parkinsonism	27%
Time between 2 measurements (days; SD)	24 (12)

Scale analyses

The completed questionnaires from both the reproducibility study (first assessment) and validity study were used for the scale analysis. The confirmatory factor analysis with varimax rotation and eigenvalues ≥ 1 extracted 4 factors explaining 72% of the variance. Since the fourth factor only explained 4% of the solution, the factor analysis was re-run forcing the solution in 3 factors which explained 68% of the variance. Now all items of every subscale loaded on one factor ('drooling', 'dysarthria' and 'dysphagia'), demonstrating a clustering of items in the *a priori* designed domains. All item-scale correlations exceeded 0.30 as required and only the swallowing and drooling subscale showed some floor effect (28% and 26%), see Table 2. Cronbach's α proved 0.95 for the total ROMP and between 0.87 and 0.94 for the subscales, demonstrating good internal consistency.

Table 2. Scale characteristics (n = 178).

ROMP total	23	(23 – 115)	0.39 – 0.75	0.95	40	(13.9)	3%	1%
Speech	7	(7 – 35)	0.67 – 0.77	0.92	14	(5.5)	7%	1%
Swallowing	7	(7 – 35)	0.51 – 0.77	0.87	11	(4.3)	28%	1%
Saliva control	9	(9 – 45)	0.45 – 0.85	0.94	14	(6.4)	26%	1%

Reproducibility

The ICC's were 0.94 for the total ROMP and ranging from 0.86 to 0.92 for the subscales (Table 3), meeting the set criteria. Means and differences were uncorrelated for the total scales and subscales as required. The mean measurement errors were almost zero for the total scales and subscales, demonstrating no systematic error. The 95% limits of agreement turned out to be approximately ± 8 points for the total scale and ± 4 points for the subscales, see Table 3.

Table 3. Reproducibility of the ROMP and subscales (n = 60).

ROMP total	0.94	(0.91-0.97)	± 8.2
Speech	0.92	(0.87-0.95)	± 4.0
Swallowing	0.86	(0.76-0.92)	± 4.4
Saliva control	0.90	(0.83-0.94)	± 4.5

* *ICC = Intraclass correlation coefficient (ICC A,1)*
† *1.96 * $SD_{difference}$*

Validity

The total scale and subscales correlated significantly with disease severity and disease duration. As expected, the subscales correlated better with the domain-specific outcomes, showing correlations well above r = 0.50, see Table 4.

Table 4. Convergent construct validity of the ROMP and the subscales (n = 118).

Disease characteristics				
Disease duration	0.32	0.32	0.35	0.19*
UPDRS III	0.42	0.42	0.37	0.30
Speech measurements				
UPDRS subscale speech	0.63	0.63		
TOM dysarthria	-0.59	-0.65		
TOM functional communication	-0.67	-0.72		
Swallowing measurements				
UPDRS subscale swallowing	0.55		0.58	
TOM dysphagia	-0.48		-0.53	
TOM functional intake	-0.55		-0.61	
Drooling related measurements				
UPDRS subscale salivation	0.68			0.82
UPDRS subscale facial expression	0.46			0.36
Modified DSFS	0.71			0.78

**Significant at <0 05 level, all other correlations were significant at 0 01 level*

All ROMP and subscale scores differentiated significantly in the 3 different known-groups. Between patients who wished attention for a complaint or not, as well as between patients who were indicated for treatment and those who were not. The scores also differentiated between patients with mild, moderate or severe PD, see Table 5.

Table 5. Known-groups validity of the ROMP and subscales (n = 118).

	mean	SD	%	mean	SD	%	mean	SD	%	
ROMP total	29	8.4	23	36	9.0	30	48	14.1	47	< 0.001
Speech	10	2.6	28	14	4.0	34	18	5.7	38	< 0.001
Swallowing	9	2.5	61	13	3.5	18	16	4.5	21	< 0.001
Saliva control	11	2.6	57	16	5.0	23	23	6.4	20	< 0.001
	mean	SD	%	mean	SD	%	mean	SD	%	
ROMP total	28	4.3	24	40	12.0	28	46	16.4	48	< 0.001
Speech	10	3.2	26	14	4.4	26	18	6.0	48	< 0.001
Swallowing	9	2.3	59	13	4.1	38	22	4.2	3	< 0.001
Saliva control	11	3.0	57	18	6.7	35	28	7.6	8	< 0.001
	mean	SD	%	mean	SD	%	mean	SD	%	
ROMP total	34	9.7	49	42	13.4	45	59	22.3	6	< 0.001
Speech	12	4.1	49	15	3.4	45	23	7.2	6	< 0.001
Swallowing	10	3.1	49	11	4.2	45	14	6.1	6	0.001
Saliva control	13	4.9	49	15	5.9	45	21	12.5	6	<0.001

The percentages are the proportions of patients in every known-group and for A and B also per domain. Desired attention patients divided based on whether they desired attention for that disorder during their visit in the centre Treatment indication patients divided based on the outcome of the consultation by the speech-language pathologist, who was unaware of the ROMP scores HY stage patients divided based on disease severity (Hoehn & Yahr stage 1 – 2 = mild, 2 5 – 3 = moderate, 4 – 5 = severe)

Discussion

The Radboud Oral Motor inventory for Parkinson's disease (ROMP) was shown to be a reliable and valid questionnaire to quantify difficulties with speaking, swallowing or controlling saliva caused by PD or atypical parkinsonism. Internal consistency and test-retest reliability are well above 0.70. This is comparable with other patient-rated questionnaires in PD, like the PDQ-39[212] and allows the ROMP to be used as an outcome measure. All parameters are even above 0.90, making scores reliable enough for individual comparisons in clinical practice.

Though arbitrary, only the parameters of the ROMP-swallowing (with α = 0 87 and ICC = 0 86) are below this limit, suggesting that this subscale might be less reliable for clinical use than the other subscales

The agreement parameters show a maximum measurement error of 8 points on an average score of 40 (maximum score of 115) which is comparable with other evaluative questionnaires used in speech pathology [213] The association of the ROMP with clinician-rated scales is substantial with most correlation coefficients between 0 50 and 0 70 and strong correlations for the ROMP-speech against functional communication (0 72) and the ROMP-saliva against the UPDRS subscale for drooling (0 82) or the modified DSFS (0 78) Again, these are satisfactory values and the scores also discriminate significantly between clinical subgroups

An additional finding was the clear difference between the manifestations of dysarthria versus dysphagia or drooling Complaints about speech (voice, intelligibility and conversation) were more frequently reported as a concern by patients (Table 5 desired attention) and are more often an indication for speech therapy than swallowing or saliva complaints (Table 5 treatment indication) This is in accordance with previous reports about average PD populations as well as late-stage PD,[142 175] but it might also be a reflection of the fact that effective treatment techniques for dysphagia and drooling in PD lag behind those for hypokinetic dysarthria [46] Remarkably, men scored worse on the ROMP than women, even after adjustment for disease severity, since women with PD seem to have a more benign phenotype than men [131] This is in accordance with gender differences reported by other,[128] but might also be related to selection bias

In the ROMP subscale for saliva control, we included 2 items of the Drooling Severity and Frequency Scale after modifying it for patients with PD In contrast with dysarthria or dysphagia, drooling in PD is only clinically visible in very severe cases Consequently, assessment is fully based on the subjective response of patients (or caregivers) to questions As a result, we suggest to use the modified DSFS as an initial measure whether and how often diurnal drooling is present and when positive to use the rest of the ROMP-saliva for further measurement

The following limitations of the present study should be taken into account Firstly, the participants in this study were referred to a tertiary centre, so selection bias cannot be ruled out and generalizability seems limited to comparable populations Nevertheless, our study was based on a cohort of community-dwelling patients with PD or a form of atypical parkinsonism, with corresponding distribution of age (mean 64 years) and disease severity (mean UPDRS score 29, median Hoehn & Yahr stage 2 5), comparable with PD populations of other validation studies [38 210] Secondly, while we aimed to include mild as well as severe complaints in every oral motor domain, the results show that most patients in our population only had mild to moderate complaints, explaining the floor effect of 2 subscales However, the current results

justify further validation of the ROMP in a population with more advanced and hospitalized PD patients Also, the outcome of this first psychometric evaluation of the ROMP substantiates further examination of the ability of the ROMP to detect clinically important differences over time (responsiveness)

Another topic for future research might be that PD patients tend to experience intelligibility problems as being less severe than their caregivers Experienced clinicians are familiar with patients claiming "I speak fine, but my wife needs a hearing aid" [214] There is evidence that, similar to limb bradykinesia, hypophonia is partially sensory-based and that PD patients overestimate their volume of speech [214] This is precisely why treatment of hypokinetic dysarthria is usually supported by the use of auditory and visual feedback [215] Therefore, it would be useful to evaluate patient-proxy agreement with the ROMP A low patient-proxy agreement necessitates clear instructions about who is supposed to complete the questionnaire or even the construction of a caregiver-rated version [216]

Conclusions

While allied health interventions that are specific for parkinsonian disorders, like cueing, cognitive movement strategies and improving amplitude of movements are rapidly developing, much work remains to be done to demonstrate effectiveness using good quality randomized trials [48 215] This is also the case for the treatment of oral motor disorders by speech pathologists, but only few outcomes measurements are specific for patients with PD or atypical parkinsonism, especially patient-rated measures The results of this first evaluation of the ROMP show that this is a reliable and valid questionnaire for both clinical and scientific use and in that perspective can prove to be a relevant addition

Acknowledgment

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APPENDIX

ROMP-speech

I. My voice is nowadays:

1. My voice sounds normal.
2. My voice sounds a bit softer or more hoarse than it used to be.
3. My voice is clearly softer or more hoarse.
4. My voice is very soft or hoarse.
5. My voice can hardly be heard.

II. My ability to speak to familiar people:

1. Familiar people find me intelligible as normal; I do not have to repeat.
2. For familiar people I am sometime less intelligible when I am tired or do not pay attention.
3. For familiar people I am frequently less intelligible; I have to repeat multiple times
4. For familiar people I am very often unintelligible, especially when I am tired
5. For familiar people I am usually unintelligible, also when I repeat.

III. My ability to speak to strange people:

1. Strange people find me intelligible as normal; I do not have to repeat.
2. For strange people I am sometime less intelligible when I am tired or do not pay attention.
3. For strange people I am frequently less intelligible; I have to repeat multiple times
4. For strange people I am very often unintelligible, especially when I am tired
5. For strange people I am usually unintelligible, also when I repeat.

IV. The use of my telephone:

1. Using the telephone is no problem for me at all.
2. I use my telephone as I used to do, but I need to pay more attention than I used to do.
3. I have to repeat regularly when I am on the phone.
4. I am reluctant to use the phone, because people do not understand me.
5. Using the phone is impossible for me, because my speech is inadequate.

V. When I start to talk:

1. I can say what I want to say, as easy as I used to do.
2. I sometimes have to think a bit longer than I used to do.
3. I need more time or easily forget what I wanted to say.
4. I need help to formulate my thoughts.
5. I usually do not know what to say and prefer to stay silent.

