

OROPHARYNGEAL DYSPHAGIA AND ITS PSYCHIATRIC COMORBIDITIES

The prevalence of affective symptoms and the unmet clinical need for integrated care in medically unexplained symptoms

Rob Verdonshot



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clinical need for integrated care in medically
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Contents

Chapter 1	General introduction	7
Section I	Affective symptoms and oropharyngeal dysphagia	21
Chapter 2	Symptoms of anxiety and depression assessed with the hospital anxiety and depression scale in patients with oropharyngeal dysphagia. <i>J Psychosom Res. 2013;75(5): 451-5.</i>	23
Chapter 3	The relationship between fiberoptic endoscopic evaluation of swallowing outcome and symptoms of anxiety and depression in dysphagic patients. <i>Laryngoscope. 2016;126(5): E199-207.</i>	37
Chapter 4	Affective symptoms in patients with oropharyngeal dysphagia: a systematic review. <i>J Psychosom Res. 2017;97: 201-210.</i>	53
Section II	Medically unexplained symptoms	73
Chapter 5	Medically unexplained oropharyngeal dysphagia at the University Hospital ENT outpatient clinic for dysphagia a cross-sectional cohort study. <i>Dysphagia. 2018 Jun 5 [Epub].</i>	75
Chapter 6	Medically unexplained otorhinolaryngological symptoms: Towards integrated psychiatric care. <i>Laryngoscope. 2015;125(7): 1583-7.</i>	89
Section III		101
Chapter 7	General discussion, future perspectives, and valorization addendum	103
Chapter 8	Summary	113
Chapter 9	Samenvatting	121
	Dankwoord	129
	List of publications	133
	Curriculum Vitae	137

Chapter 1

General introduction

General introduction

Oropharyngeal dysphagia

Swallowing is a critical and complex process involving the central nervous system and many different muscles and peripheral nerves, together enabling the bolus to be ingested via the mouth through the pharynx and esophagus into the stomach.^{1,2} Patients with oropharyngeal dysphagia (OD) have problems transferring a bolus from the mouth to the esophagus, and many different structures are involved in this complex procedure. The swallowing response is triggered mainly by afferent sensory input from the bolus. Stimuli like taste and temperature are transmitted via four cranial nerves with sensory function (V, VII, IX, X) to a central pattern generator within the nucleus solitarius, located in the medulla oblongata. A central pattern generator is a neuronal circuit that, when activated, can produce rhythmic motor patterns such as sequential and rhythmic swallowing movements.³⁻⁶ Certain cerebral areas are important in swallowing: the main ones are the primary sensorimotor cortex, the lateral premotor cortex, the temporopolar cortex, the supplementary motor area, the cingulate cortex, and the insular cortex (secondary somatosensory cortical areas). Also, the basal ganglia seem to be involved (see Figure 1.1). The amygdala appears to be involved in modulating swallowing inhibition, which is also likely to occur via the central pattern generator. Sensory stimuli, motor cortex information, and input from the amygdala are all processed by the activated central pattern generator, which triggers the swallowing reflex.³⁻⁵ With regard to this reflex, motor neurons in the brainstem and different cranial nerves with motor function (V, VII, IX, X, XI, XII) are involved.^{4,5} The literature suggests a hemispheric specialization for phases of deglutition: left side for the oral phase, and right side for the pharyngeal phase. However, this neurotopographic hypothesis remains debatable. Sensory input is important for activation of these processes, and disruption of afferent sensory stimuli obstructs the cortical control of swallowing.⁵ In the literature, the incidence of OD ranges from 6% to 50%, depending on the patient population and etiology of the dysphagia studied.⁷ Overall, the etiology of OD can be divided into neuromuscular dysfunction, disorders of the central nervous system, abnormalities of the anatomy of the oral cavity, pharynx and/or larynx, and combinations of these.² It is commonly caused by neurological diseases such as stroke, myotonic dystrophy, Parkinson's disease, and multiple