VI. Having a conversation in a group:

1. I can take part in conversations as always
2. I can take part in a conversation, but I need to pay more attention
3. I can only take part in a conversation when others take into account that I need more time.
4. I can only take part in a conversation when familiar people assist me.
5. I feel left out, because I cannot take part.

VII. How bothered are you as a result of your difficulty with speaking?

1. I have no difficulty with speaking.
2. My difficulty with speaking bothers me a little.
3. I am bothered by my difficulty with speaking, but it is not my priority concern.
4. My difficulty with speaking bothers me a lot, because it is very limiting.
5. Difficulty with speaking is the worst aspect of my disease.

ROMP-swallowing

I. How many times do you choke when eating or drinking?

1. I do not choke at all or not more than I used to do.
2. I choke about once a week.
3. I choke almost daily.
4 I choke about than 3 times a day or during every meal.
5. I choke more than 3 times a day or multiple times during meals.

II. Are you limited during drinking?

1. I can drink liquids as easy as I used to do.
2. I can easily drink liquids, but I choke a little easier than I used to do.
3. I can only drink safely when I concentrate on it
4. In order to drink safely, I need to use a special cup or technique
5. I can only drink safely when I take thickened liquids.

III. Are you limited during eating?

1. I can eat as easy as I used to do.
2. I can eat everything, but it takes me longer time than earlier.
3. I have to avoid tough or hard solid foods (meat, peanuts etc.).
4. I can only eat soft or easy chewable food.
5 I have to use supplemental or non-oral feeding.

IV. Do you have difficulty swallowing pills?

1. I take my pills just like I used to do.
2. I have a little more difficulty to swallow my pills than I used to do.
3. I can only take my pills with apple sauce of a specific technique.
4. Swallowing my pills is quite a struggle nowadays
5. I cannot swallow pills anymore and need another way of taking medication.

V. Does you swallowing difficulty limit you dining with others?

1 Eating with others is no problem for me at all.
2. I dine and drink with others, but I have to take my swallowing difficulty into account.
3. I prefer eating in the presence of familiar people in familiar places.
4. I only eat at home and in the presence of familiar people
5. I can only eat at home and with the assistance of a skilful caregiver.

VI. Are you concerned about your difficulty with swallowing?

1. I do not experience any difficulties.
2. I have some difficulty with swallowing, but I am not concerned about it.
3. I am a little concerned about my difficulty with swallowing
4 I am becoming more concerned about my difficulty with swallowing.
5. I am very much concerned about my difficulty with swallowing.

VII. How bothered are you as a result of your difficulty with swallowing?

1. I have no difficulty with swallowing.
2. My difficulty with swallowing bothers me a little.
3. I am bothered by my difficulty with swallowing, but it is not my priority concern.
4. My difficulty with swallowing bothers me a lot, because it is very limiting.
5. My difficulty with swallowing is the worst aspect of my disease.

ROMP-saliva

I. Do you experience loss of saliva during the day?

1. I do not lose saliva during the day, neither do I feel accumulation of saliva in my mouth.
2. I do not lose saliva, but I feel accumulation of saliva in my mouth.
3. I lose some saliva in the corners of my mouth or on my chin.
4. I lose saliva on my clothes.
5. I lose saliva on my clothes, but also on books or on the floor.

II. How often do you experience increased amounts or loss of saliva?

1. Less than once a day.
2. Occasionally: on average once or twice a day.
3. Frequently: 2 to 5 times a day.
4. Very often: 6 to 10 times a day
5. Almost constantly

III. Do you experience loss of saliva during the night?

1. I do not experience loss of saliva during the night at all
2. My pillow sometimes gets wet during the night
3. My pillow regularly gets wet during the night.
4. My pillow always gets wet during the night.
5. Every night my pillow and other bedclothes get wet.

IV. Does your (loss of) saliva impair your eating and drinking?

1. No, my (loss of) saliva does not impair my eating or drinking.
2. Yes, my (loss of) saliva occasionally impairs my eating or drinking
3. Yes, my (loss of) saliva frequently impairs my eating or drinking.
4. Yes, my (loss of) saliva very often impairs my eating or drinking.
5. Yes, my (loss of) saliva always impairs my eating or drinking.

V. Does your (loss of) saliva impair your speech?

1. No, my (loss of) saliva does not impair my speech.
2. Yes, my (loss of) saliva occasionally impairs my speech.
3. Yes, my (loss of) saliva frequently impairs my speech.
4. Yes, my (loss of) saliva very often impairs my speech.
5. Yes, my (loss of) saliva always impairs my speech.

VI. What do you have to do to remove saliva?

1. I do not have to remove saliva.
2. I always carry a handkerchief to remove possible saliva.
3. I daily use one or two handkerchiefs to remove some saliva
4. I daily need more than two handkerchiefs to remove saliva
5. I need to remove saliva so frequently, that I always keep tissues near me or use a towel to protect my clothes.

VII. Does the loss of saliva limit you in contacts with others?

1. My loss of saliva does not limit me in contacts with others
2. I have to pay attention, but that does not bother me.
3. I have to pay more attention, because I know that others could see me losing saliva.
4. I try to avoid contact when I know that I lose saliva.
5. I notice that others avoid having contact with me because I lose saliva

VIII. Does your loss of saliva limit you in doing activities inside or outside your home (work, hobbies)?

1. My (loss of) saliva does not limit me in activities
2. I have to pay attention when I am busy, but that does not bother me.
3. I have to pay more attention, which is rather effortful.
4. My loss of saliva limits me in being active
5. Due to my loss of saliva, important activities are no longer possible for me

IX. How bothered are you as a result of your (loss of) saliva?

1. I hardly notice loss of saliva.
2. Feeling more saliva or losing it bothers me a little
3. I am bothered by my loss of saliva, but it is not my priority concern
4. My loss of saliva bothers me a lot, because it is very limiting.
5. Loosing saliva is the worst aspect of my disease

4.2

Botulinum toxin A for drooling in Parkinson's disease: a pilot study to compare submandibular to parotid gland injections.

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Abstract

Drooling in patients with Parkinson's disease (PD) is a common and incapacitating problem Several studies have shown the benefit of botulinum neurotoxin (BoNT) to decrease saliva production and complaints of drooling In all studies, BoNT was injected into the parotid glands, with or without the submandibular glands Because the submandibular glands are responsible for up to 70% of the unstimulated saliva during the day, we compared treatment of the submandibular glands alone with treatment of the parotid glands alone, in an open-label pilot study A total of 17 patients, scoring ≥ 3 on the Drooling Severity and Frequency Scale (DSFS) and ≥ 2 on the UPDRS item for drooling, were randomly assigned to either the submandibular group or parotid group Patients in both groups received 150 MU BoNT bilaterally, using ultrasound guidance Outcomes were scores on the DSFS, UPDRS (item for drooling) and a drooling-specific quality of life questionnaire Within-group improvements were significant for the submandibular group, but not for the parotid group Between-group differences showed a trend towards superiority for the submandibular group Injecting the submandibular glands instead of the parotid glands seems a promising approach and larger studies are justified

Introduction

Loss of saliva or drooling is a well recognized problem in Parkinson's disease (PD), with a prevalence of 30% and higher and frequently causing limitations in activities or social embarrassment [217] Several studies have shown that excessive drooling in PD can be treated with injections of botulinum neurotoxin (BoNT) into the salivary glands [218]

Saliva is produced continuously (unstimulated saliva) to lubricate the oral, pharyngeal and oesophageal mucosa and to protect the teeth from acids and oral bacteria The submandibular glands produce up to 70% of this seromuceus saliva, despite the fact that they are half as large as the parotid glands During mastication and bolus formation saliva production is stimulated, in order to moisten and breakdown the food by adding water and a-amylase [219] The parotid glands produce this sereus (watery) saliva upon stimulation and more than half of it is produced during deglutititon [220] Indeed, Sreebny[91] estimated that the unstimulated saliva is reduced by 20% if the parotid glands are non-functional, but by 75% if the submandibular (and sublingual) glands are non-functional Therefore, when aiming to diminish saliva production during the day, it seems more rational to treat the submandibular glands

The effect of BoNT treatment on drooling in PD has been evaluated in open-label and placebo-controlled studies In these studies, injections were given in either the parotid glands alone[218] or simultaneously into both the parotid and submandibular glands However, in a recent study BoNT was injected solely into the submandibular glands of children with cerebral palsy, who suffered from severe drooling, and the investigators found a gratifying response in the majority of patients [221] Stimulated by these findings, we now report the results of a pilot study, aimed to investigate the possible superiority of injecting the submandibular glands over the parotid glands, using botulinum neurotoxin A (BoNT-A)

Patients and methods

PD-patients with drooling symptoms were recruited from our movement disorders out-patient clinic and via an advertisement in the journal of the Dutch Parkinson's Disease Association Inclusion criteria were idiopathic PD according to the UK Brain Bank criteria[211], 2 points or more on the UPDRS subscale drooling, 3 points or more on the Drooling Severity and Frequency Score (DSFS)[139] and a stable regime of anti-parkinson medication over the last two months Seventeen patients (15 men) were included Four had been treated unsuccessfully with anticholinergic medication and none of these patients had previously been treated with botulinum neurotoxin

After written informed consent patients were randomly allocated to either the submandibular group, (injected bilaterally into the submandibular glands) or the parotid group (injected bilaterally into the parotid glands) An independent investigator assigned patients to one of the groups using a list of random numbers Both groups received a total dose of 150 MU BoNT-A (Dysport, Ipsen, 500 units diluted in 2,5 mL 0 9% sodium chloride saline solution), divided over the left and right gland Although the parotid glands are larger than the submandibular glands, we aimed to compare the effect on drooling complaints by using equal amounts of BoNT for both injection sites and thus blocking equal amounts of nerve endings that are responsible for the acetylcholine release We chose to inject 150 MU based on earlier findings that smaller amounts are probably ineffective [222] Treatment was administered via subcutaneous injections (1-mL syringe using a 21-gauge needle) into the glands and all injections were ultrasound-guided

Patients were assessed at baseline, immediately prior to receiving the injection and were re-assessed four weeks after the injections Outcomes measures included the following clinical drooling scales the DSFS[139], which is the sum of a 5-point severity scale and a 4-point frequency scale (total score 2 – 9) , the UPDRS II item for drooling (5-point scale) and a previously described brief questionnaire consisting of four items about the severity of the social consequences of drooling [217] At post-treatment evaluation, patients were also asked to report side-effects, i e swallowing problems or dry mouth Because our inclusion criterion was a score of 2 or more on the UPDRS subscale drooling, we considered a post-treatment score of 1 ("slight but noticeable increase in saliva production, may have night time drooling") or 0 (normal) as a successful outcome The study was approved by the local ethics committee

To conduct the data analyses we used SPSS 12 0 1 (SPSS, Chigago IL, USA) Differences between related samples were calculated using the Wilcoxon signed ranks test, differences between independent samples were calculated with the Mann-Whitney U-test Linear regression was used to calculate the effect sizes of injection location (weighted differences between the two outcomes), with the post-treatment scores as dependent variable and the pre-treatment scores and treatment site as the independent variables Odds ratios were calculated for nominal outcomes A p-value of 0 05 was used to determine significance for all statistical analyses

Results

Patient characteristics at baseline did not differ between both treatment groups (Table 1) In the submandibular group the within-group improvement was significant for two out of three outcomes (DSFS p = 0 04, social consequences p = 0 02) In contrast, for the parotid group the within-group improvement was not significant for any of the three outcome measures All differences between the submandibular and parotid group were in favour of the submandibu-

lar group, but this difference was not statistically significant. Also, linear regression showed small but statistically insignificant better outcomes on all scales in favour of the submandibular injections. Four (50%) of the patients in the submandibular group were positive responders (defined as post-treatment score of 0 or 1 for the UPDRS item for drooling, against 2 (22%) in the parotid group (OR = 3.5; 95% CI 0.43 – 28.45). Total response rate was 35% (6/17).

Table 1. Demographic data and results pre- and post treatment.

	pre	post	P^b	pre	post	P^b	p^c	
N	8	8		9	9			
age (y)	66 (7.7)			69 (6.0)			0.53	
disease duration (y)	11 (8.8)			15 (8.8)			0.78	
drooling duration (y)	2.6 (2.8)			3.9 (3.6)			0.13	
UPDRS	42.0 (9.5)			41.9 (11.8)			0.69	
DSFS[d]	6.5 (1.1)	4.8 (1.9)	0.04	7.0 (1.2)	5.9 (2.4)	0.13	0.54	- 0.59 (-2.86 – 1.69)
UPDRS-drooling[e]	2.6 (0.5)	1.6 (1.4)	0.12	2.9 (0.8)	2.4 (1.3)	0.16	0.48	- 0.63 (-2.16 – 0.90)
social consequences[f]	11.0 (3.5)	8.8 (3.0)	0.02	10.6 (3.6)	10.0 (3.6)	0.75	0.19	- 1.80 (-4.49 – 0.89)
UPDRS < 2[e]		4 (50%)			2 (22%)			

Between brackets: standard deviations.
[a] mean difference in improvement against baseline, between submandibular and parotic group, adjusted for duration of PD and duration of drooling
[b] p-value of change against baseline
[c] p-value of comparison between post treatment scores of submandibular and parotic group
[d] DSFS: scale 2 – 9 (2 = no drooling)
[e] UPDRS-drooling: scale 0 – 4 (0 = no drooling)
[f] social consequences: score 4 – 16 (4 = no complaints)

Some side effects were reported. Two patients complained of transient swallowing difficulties, one after 150 MU in the submandibular glands and one after 150 MU in the parotid glands. Remarkable dry mouth (xerostomia) during the night or at some time during the day was reported 3 times after submandibular injections (37%) and once after (11%) parotid injections (OR = 4.8; 95% 0.39 – 59.90).

Discussion

This is the first botulinum toxin study in PD comparing injections in the submandibular glands alone with injections in the parotid injections alone This specific comparison was also recently recommended in review of the use of botulinum toxin in the management of sialorrhoea [223] The results of our pilot show a trend in favour of the superiority of injections in the submandibular glands This demonstrates that only reducing the saliva secretion of the submandibular glands, which produce the main part of the unstimulated saliva throughout the day, indeed could be an important option in PD The statistical insignificance of the differences is most likely due to the small sample size, therefore larger controlled studies are required to find definite results In all prior studies in PD, either the parotid glands were injected or – in order to administer a larger total amount of botulinum neurotoxin – both the parotid glands and the submandibular glands Arguments to support this treatment strategy are that the parotids are the largest and most easily accessible salivary glands and injecting the parotid glands may not necessitate ultrasound guidance [224] Others did not inject the submandibular glands because of the risk of xerostomia Indeed, local application of BoNT only blocks the cholinergic component of the saliva production, which is responsible for the discharge of fluid At the same time the production of proteins and mucins remains intact [225] However, Jongerius et al ,[221] who injected solely the submandibular glands in children with cerebral palsy, did not report xerostomia as adverse effect In the present study, three patients in the submandibular group complained of dry mouth, against only one in the parotid group In general, the remaining salivary glands seem to produce enough fluid to sustain basal secretion,[225] but in future studies with PD-patients this side-effect should be evaluated more thoroughly

Compared to previous (placebo-controlled) studies, who used BoNT doses ranging from 150 MU until 300 MU[218], our dose of 150 MU for one pair of glands already seemed adequate When taking into account a ratio of 3 1 for Dysport® versus Botox®, Lagalla et al [224] e g used 300 MU total in the parotid glands Using the same definition of a successful outcome ('disability-free' or < 2 on the UPDRS-subscale drooling) they found a response rate of 38% (6/16) in their treatment group The present study showed a comparable response rate of 35% (6/17) after 150 MU

We should note that many patients (in the present study 47%) did not benefit from the BoNT-injections There is increasing evidence to suggest that drooling in PD is not the result of hypersalivation or primary sialorrhea, but must be acknowledged as secondary sialorrhea [79] In other words, drooling in PD appears to be caused mainly by a combination of pooling of saliva in the mouth (due to oral dysphagia or decreased frequency of swallowing), diminished lip closure and antecollis, all typical aspects in many patients with PD

We therefore suggest that non-responding patients might be treated more effectively using techniques that improve these underlying impairments, including oral-motor and swallowing training. Trials to demonstrate the efficacy of these latter interventions are underway.

In summary, injecting the submandibular glands instead of the parotid glands seems a promising approach and larger studies seem justified to further evaluate the merits of this treatment strategy.

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Chapter 5
General discussion, summary and conclusion

5

The purpose of this thesis was to answer the following questions

1 What causes drooling in Parkinson's disease (PD)?
2 What is the impact of drooling in PD?
3 How prevalent are drooling and dysphagia in PD?
4 How can drooling in PD and its severity be assessed?
5 What are the treatment options for drooling in PD?

This chapter summarizes and discusses the main findings of this thesis, and places these results into perspective with respect to the present literature Note that this thesis deals with patients with PD only (except in Chapter 8) However, we feel that many of the findings – and in particular most treatment recommendations reviewed in this chapter – are also applicable to patients with atypical parkinsonism, realizing that these latter patients may have specific complications that can further challenge the clinical management [32]

1. What causes drooling in Parkinson's disease?

In Chapter 2 we used an enriched cohort study (15 droolers versus 15 non-droolers) to test the hypothesis that the cause of diurnal drooling in PD is multifactorial, resulting from a combination of the following factors decreased frequency of saliva swallowing, causing pooling of saliva in the mouth, unintentional mouth opening due to hypomimia, making accumulated saliva more likely to drip from the mouth, stooped posture with a dropped head, allowing gravity to aggravate the dripping of saliva, reduced swallowing ability, resulting in inefficient saliva collecting and removal by swallowing, and difficulty with nose-breathing ability because the inability to breathe through the nose would force patients to resort to mouth breathing, which in turn may contribute to lip parting and thereby to drooling

The results showed that drooling has a multifactorial pathophysiology, with hypomimia (adjusted for age and disease severity) as the best predicting factor Advanced PD, dysphagia and male sex were the other main contributing factors In contrast, stooped posture, decreased swallowing frequency and difficulty with nose-breathing did not contribute to drooling We will next discuss these findings in more detail

Table 10.1. The subscale Facial expression of the UPDRS (used in this thesis) compared to the MDS-UPDRS (to be used in the future).[37]

0	Normal	Normal facial expression
1	Slight hypomimia, could be poker face	Minimal masked facies manifested by decreased frequency of blinking
2	Slight but definite abnormal diminution in expression	In addition to decreased eye-blinking frequency, masked facies present in the lower face as well, namely fewer movements around the mouth, such as less spontaneous smiling, but lips not parted
3	Moderate hypomimia, lips parted some of time	Masked facies with lips parted some of the time when the mouth is at rest
4	Masked or fixed face, lips parted 1/4 of inch or more with complete loss of expression	Masked facies with lips parted most of the time when the mouth is at rest

That hypomimia, which includes involuntary mouth opening at rest (see Table 10 1), was strongly associated with drooling is a new finding We confirmed the important contribution of hypomimia in a larger cohort (see Chapter 6) Why patients are inclined to have such parted lips is unclear, but there is some evidence that jaw proprioception in PD patients is lower compared to healthy controls, suggesting that PD patients are less aware of having an open mouth [226]

Drooling can already be present before onset of the motor manifestations of PD (see e g Chapter 3), but our results underscore that it usually starts several years into the disease, and that drooling becomes more prevalent with advancing disease This was also demonstrated in Chapter 6, where we showed that drooling is especially common in patients with more advanced PD

We found that droolers are worse swallowers than non-droolers in terms of swallowing capacity and functional intake of food, independent of disease severity This may be associated with tongue bradykinesia,[123 124 117] but also with reduced sensation in the hypopharynx and larynx, resulting in silent aspiration of saliva [226 227] However, unlike the case described in Chapter 4, none of the participants in our studies had severe dysphagia, because we were unable to recruit patients with Hoehn & Yahr stage 5 with almost constant and profuse drooling

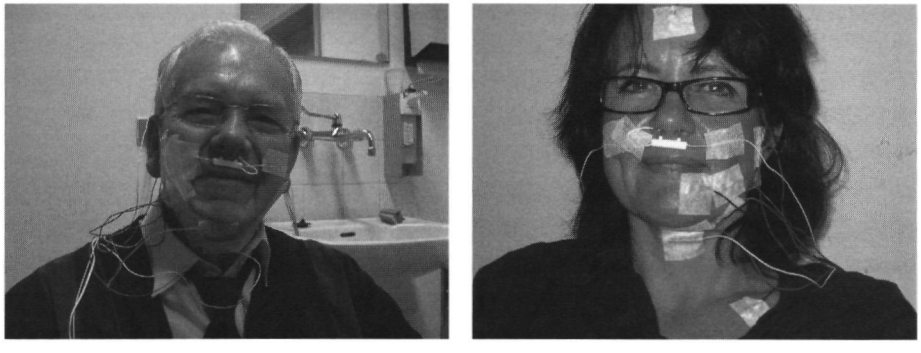
Male sex was another factor associated with hypomimia and drooling The study with 104 patients in Chapter 6 showed this male predominance when comparing non-droolers (excluding the patients who only experience accumulation of saliva, which we called pre-droolers, see paragraph 3) with droolers (37% men vs 69% men), but not when the non-droolers and pre-droolers were taken together (64% vs 69%) This suggests that men do not have an increased risk for drooling than women The overall ratio of men to women was 2 1 in our study, but this reflects the gender distribution of patients who visit our Parkinson centre [131]

The explanation of this gender difference may be that men are either more willing or are being more stimulated by their spouse to cooperate in scientific experiments.[116;228;229]

The factors that did not contribute to drooling are also interesting to discuss. Although droolers were more prone to have an open mouth, mouth breathing was rare and was not associated with drooling. And posture, which is believed to have multifactorial pathophysiology,[230] is more severely stooped in droolers, but factor analysis showed that posture was a part of disease severity and did not contribute to drooling independently.

An unexpected finding was the outcome of the swallowing frequency measurements (see Figure 10.1). The droolers did not swallow less often than non-droolers, and in fact even tended to swallow more often (on average 5 times more during a 45-minute observation period; 95% -5.0 – 16.3). This can be explained by the fact that droolers likely want to prevent drooling (and indeed, none of them lost any saliva during the assessments, except for one), and to achieve this patients must compensate for their reduced swallowing capacity by swallowing more frequently. This compensatory mechanism resembles gait hypokinesia in PD, where the reduced stride length is compensated for by an increased cadence (steps per minute).[127]

Figure 10.1. Two participants with surface electrodes and airflow sensor in place to measure swallowing frequency (with permission).



Our experiment also points to a possible influence of cognition on drooling. Most patients drool mainly when their attention is needed for a specific task, such as reading, typing, dressing, etc. Under such circumstances, timely switching to (attentional) saliva swallowing may become too difficult and swallowing frequency may decrease. The functions of the basal ganglia are not fully understood, but there is evidence demonstrating that PD patients have difficulties with switching between tasks,[231-233] so we speculate that this is also true for paying attention to the urge to swallow saliva during activities ('dual tasking'). This implies that if clinicians or researchers wish to demonstrate a reduced swallowing frequency, covert monitoring is needed and attention has to be distracted.

2. What is the impact of drooling in Parkinson's disease?

Although drooling is frequently reported (see also next paragraph), information about the consequences of drooling on daily and social functioning was thus far absent To better appreciate the impact of drooling in PD, we used an extensive drooling questionnaire (Chapter 3), which was completed by 63 patients with drooling Most patients (73%) scored drooling as mild or moderate, but a quarter found drooling to be severe and incapacitating Furthermore, the results showed that drooling can have serious physical and emotional consequences and a negative impact on social functioning, especially in patients with severe drooling An extreme, but fortunately rare consequence was displayed by a single patient with severe skin irritation around the mouth and marked saliva stains on his shoes, all caused by an uncontrolled flow of saliva (CHAPTER 4) Our findings also emphasize that many patients are currently being undertreated, because 40% of our respondents expressed a wish to be treated, but only a minority of them had actually received dedicated treatment to decrease drooling Importantly, our findings confirm that although drooling may be difficult to observe in the clinic, any subjective complaints should be taken very seriously History taking should therefore be detailed and specific enough to grasp the full impact of drooling for every individual patient

3. How prevalent are drooling and dysphagia in Parkinson's disease?

While drooling is a frequently reported symptom, prevalence rates vary widely and an accurate estimate was lacking Therefore, we performed a systematic review and meta-analysis (Chapter 5) Eight studies met our inclusion criteria The meta-analysis showed that the pooled prevalence estimate with random effect analysis of drooling is 56% (95% CI 44–67) for PD patients and 14% (95% CI 3–25) for healthy controls, the pooled relative risk (RR) was 5 5 (95% CI 2 1–14 4) (CHAPTER 5) [111] The heterogeneity of the studies was mainly caused by differences in definition of drooling The highest prevalence rates included accumulation of saliva and nocturnal drooling, where others only investigated diurnal drooling Based on these findings we recommended to report drooling in future studies in more detail, considering severity or frequency and nocturnal versus diurnal complaints

We used this recommendation in a subsequent study to further analyze the severity and prevalence of drooling (CHAPTER 6) We studied 104 consecutive PD patients who visited our Parkinson centre Our assumption was that accumulation of saliva or mere nocturnal saliva loss is an intermediate stage leading up towards the most severe condition of diurnal drooling, as this is identified by the MDS-UPDRS [37] For this purpose, we categorized patients into 'non-droolers', 'pre-droolers' (only accumulation of saliva or only nocturnal drooling) and 'droolers' (diurnal drooling with or without nocturnal drooling) All disease characteristics and oral-facial characteristics showed a clear trend of increasing difficulty from non-droolers to pre-droolers to droolers This classification divided our cohort into 29% non-droolers, 43% pre-droolers and 28% droolers So, when taking all complaints together the prevalence rate is 71%, which is

similar to the rates that are usually cited in publications [78 79 116 156] But only about a quarter of patients has actual drooling This latter figure seems more in agreement with observations in everyday clinical practice The consequences of these findings for the management of drooling will be discussed in paragraph 5

In Chapter 7 we showed in a review based on twelve studies that subjective dysphagia in PD occurs in 35% (95% CI 28-41) of home-living patients When subclinical dysphagia signs (based on swallowing assessments) are included, the prevalence rate is twice as high (82%, 95% CI 77-87) Here the heterogeneity across studies was best explained by disease severity those studies with the highest proportion of patients with late stage PD also reported the highest prevalence of dysphagia Further, the distribution of the ROMP scores (a rating scale for drooling severity, see next paragraph and CHAPTER 8) also shows that swallowing complaints (39%) and saliva complaints (43%) are less frequent than speech complaints (72%) While the prevalence rates of speech impairment in PD are similar between subjective (68%) and objective measures (71%),[165] the large difference between subjective dysphagia and subclinical signs of dysphagia was an unexpected finding, suggesting underreporting Overall, these rates justify a proactive clinical approach to dysphagia, using structured interviews or patient-rated questionnaires, particularly in light of the serious clinical consequences in advanced PD, including drooling and aspiration pneumonia A final general remark is that hospitalized PD patients were usually excluded from these prevalence studies, so the overall rates of drooling and dysphagia might be even higher than what was reported

4. How can drooling in Parkinson's disease and its severity be assessed?

In CHAPTER 8, we describe the development of the Radboud Oral Motor inventory for Parkinson's disease (ROMP), because no PD specific questionnaires were available in the oral motor domains (i e speech, swallowing and saliva control) In clinical practice, the patient's response using the ROMP is used as a starting point for further investigation [9] But our clinimetric evaluation showed that the scores on the total ROMP and its three subscales (ROMP-speech, ROMP-swallowing and ROMP-saliva) could also be summarized as a severity score We also showed that the ROMP is a reliable and valid instrument to evaluate patient-perceived problems with speech, swallowing, and saliva control, both in patients with PD and atypical parkinsonism When focusing on the assessment of drooling, the results showed that the ROMP-saliva had excellent reproducibility (ICC = 0 90) and internal consistency (Cronbach's α = 0 94), moderate to substantial construct validity against UPDRS subscales (r = 0 36 to 0 82) and that the mean scores differentiated between clinically different subgroups In other words, this subscale is sufficiently reliable and valid for scientific use as a continuous scale in between-group evaluations However, there is no minimal clinically important difference (MCID) available yet to judge whether an individual patient has improved or worsened

In addition to using the ROMP, several contributing factors to drooling identified in this thesis

should be observed or tested too. Hypomimia can be observed with the MDS-UPDRS subscale for Facial Expression (see Table 10.1) or the Mouth Opening scale (see Chapter 2). Swallowing complaints can be investigated using the ROMP-swallowing (Chapter 8), while swallowing capacity can be observed and tested (see CHAPTER 1) According to our experience, also the ability to swallow saliva upon request is relevant If a patient is unable to swallow saliva or a small amount of liquid when requested, it is probably useless to focus on improving saliva swallowing. During all of these assessments, the examiner should take into account whether the patient is in an *on*-state or *off*-state (and preferentially examine the patient in both conditions).

5. What are treatment options for drooling in Parkinson's disease?

The most commonly used technique to reduce saliva production is injection of the salivary glands with botulinum neurotoxin.[108] Because the submandibular glands produce the main part of the unstimulated saliva throughout the day, we investigated the possible superiority of injecting the submandibular glands over the parotid glands, using botulinum neurotoxin A (Chapter 9) The results of this pilot showed a trend in favour of injections into the submandibular glands This demonstrates that reducing saliva secretion of the submandibular glands could potentially be the preferred approach. We acknowledge that this was only a pilot study, but new studies addressing this issue are underway.[234]

Because drooling is a multifactorial motor disorder, behavioral treatments like cueing or movement strategies are also likely to be useful Although this thesis does not include any other studies on the treatment of drooling, we conclude this chapter with an overview of treatment options, based on our findings about the pathophysiology of drooling (Chapter 2) and drooling stages (Chapter 6), evidence from other behavioural treatment for PD,[46] the Dutch Multidisciplinary Guideline for Parkinson's disease (p 165)[17] and our own clinical experience.

We will divide the management of drooling into the following two main categories:

- *behavioral treatment* education, compensation and training, by a speech therapist;
- *saliva reduction*, when behavioral treatment is no longer successful, by a physician

Behavioral treatment

Education

It is vital to begin with the normal physiology of saliva production and swallowing. Asking whether a patient experiences accumulation of saliva (e.g. when using the ROMP-saliva) already suggests abnormal production and that notion should be corrected. In our experience, the explanation to patients that saliva production is normal, that saliva is a necessary fluid needed to keep the mouth moist and healthy, and that saliva swallowing occurs once every few minutes (but usually unconsciously), may already be helpful in mildly affected cases. See examples described in cases #1 and #2.

Case #1

A 76-year-old woman with PD (Hoehn & Yahr stage 3). Speech, conversation and swallowing were unremarkable, but drooling was a severe complaint since two years. She received information about the physiology of saliva swallowing and was instructed to swallow every time she felt saliva accumulating in her mouth. Because of the severity of her complaint, she was asked to use a drooling diary to observe in more detail when drooling occurred at home. During the very first telephone call to check whether she had managed to use the diary, she reported that her problem had solved already. She had applied the instructions and was relieved to find out that she could control her saliva flow relatively easy.

Case #2

A 81-year-old man with left-sided resting tremor, very mild hypokinetic dysarthria but no swallowing complaints, lost saliva several times a day, since half a year. He had slightly parted lips all the time. He was instructed to try and keep his lips closed and breath more consciously through his nose, and also to swallow saliva as soon as he felt it accumulating in his mouth. During the second treatment session he reported that he was able to keep his lips closed for most of the day when he focussed on nose breathing. During the third session he indicated that he no longer lost saliva, because with his mouth closed, it was much easier to swallow when he felt saliva pooling in his mouth.

Compensation

Several behavioural compensation techniques have proved to be effective for PD patients [9 49 50]. Treatment should be tailored to the patient's specific complaints. In order to find the right compensation, the speech therapist and the patient together need to analyze when exactly drooling occurs. After the patient (or caregiver) has kept a drooling diary for a week, a pattern may appear. A frequent outcome is losing saliva while standing up from a chair or putting on trousers, because the associated stooped posture allows gravity to aggravate the dripping of saliva. When a physiotherapist teaches a patient how to rise from a chair with a cognitive movement strategy,[50] is it relatively easy to include the instruction "Close your mouth and swallow", before standing up. This can prevent saliva loss during this activity. See also the examples in cases #3 and #4.

Another option is to use tactile, visual of audible cues, which are known to be effective for treating gait impairment in PD [235] There is ongoing research in the UK with the development and evaluation of a wrist-worn auditory cueing device to help trigger swallowing, and the first pilot results seem promising [236]

Finally, there is a hypothesis that gum chewing could be helpful to initiate swallowing more often One study showed that swallowing frequency was significantly higher during and 5 minutes after gum chewing, as compared to baseline [237] However, patients with dysphagia were excluded, and whether the included patients had drooling complaints was not reported Moreover, chewing stimulates saliva production, so how PD patients with (pre)drooling would respond to this intervention remains unknown

Training

The most successful rehabilitation techniques in speech-language pathology with PD patients are based on training, like the Lee Silverman Voice Treatment (LSVT)[238] or the Pitch Limiting Voice Treatment (PLVT)[239] to overcome hypokinetic speech [9] Another training technique called expiratory muscles strength training (EMST) was initially developed to improve strength of coughing, but has now been shown to also improve swallowing efficiciency in PD [74] This techniques might also be helpful for PD patients with drooling, when this is clearly related to dysphagia

Case #3

A 67-year-old man with PD since 10 years and camptocormia He had mild complaints about his speech, hardly any difficulty with swallowing, but mild difficulty with saliva control He reported that his dentist always complained about his excessive saliva secretion during dental treatment, but he explained that this always had been the case But recently he started to feel saliva accumulating in his mouth, especially while speaking And a few times a day he felt saliva in the corners of his mouth Swallowing assessment revealed mild signs of dysphagia (slightly reduced speed of eating and drinking, no aspiration risk and normal pill swallowing) and his speech was clearly hypokinetic He received education about the physiology of saliva control and the instruction to stop speaking when he felt saliva accumulating, to swallow firmly and then continue to speak At evaluation after two weeks he reported that saliva control was no problem anymore

Case #4

A 87-year-old man with PD (Hoehn and Yahr stage 3) complained of diurnal drooling at home with stains on the floor, several times a day After keeping a drooling diary for a week, it became clear that he mainly drooled in the morning while putting on his socks and shoes, which took him at least 10 minutes After explaining that bending over for several minutes was simply too challenging to keep his mouth closed and too swallow a few times, he agreed to find a compensation He was instructed and trained to swallow firmly everytime before bending over And an occupational therapist was asked to provide him with an aid to put on his socks and shoes much quicker This proved to be sufficient to prevent drooling for the time being Soon after he was hospitalized with a broken hip After six months of rehabilitation he came for a follow-up visit of his drooling He reported that he no longer drooled, because his wife had now taken over putting on his shoes and socks!

Saliva reduction

Several treatments are available to reduce saliva secretion. The aim of the treatment is to achieve hyposalivation (measured objectively using sialometry). A subjective sensation of a dry mouth (xerostomia) is high on the list of side-effects. These two signs (hyposalivation and xerostomia) are not necessarily , because individuals can have xerostomia without hyposalivation and vice versa,[91] but the two are obviously related. Again, treatment should be individually tailored, based on the severity of the complaints, while the response of the patient is carefully monitored.

The treatment options are, briefly:[108,109,115,234,240]

Anticholinergic drugs (scopolamine, amytriptyine) are used to reduce saliva production, but can have side-effects, like nausia or drowsiness.[108,115] Locally applied drugs are less likely to cause these side-effects and sublingual atropine (1 drop twice daily)[241] and oral glycopyrrolate (1 mg 3 times daily) are effective in about a third of PD patients.[116]

A more invasive, but still a relatively simple and safe procedure is injection of the salivary glands with botulinum-neurotoxin injections, under ultrasound guidance. The seemingly best approach is to start with injections into the submandibular glands with 75 MU Dysport or 25 MU Botox per gland using ultrasound guidance.[224,242] When insufficient, the amount can be increased (see Table 10.2), or the parotid glands are also injected.

Salivary glands are very sensitive to ionizing radiation, as is known from radiotherapy of carcinomas in the head-neck area.[243] Limited radiation dosages (e.g. 2 fractions of 6 Gy) can be used to reduce salivation and lessen the risk of drooling in PD.[157] There is an ongoing study comparing the effects and side-effects between radiation of the submandibular versus the parotid glands.[244]

Finally, a much longer lasting effect can be established using ligation of the salivary ducts. This is applied in children with severe drooling,[245,246] but we are unaware of studies with PD patients.

Table 10.2. Suggested minimal and maximum amounts of botulinum-neurotoxin.

per gland	*total*	*per gland*	*total*
75 MU	150 MU	25 MU	50 MU
150 MU	300 MU	50 MU	100 MU
145 submandibular + 80 parotid	450 MU	75 MU	150 MU

Based on the studies by Lagalla et al.[224] and Mancini et al.[242]

Case #5

A 74-year-old man with PD and profuse drooling He did not have stains on his clothes when he entered the examination room, but within 5 minutes he started losing some saliva His speech was clearly hypokinetic, but still intelligible He was able to swallow upon request, but only a few times He had increasing difficulty to keep his mouth closed When saliva was visible behind his lower lip he was able to close his mouth and swallow when asked, but this was hardly effective, because his swallowing was too weak Saliva kept pooling in his mouth and only occasionally he was able to swallow effectively After a few minutes he had to start collecting and swallowing saliva again with even greater effort It was clear that with strict instruction and verbal cueing his saliva control could only be improved partially Moreover, it is not realistic to have someone instructing him to swallow saliva timely every time all day In conclusion, he was referred to medical treatment to reduce his saliva production, using botulinum toxin injections

Case #6

A 70-year-old man with hypokinesia and rigidity since 4 years and early cognitive deterioration, paranoid behaviour and hallucinations, diagnosed with probable Lewy body disease Evaluation of speech and swallowing revealed that drooling was a major complaint, with maximum scores for diurnal and nocturnal drooling, as identified using the ROMP-saliva Analysis of activities at home showed that drooling occurred more than 10 times a day, while sleeping, but also during eating, talking, dressing, gardening etc However, drooling was not at all visible during consultation Also, swallowing proved to be completely normal when he drank coffee and ate a sandwich Education was provided and several compensations were tried These seemed to help a little, but in the end this approach proved to be unsuccessful, because he was mainly dependent on the cues of his wife, which he found difficult to accept as a result of his paranoid behaviour So behavioural treatment was insufficient and medical treatment to reduce salivation was suggested

Future perspectives

With the results of this thesis, we now better understand the phenomenology and epidemiology of drooling in PD, and also how drooling can be assessed But the treatment of drooling still requires more systematic evaluation

In our study, swallowing frequency was not reduced in droolers, presumably because during our experiment droolers were able to prevent drooling by swallowing frequently enough We suspect that droolers, when they do loose saliva, do not swallow as often as they should do New approaches like an auditory cueing device are based on this assumption [236] To prove that a low swallowing frequency does contribute to drooling, covert monitoring is needed to reveal any changes in swallowing frequency when patients start to drool

Nocturnal drooling is also a prevalent complaint in PD, but our understanding of this mechanism is very limited Is swallowing frequency also more reduced in nocturnal droolers, compared to non-droolers and healthy individuals? Are parted lips also the main cause during the night? Or is nocturnal drooling related to sleep disorders? Only observation and (video) polysomnography can reveal what happens with saliva swallowing during the night

After we started to develop the ROMP, no new severity scales or questionnaires on oral motor functioning in PD have been published or presented at congresses So if this is a useful instrument, it should also be evaluated in other PD populations, like hospitalized patients Treatment

studies are needed to estimate minimal clinically important differences (MCID), to make the summarized scores relevant for individual comparisons And finally, the ROMP is potentially a more sensitive measure to evaluate the effectiveness of anti-parkinson medication on speech, swallowing or drooling

Systematic evaluations of behavioral techniques as discussed above are currently absent, including the duration of any positive effects, so dedicated trials are needed to improve the credibility of these approaches The saliva reduction techniques are diverse, but one side-effect seems to be have been overlooked until now Saliva is necessary to protect the teeth against decay (caries) and to prevent oral infections (see Chapter 1), which means that hyposalivation can have negative consequences for oral health and dental condition [247 248] Many elderly patients nowadays still have their own teeth, while dental condition is already decreased in advanced PD patients [249] This suggests that dental condition should be measured as a side-effect in future studies on saliva reduction to treat drooling For these patients more frequent dental visits may then be warranted

Finally, we have shown that drooling is a multifactorial disorder and that several treatment options are available, but it is unknown whether patients receive these treatments when they need it Pending the outcomes of controlled trials, professionals and patients should be aware of the current best practice, through publications, continued education, multidisciplinary cooperation in ParkinsonNet (www parkinsonnet nl, see Chapter 1) and patient-based social media, like MijnZorgnet (www mijnzorgnet nl)

Chapter 6
Nederlandse samenvatting

6

Hoofdstuk 1 geeft een overzicht van de ziekte van Parkinson, slikken en slikstoornissen, speekselproductie en speekselverlies

Ongeveer 50 000 mensen in Nederland hebben de ziekte van Parkinson, een neurodegeneratieve ziekte die wordt gekenmerkt door motorische en niet-motorische stoornissen De motorisch stoornissen bestaan uit hypokinesie (kleinere bewegingen van handen, armen, benen, gelaat tot en met de stembanden), spierstijfheid, tremoren en houdingsinstabiliteit De niet-motorische kenmerken zijn autonome stoornissen (obstipatie), cognitieve stoornissen (traag reageren, woordvindingsproblemen), slaapstoornissen en neuropsychiatrische stoornissen (depressie, hallucinaties) Deze zijn minder zichtbaar, maar op den duur het meest verantwoordelijk voor de afname van de kwaliteit van leven Slikstoornissen (moeite met slikken van vocht of voeding en verslikken) komt bij veel neurologische ziekten voor, waaronder de ziekte van Parkinson Ook kunnen parkinsonpatienten last hebben van speekselverlies (kwijlen), maar over de oorzaken, ernst en behandeling was tot nu toe onvoldoende bekend

Het doel van dit proefschrift was het vinden van antwoorden op de volgende vragen

1 Wat veroorzaakt speekselverlies bij parkinsonpatienten?
2 Wat zijn de gevolgen van speekselverlies?
3 Hoe vaak komen speekselverlies en slikstoornissen voor bij parkinsonpatienten?
4 Hoe kan speekselverlies en de ernst ervan het beste worden vastgesteld?
5 Wat zijn de behandelmogelijkheden?

Dit hoofdstuk geeft een samenvatting van de antwoorden

1. Wat veroorzaakt speekselverlies bij parkinsonpatiënten?

In **hoofdstuk 2.1** hebben we bij 15 parkinsonpatienten met en 15 zonder speekselverlies vergeleken om de hypothese te toetsen dat de oorzaak van speekselverlies multifactorieel is en bestaat uit de combinatie van de volgende factoren minder vaak slikken waardoor speeksel ophoopt, openhangende mond als onderdeel van maskergelaat waardoor speeksel makkelijker de mond uitloopt, voorovergebogen houding waardoor zwaartekracht van invloed wordt, minder efficient speeksel verzamelen en slikken en moeite met neusademen, waardoor de mond nog makkelijker open blijft staan

Het resultaat was dat maskergelaat of hypomimie, waar een openhangende mond onderdeel van is de enige onafhankelijke voorspeller is van speekselverlies En maskergelaat is geassocieerd met ernstiger parkinson, slikstoornissen en man-zijn Dat een open mond in rust geassocieerd is met speekselverlies vonden we ook in een cohortonderzoek met 104 parkinsonpatienten in **hoofdstuk 3.2** We vermoeden dat parkinsonpatienten die eenmaal ernstiger maskergelaat hebben, niet goed meer waarnemen dat hun mond open hangt en daarom hun mond niet spontaan sluiten

De resultaten laten zien dat de kans op speekselverlies toeneemt met de ernst van de ziekte Dat speekselverlies is geassocieerd met slikstoornissen is volgens verwachting, maar geen van

de patienten had een ernstige slikstoornis Aan de andere kant was het evenmin gelukt om parkinsonpatienten met zeer ernstig speekselverlies, die vermoedelijk vrijwel niet meer slikken, in ons onderzoek mee te nemen
In deze relatief kleine studie in (**hoofdstuk 2.1**) hadden mannen 6x meer kans op speekselverlies dan vrouwen, maar in een grotere studie (**hoofdstuk 3.2**) vonden we dat verschil niet, dus we kunnen niet zondermeer zeggen dat speekselverlies meer bij mannen dan bij vrouwen voorkomt

Er waren ook factoren die niet bleken te verschillen Ademen door de mond kwam nauwelijks voor, en de mate van voorovergebogen houding was significant verschillend tussen de groepen, ook na adjusteren voor leeftijd en ziekte-ernst, maar ging na factoranalyse op in de totale score voor ziekte-ernst (UPDRS)
Een onverwachte bevinding was de uitkomst van de polygrafische metingen van de spontane slikfrequentie We hadden van alle 30 patienten met oppervlakte EMG gedurende drie kwartier elke slikbeweging vastgelegd Maar de slikfrequentie bleek niet te verschillen, sterker nog de patienten met klachten over speekselverlies hadden de neiging om juist vaker te slikken Op één na verloor geen enkele patient speeksel tijdens het onderzoek, dus ze waren in staat om tijdens het onderzoek voldoende vaak te slikken ('observer paradox') en moesten waarschijnlijk vaker slikken om te compenseren voor hun slikstoornis Dat is vergelijkbaar met het lopen van parkinsonpatienten die een hogere stapfrequentie hebben om te compenseren voor hun kleinere staplengte Net als bij onderzoek naar loopstoornissen van parkinsonpatienten zou het meten van de speekselslikfrequentie dus beter kunnen gebeuren zonder dat de patient in de gaten heeft dat hij geobserveerd wordt

2. Wat zijn de gevolgen van speekselverlies?

Om te onderzoeken wat de gevolgen zijn van speekselverlies en hoe parkinsonpatienten die ervaren hebben we 63 patienten, die in een eerdere vragenlijst hadden aangegeven dat ze last hadden van speekselverlies, een uitvoerige vragenlijst laten invullen (**hoofdstuk 2.2**) De meeste patienten (73%), vonden hun speekselverlies licht of matig en 27% vond het een ernstig tot zeer ernstig probleem Speekselverlies kan praktische consequenties hebben, zoals meer dan 1x per dag een nieuwe zakdoek nodig hebben om speeksel weg te vegen (62%) Maar ook sociale en emotionele consequenties, significant vaker gescoord door de patienten met ernstige klachten , zoals minder zelfvertrouwen (88%) en zelfs vermijden van contact door anderen (41%)
Soms zijn de gevolgen nog ernstiger zoals in **hoofdstuk 2.3**, waarin we een uitzonderlijke patient beschrijven met dermate ernstig speekselverlies en moeizaam slikken dat de huid rond zijn mond en kin ernstig was beschadigd en zijn schoenen zo vol vochtvlekken dat hij elke paar maanden nieuwe schoenen nodig had De resultaten van de vragenlijst laten tevens zien dat er sprake is van onderbehandeling, omdat 40% behandeld zou willen worden, terwijl maar enkele

patienten behandeling kregen Bovendien maakt het duidelijk dat klachten over speekselverlies goed uitgevraagd moeten worden om zich te krijgen op de individuele gevolgen voor de patient

3. Hoe vaak komen speekselverlies en slikstoornissen voor bij parkinsonpatiënten?

Hoewel speekselverlies in veel studies wordt genoemd als een problemen waar driekwart van de parkinsonpatienten last van heeft, lopen de getallen over het voorkomen van speekselverlies sterk uiteen In een systematisch review (**hoofdstuk 3.1**) hebben we studies vergeleken waarin de prevalentie van speekselverlies is te vinden op basis van vragenlijstonderzoek De getallen varieerden van 32 tot 74% De gepoolde prevalentie (met random effect analyse) was 56% (95% BI 44-67) voor parkinsonpatienten en 14% (95% BI 3-25) voor gezonde proefpersonen Het relatieve risico is 5 5 (95% BI 2 1-14 4) De heterogeniteit tussen de studies werd voornamelijk bepaald door verschillen in definitie en frequentie In **hoofdstuk 3.2** doet we verslag van ons eigen onderzoek onder 104 parkinsonpatienten, die we verdeelden in patienten zonder klachten (non-droolers), patienten met alleen een gevoel van speekselophoping of alleen speekselverlies 's nachts (pre-droolers) en patienten met daadwerkelijk speekselverlies overdag (droolers) De groepen verschilden significant in ziekte-ernst (UPDRS en HY stadium) en ziekteduur, dat wil zeggen dat de droolers langer en ernstiger ziek waren dan de pre-droolers, die langer en ernstiger ziek waren dan de non-droolers Dertig patienten (29%) hadden geen klachten, pre-drooling kwam voor bij 43% en 28% had speekselverlies overdag (waarvan de meesten daarbij ook 's nachts) Op deze manier gedefinieerd is de prevalentie dus lager dan tot nu is gerapporteerd, maar klopt wel beter met de klinische praktijk De droolers waren gemiddeld 10 jaar ziek (SD 5 4) en speekselverlies was onafhankelijk geassocieerd met vaker een open mond (OR = 2 0, 95% BI 1 02-3 99) en slikklachten (OR = 1 2, 95% BI 1 03-1 31)

Van slikstoornissen bij parkinsonpatienten was de prevalentie evenmin goed bekend We vonden 12 studies (**hoofdstuk 3.3**) die te verdelen waren in subjectief vastgestelde klachten (oordeel van de patient) en objectief vastgestelde slikstoornissen (oordeel op basis van slikonderzoek) De gepoolde prevalentie van subjectieve klachten bedroeg 35% (95% BI 28 – 41) en die van objectieve slikstoornissen was 82% (95% CI 77 – 87) Het relatieve risico ten opzichte van gezonde personen was 3 2 voor zowel subjectieve (95% CI 2 32 – 4 41) als objectieve uitkomsten (95% CI 2 08 – 4 98) Dat objectieve slikstoornissen 2x zo vaak voorkomen als subjectieve klachten suggereert onderrapportage Vanwege de mogelijke klinische consequenties zoals ondervoeding en aspiratiepneumonie zouden slikklachten systematisch moeten worden opgespoord met vragenlijsten Anderzijds zijn in alle studies uitsluitend thuiswonende parkinsonpatienten onderzocht en is de prevalentie en de kans op ernstige gevolgen waarschijnlijk het hoogst bij gehospitaliseerde patienten

4. Hoe kan speekselverlies en de ernst ervan het beste worden vastgesteld?

Speekselverlies is bij parkinsonpatienten niet objectief te observeren of te meten, omdat het maar bij weinig patienten tijdens consulten zichtbaar is Dus moet het de patienten worden gevraagd Omdat er geen gevalideerde vragenlijst voor parkinsonpatienten beschikbaar was, hebben we de Radboud Oral Motor inventory for Parkinson's disease (ROMP) ontwikkeld (**hoofdstuk 4.1**), een vragenlijst met drie domeinen en zeven items per domeinen spreken, slikken en speekselbeheersing We hebben de ROMP klinimetrisch geevalueerd met 129 patienten met de ziekte van Parkinson en 49 patienten met een atypisch parkinsonisme Zowel de totale ROMP als de drie subschalen hebben een goede reproduceerbaarheid en zijn valide ten opzichte van andere schalen zoals UPDRS subschalen De subschaal voor speekselverlies heeft een uitstekende reproduceerbaarheid (ICC = 0 90) en interne consistentie (α = 0 94) en voldoende tot uitstekend valide ten opzichte UPDRS subschalen (r = 0 36 tot 0 82) Gemiddelde scores zijn significant verschillend tussen known groups, in dit geval tussen patienten die wel of geen aandacht willen voor klachten over speekselverlies, patienten die volgens de logopedist wel of niet geindiceerd zijn voor logopedische behandeling van het speekselverlies en tussen patienten met HY stadium 1-2, 3 of 4-5 Echter, er is nog geen minimal clinically important difference (MCID) beschikbaar om van een individuele patient vooruitgang of achteruitgang vast te stellen

5. Wat zijn de behandelmogelijkheden?

De meest toegepaste medische behandeling van speekselverlies is het injecteren van de speekselklieren met botuline-neurotoxine Omdat de submandibulaire klieren continu rustspeeksel produceren hebben we in een pilot studie gekeken of injecties in de submandibulaire klieren een beter resultaat geven dan in de parotisklieren (**hoofdstuk 4.2**) We vonden een significant verschil tussen klachten voor en na behandeling in de submandibulaire groep en niet in de parotisgroep, maar geen verschil tussen de groepen Dus uitvoeriger vervolgonderzoek moet uitwijzen wat het klinische belang van deze benadering kan zijn

Op basis van de conclusie over de pathofysiologie van speekselverlies (**hoofdstuk 2.1**), de 'Multidisciplinaire richtlijn Ziekte van Parkinson' en onze klinische ervaringen stellen we enkele behandelmogelijkheden voor verdeeld in de gedragsmatige behandelmogelijkheden van logopedisten en de speekselreducerende behandeling van de artsen (**hoofdstuk 5**)
Gedragsmatige behandeling bestaat ons inziens uit

- Educatie leg de patient de normale fysiologie uit Speekselproductie is bij de ziekte van Parkinson niet verhoogd, ongeveer elke paar minuten moeten slikken is normaal en het kondigt zich aan doordat speeksel ophoopt in de mond Speeksel voelen ophopen een goede 'cue' is om te stoppen met wat je doet, je mond te sluiten, te slikken en dan weer verder te gaan

- Compensatie speekselverlies treedt vaak op in bepaalde situaties, maar dat wordt pas duidelijk als de patient dat in een dagboek een aantal dagen heeft bijgehouden Voor elke situatie moet een specifieke aanpassing worden gezocht, zoals een specifieke auditieve of visuele cue of cognitieve bewegingsstrategie
- Training er zijn aanwijzigen dat intensief trainen van het spreken of het slikken (met PLVT of LSVT) het hele mondgebied zodanig activeert dat ook het verliezen van speeksel afneemt

Tenslotte zijn er aanwijzingen dat kauwgom kauwen de slikfrequentie doet toenemen, maar het is onbekend of parkinsonpatienten met speekselverlies en een slikstoornis daar baat bij hebben Bovendien stimuleert kauwen ook de speekselproductie

Speekselreductie is niet de aanpak van de oorzaak, maar wordt belangrijk als logopedische behandeling niet (meer) helpt De speekselproductie kan vermindert worden met

- Anticholinerge medicatie, waaronder glycopyrronium (1 mg 3x daags)
- Injecties met botuline-neurotoxine in de speekselklieren waardoor de speekselproductie afneemt, maar na 3 tot 4 maanden weer hersteld is
- Radiotherapie op de speekselklieren (resultaten van een gerandomiseerde trial in Groningen zijn onderweg)
- Chirurgische behandeling, waarbij de speekselklierkanalen worden verlegd Bij kinderen met cerebrale parese en ernstig speekselverlies zijn daar goede ervaringen mee, maar het is onbekend of deze ingreep ook bij parkinsonpatienten succesvol wordt uitgevoerd

Deze behandelingen verminderen de speekselproductie, maar hebben niet altijd voldoende invloed op de afname van het speekselverlies Voor de patienten met zeer ernstig speekselverlies is speekselreductie echter de enige behandeloptie

Vervolgonderzoek

Hoewel we de oorzaken van speekselverlies beter zijn gaan begrijpen, zijn er nog diverse vragen onbeantwoord

Om te onderzoeken of speekselverlies ook te wijten is aan afname van de speekselslikfrequentie moeten patienten gemeten kunnen worden zonder dat ze het merken En waarom parkinsonpatienten 's nachts kwijlen is evenmin goed onderzocht Ligt dat aan de slikfrequentie, komt het door slapen met open mond of is het gerelateerd aan slaapstoornissen? Nachtelijke registratie met (video)polysomnografie is nodig om dat te kunnen vastleggen

Terwijl de ROMP werd ontwikkeld zijn er geen nieuwe vragenlijsten voor spreken, slikken of kwijlen bij parkinsonpatienten verschenen Maar de ROMP zou ook gevalideerd moeten worden voor parkinsonpatienten die zijn opgenomen in een verpleeghuis En interventieonderzoek is nodig om een MCID te kunnen bepalen, dat wil zeggen welke minimale scoreverschillen aangeven of een individuele patient op de ROMP vooruit of achteruit is gegaan

Gecontroleerd onderzoek van de gedragsmatige behandeling van speekselverlies is nog vrijwel afwezig, maar ook de beste behandelwijze voor speekselreductie ten opzichte van de minste bijwerkingen zou nog beter onderzocht moeten worden En een bijwerking die tot nu toe in studies nog niet wordt genoemd is de invloed van speekselafname op de gebitsconditie, speeksel beschermt immers het gebit

Tenslotte is niet goed bekend of parkinsonpatienten met speekselverlies de juiste behandeling krijgen wanneer ze dat willen Patienten en behandelaars zouden op de hoogte moeten zijn van de huidige behandelopties en multidisciplinaire samenwerking zoals in ParkinsonNet en op patienten gerichte sociale media zoals MijnZorgnet kunnen daarin een faciliterende rol spelen

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Lekensamenvatting (Lay summary)

A

Ziekte van Parkinson

De ziekte van Parkinson is een hersenziekte die geen verlammingen veroorzaakt, maar spierstijfheid, kleinere, tragere bewegingen en trillen, waardoor dagelijkse handelingen, lopen en spreken langzaamaan steeds moeilijker worden Bovendien gaan trager denken, vermoeidheid, slaapstoornissen en stemmingsstoornissen er op den duur bij horen Parkinsonpatienten kunnen ook last krijgen van speekselverlies (kwijlen), maar tot nu toe was niet goed bekend hoe het ontstaat, hoe vaak het precies voorkomt, hoe groot de last voor patienten is en wat er aan te doen is (**1**)

Oorzaak van speekselverlies

Speekselverlies komt voorbij diverse neurologische ziekten, maar zonder dat sprake is van overproductie van speeksel en dat geldt ook voor parkinsonpatienten Door parkinsonpatienten met en zonder speekselverlies goed te observeren en te vergelijken hebben we laten zien dat speekselverlies bij de ziekte van Parkinson wordt veroorzaakt door de combinatie van onbewust de mond open laten (als onderdeel van het zogenoemde 'maskergelaat') en speeksel minder makkelijk weg kunnen slikken (**2.1**) Ook hadden patienten met speekselverlies in sterkere mate een voorovergebogen houding, wat de kans op verliezen van speeksel verder doet toenemen Parkinsonpatienten moeten steeds meer nadenken bij wat vroeger automatisch goed ging (lopen, aankleden, articuleren) Speeksel wegslikken gaat onbewust, dus we hadden het vermoeden dat bij parkinsonpatienten dat automatisme zou zijn verminderd Daarom hebben we met gevoelige meetapparatuur onderzocht of parkinsonpatienten 'vergeten' om op tijd te slikken Maar juist tijdens ons onderzoek kwijlden patienten niet ('observer paradox') en ze leken zelfs iets vaker te slikken, vermoedelijk om te compenseren voor hun mindere slikcapaciteit Dus om aan te tonen dat afname van de speekselslikfrequentie een rol speelt in het ontstaan van speekselverlies moeten patienten geobserveerd worden zonder dat ze zich dat bewust zijn (**2.1**)

De relatie tussen speekselverlies en moeite met slikken is bij parkinsonpatienten waarschijnlijk anders dan bij patienten met verlamming van de mondspieren Onze gegevens laten zien dat patienten met klachten over speekselverlies inderdaad slechter slikken, maar ernstige slikstoornissen kwamen niet voor We hebben dat nagezocht in de literatuur door twaalf studies te vergelijken op het vóórkomen van slikstoornissen bij de ziekte van Parkinson We vonden dat gemiddeld een derde van de patienten (35%) slikklachten heeft (**3.3**) en dat komt overeen met één van onze andere onderzoeken waarin niet meer dan 39% van de parkinsonpatienten aandacht wilde voor slikklachten bij een bezoek op het dagcentrum van het Parkinsoncentrum Nijmegen (ParC) (**4.1**) In een apart artikel hebben we een uitzonderlijke parkinsonpatient beschreven die vrijwel voortdurend speeksel verloor, waardoor hij onder andere ernstige huiduitslag kreeg Deze patient had duidelijk wèl grote moeite met slikken en ook met spreken (**2.3**)

Vóórkomen van speekselverlies

Aan de hand van gegevens die we hadden verzameld van 104 parkinsonpatienten vonden we verdere aanwijzingen dat het verliezen van speeksel overdag wordt voorafgegaan door een periode van een paar jaar, waarin de patient het gevoel heeft dat speeksel zich in de mond ophoopt of speekselverlies alleen 's nachts optreedt (nat kussen bij het wakker worden) Deze eerste klachten ontstaan in het algemeen niet eerder dan 5 jaar na het begin van de ziekte en nemen toe met de ernst van de ziekte (**3.2**) Dus door toename van de spierstijfheid met kleinere en tragere bewegingen in het gelaat, de mond en de keel ontstaat op den duur speekselverlies Vooral bij vooroverbuigen of concentratie op eén taak

Het vóorkomen van speekselverlies hangt af van de definitie Vergelijking van 8 studies met uiteenlopende definities liet een gemiddelde zien van 56% (**3.1**) Uit ons eigen onderzoek bleek dat speekselophoping of enkel speekselverlies 's nachts (nat kussen bij wakker worden) voorkomt bij 43%, maar daadwerkelijk speekselverlies overdag bij 28%, terwijl het maar bij 2% ook zichtbaar was tijdens het onderzoek (**3.2**) Door de strakkere definitie zijn dat lagere getallen dan tot nu in studies werd gerapporteerd, maar dat betekent allerminst dat speekselverlies een gering probleem is We hebben 63 parkinsonpatienten met klachten over speekselverlies gevraagd naar de last die ze er van hebben(**2.2**) Ruim een kwart van hen (27%) had ernstig tot zeer ernstig speekselverlies, dat wil zeggen vlekken op kleren of op de grond Deze patienten scoorden ook het meest op vragen als 'Heeft u gemerkt dat mensen door het speekselverlies contact met u vermijden?' (41%) of 'Heeft het speekselverlies invloed op uw zelfvertrouwen?" (88%) En terwijl enkele van die patienten al werden behandeld, wilde 40% graag behandeling voor hun speekselverlies

Onderzoek en behandeling

Om er achter te komen of sprake is van speekselverlies en hoe ernstig het is, hebben we een vragenlijst ontwikkeld die na uitvoerige evaluatie voldoende betrouwbaar en valide bleek te zijn (**4.1**) De neuroloog of logopedist zou verder ook kunnen kijken naar de ernst van het maskergelaat (mond open laten hangen) en de ernst van de slikstoornis, maar met name ook de mate waarin de patient te stimuleren is om vaker en beter zijn speeksel weg te slikken

Nieuw onderzoek is nodig om duidelijker te krijgen wat de beste behandeling van speekselverlies is, maar op basis van de gegevens uit dit proefschrift en onze ervaringen met patienten hebben we wel ideeen over behandeling (**5**) Om te beginnen maken we onderscheid tussen de gedragsmatige behandelmogelijkheden van logopedisten en de speekselreducerende behandeling van de artsen

Gedragsmatige behandeling bestaat ons inziens uit

- Educatie leg de patient de normale fysiologie uit en dat speeksel voelen ophopen een goed 'cue' is om te stoppen met wat je deed, eventueel je mond te sluiten, te slikken en dan weer verder te gaan

- Compensatie speekselverlies treedt vaak op in bepaalde situaties, maar dat wordt pas duidelijk als de patient dat in een dagboek een aantal dagen heeft bijgehouden Voor elke situatie moet een specifieke aanpassing worden gezocht
- Training er zijn aanwijzigen dat intensief trainen van het spreken of het slikken het hele mondgebied zó activeert dat ook het verliezen van speeksel afneemt

Speekselreductie is niet de aanpak van de oorzaak, maar wordt belangrijk als logopedische behandeling niet meer helpt De speekselproductie kan vermindert worden met medicijnen, botuline-injecties die de speekselklieren stilleggen (**4.2**) of radiotherapie waarmee de speekselklieren door middel van bestraling worden beschadigd Deze behandelingen zijn niet altijd even succesvol en ook nog niet in voldoende mate onderzocht, maar voor de patienten met ernstig speekselverlies op den duur de enige behandeloptie

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B

Op de kaft staat eén auteur, maar in werkelijkheid is een proefschrift het resultaat van vruchtbare samenwerking tussen experts en de medewerking en steun van talloze mensen

Allereerst ben ik dank verschuldigd aan alle parkinsonpatienten die aan de onderzoeken hebben meegewerkt, door zich geduldig te laten observeren en te antwoorden op al onze vragen

Evenmin had ik dit proefschrift kunnen realiseren zonder de inzet en begeleiding van mijn promotoren en copromotoren

Prof dr Bloem, beste Bas, je grenzeloze optimisme en deskundigheid zijn enorm aanstekelijk Het was een voorrecht om samen met je te schrijven en om te leren van je professionaliteit in het presenteren van relevante uitkomsten Of zoals een Italiaanse neuroloog tegen mij zei "You must be crazy too, otherwise you wouldn't work with this man " En zo is het

Prof dr Zwarts, beste Machiel, je hebt me geïntroduceerd in neurofysiologische metingen en op de afdeling klinische neurofysiologie, waar ik me vanaf het begin welkom voelde Je rustige begeleiding en belangstelling voor logopedie hebben een belangrijke bijdrage geleverd aan de ontwikkeling van mijn vak Ik vond het eer om met je samen te werken

Dr Munneke, beste Marten, de afgelopen jaren heb ik dankbaar van je brede deskundigheid en ervaring gebruik mogen maken voor het produceren van steekhoudende artikelen De ontwikkeling van ParkinsonNet, tegelijkertijd en samen met Bas, was niet alleen een prettig avontuur waarvan het einde nog lang niet in zicht is, maar heeft vooral de aandacht voor dit ziektebeeld vergroot en daarmee de logopedische behandeling ervan een kritische impuls gegeven

Dr de Swart, beste Bert, met jou deel ik alle inspanningen om neurologen meer te laten kijken als logopedist en logopedisten meer te laten kijken als neuroloog Ik ben je dankbaar voor het creeren en in stand houden van een voortreffelijk professioneel en academisch werkklimaat op onze afdeling

Diverse publicaties waren niet mogelijk geweest zonder de bijdragen van andere deskundigen Ik heb gebruik mogen maken van de hulp van prof dr George Borm, die me het verschil geleerd heeft tussen statistiek in theorie en relevante berekeningen en interpretaties in praktijk En hoewel ze anoniem zijn en vaak meer verguisd dan gewaardeerd worden, ben ik ook mijn internationale peer-reviewers dankbaar voor hun bijdragen aan het vinden van (denk)fouten en het verwerken van andere ideeen en interpretaties Tevens dank ik mijn andere medeauteurs, Wim Mulleners, Peter van de Kerkhof en Lenie van den Engel voor de prettige samenwerking

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Patientenzorg, onderwijs, onderzoek en projecten deel ik met ontelbare collega's die hebben meegeleefd, in het bijzonder het ParkinsonNetteam en de parkinsononderzoeksgroep Maar de continue factor was en is het team logopedie Lieve Simone, Janneke, Judith, Anne, Pauline, Frieda, Emmelien, Kim, Bert, Lenie, Karen, Marjo, Leenke en Sandra, jullie zijn mijn professionele basis en mijn logopedische referentie en ik dank jullie voor de beste collegialiteit en optimistische werksfeer die een mens maar wensen kan

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Mijn toegewijde paranimfen Annette en Lenie dank ik voor hun ondersteuning bij de laatste voorbereidingen en het gewoon doen van de dingen die ik niet zelf moet willen doen

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List of publications

C

C

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- Kalf, H. Evidence-based speech and language therapy: do we use the evidence? Journal of Clinical Speech & Language Studies, 2003, 12/13, 108-117.
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Curriculum vitae

D

D

Johanna Gezina (Hanneke) Kalf werd geboren op 6 juni 1961 in Utrecht In 1979 haalde ze haar vwo-diploma aan het College Blaucapel (nu Gerrit Rietveld college) in Utrecht en studeerde aansluitend aan de Opleiding voor Logopedie en Akoepedie in Utrecht (nu Hogeschool Utrecht), waar ze in 1982 haar diploma Logopedist kreeg Ze werkte 17 jaar als klinisch logopedist in ziekenhuis de Lichtenberg (nu Meander MC) in Amersfoort en combineerde dat met parttime aanstellingen in Utrechtse verpleeghuizen Van 1990 tot 2002 combineerde ze klinisch werken met de functie van hogeschooldocent aan de Fontys Paramedische Hogeschool in Eindhoven, waar ze verantwoordelijk was voor het onderwijs over afasie, dysartrie en dysfagie In 2000 kwam ze naar het UMC St Radboud, waar ze vanaf 2002 fulltime werkt op de afdeling Revalidatie Naast haar brede vakkennis is haar klinische specialisatie orofaryngeale dysfagie, waarover ze regelmatig publiceert in Nederlandse tijdschriften en boeken, en lezingen en cursussen geeft in binnen- en buitenland

Haar interesse in evidence-based practice mondde uit in een handboek voor logopedisten, waarvoor ze in 2005 de Branco van Danzigprijs ontving van de NVLF (Nederlandse Vereniging voor Logopedie en Foniatrie), en in een masterdiploma in klinische epidemiologie en biostatistiek in 2005 aan de Universiteit van Amsterdam Daarna begon ze haar promotieonderzoek in samenwerking met het Parkinsoncentrum Nijmegen (ParC) Ondertussen raakte ze betrokken bij de ontwikkeling en uitbreiding van ParkinsonNet, het landelijke netwerk van regionale multidisciplinaire samenwerkingsverbanden in de behandeling van parkinsonpatienten en is ze sinds 2007 verantwoordelijk voor de scholing van logopedisten in ParkinsonNet In dat kader verscheen in 2008 de NVLF-richtlijn "Logopedie bij de ziekte van Parkinson", waar ze de eerste auteur van is

Sinds 2003 is ze één van de vaste vertegenwoordigers van de NVLF in CPLOL (Comité Permanente de Liaison des Orthophonistes et Logopède de l'Union Européenne), de Europese koepelorganisatie van logopedieverenigingen, waarvan ze sinds 2009 voorzitter is

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Johanna Gezina (Hanneke) Kalf was born on June 6, 1961 in Utrecht, the Netherlands After graduation from secondary school in 1979 (College Blaucapel, now Gerrit Rietveldcollege) in Utrecht, she studied Speech-language therapy in Utrecht (HU University of Applied Sciences Utrecht), were she received her bachelor diploma in 1982 She worked from 1982 as a clinician in a general hospital (currently Meander MC) in Amersfoort in combination with parttime work in nursing homes in Utrecht From 1990 to 2002 she combined her clinical work with lecturing aphasia, dysarthria and dysphagia at the Fontys University of Applied Sciences in Eindhoven In 2000 she moved to the Radboud University Nijmegen Medical Centre and started to work fulltime from 2002 at the department of Rehabilitation Her clinical expertise is oropharyngeal dysphagia and she publishes regularly about dysphagia in Dutch journals and books and provides courses in the Netherlands and abroad

Her interest in evidence-based practice resulted in a manual for speech-language therapists, which was awarded in 2005 with the 'Branco van Danzigprijs' from the NVLF (Dutch Association for Logopedics and Phoniatrics), and in her master's degree in clinical epidemiology and biostatistics in 2005 at the University of Amsterdam Next, she started her PhD research in collaboration with the Parkinson Centre Nijmegen (ParC) Meanwhile, she became involved in the development of ParkinsonNet, the national system of regional multidisciplinary networks of health professionals dedicated to Parkinson's disease From 2007 she is responsible for the educational programme of the SLTs in ParkinsonNet Subsequently, she became the 1st author of the NVLF guideline "Speech-language therapy in Parkinson's disease", which was published in 2008

Since 2003 she is one of the delegates of the NVLF in CPLOL (Comité Permanente de Liaison des Orthophonistes et Logopede de l'Union Européenne), the European umbrella organisation of 31 SLT associations in 28 countries, of which she became the president in 2009

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Dissertations of the Parkinson Centre Nijmegen (ParC)

E

1. Jasper E. Visser. The basal ganglia and postural control. Radboud University Nijmegen, 17 June 2008.

2. Maaike Bakker. Supraspinal control of walking: lessons from motor imagery. Radboud University Nijmegen, 27 May 2009

3. W. Farid Abdo. Parkinsonism: possible solutions to a diagnostic challenge Radboud University Nijmegen, 7 October 2009

4. Corinne G.C. Horlings. A weak balance: balance and falls in patients with neuromuscular disorders. Radboud University Nijmegen, 1 April 2010.

5. Samyra H.J. Keus. Physiotherapy in Parkinson's disease towards evidence-based practice Leiden University, 29 April 2010.

6. Lars B. Oude Nijhuis. Modulation of human balance reactions. Radboud University Nijmegen, 29 November 2010.

7 Maarten J. Nijkrake. Improving the quality of allied health care in Parkinson's disease through community-based networks: the ParkinsonNet health care concept Radboud University Nijmegen, 29 November 2010

8. Rick C.G Helmich. Cerebral reorganization in Parkinson's disease. Radboud University Nijmegen, 24 May 2011.

9. Karlijn F. de Laat. Motor performance in individuals with cerebral small vessel disease: an MRI study. Radboud University Nijmegen, 29 November 2011.

10 Anouk G.W. van Norden. Cognitive function in elderly individuals with cerebral small vessel disease. An MRI study. Radboud University Nijmegen, 30 November 2011.

11 Charlotte A Haaxma. New perspectives on preclinical and early stage Parkinson's disease. Radboud University Nijmegen, 6 December 2011.

12 Johanna G Kalf. Drooling and dysphagia in Parkinson's disease. Radboud University Nijmegen, 22 December 2011.

1. Speekselverlies bij de ziekte van Parkinson ontstaat niet door hypersalivatie, maar door faciale en orale hypokinesie. Het is dus geen 'non-motor', maar een 'motor' symptoom van de ziekte (dit proefschrift).

2. Speekselslikfrequentie kan bij parkinsonpatiënten het beste gemeten worden als de patiënt niet weet dat hij geobserveerd wordt (dit proefschrift).

3. Ongeveer een kwart van de thuiswonende parkinsonpatiënten heeft last van speekselverlies , maar bij minder dan 5% kunnen behandelaars dit ook zelf observeren (dit proefschrift).

4. Een lichte afname in slikcapaciteit is voor de helft van de parkinsonpatiënten geen aanleiding om over slikproblemen te klagen (dit proefschrift).

5. De conclusie "The solution was staring us in the face all the time" (Bas Bloem) mag je in het geval van hypomimie als voorspeller van speekselverlies letterlijk nemen.

6. Parkinsonpatiënten met speekselverlies zouden eerst door een ervaren logopedist onderzocht en behandeld moeten worden, voordat met medische behandeling geprobeerd wordt om de speekselproductie te verminderen (Multidisciplinaire richtlijn Ziekte van Parkinson, 2010).

7. Adequate logopedische behandeling van ernstige orofaryngeale slikstoornissen vraagt veel ervaring. Betere samenwerking tussen generalisten en specialisten kan onderbehandeling, waaronder te restrictieve beperkingen van voedingsconsistenties, voorkomen.

8. Ook voor het voltooien van een proefschrift geldt de wet van Hofstadter: alles duurt langer dan je denkt, ook al houd je rekening met de wet van Hofstadter.

9. Iedere keer als je een blog schrijft over spelfouten zal er een nieuwe spelfout in staan die alleen een ander ziet (aangepaste wet van Muphry).

10. Met het toenemend professionele gebruik van Twitter, is het moderne #spreekwoord "Een dag niet getwitterd is een dag hard gewerkt" (@modernespraak) nu al betekenis aan het verliezen.

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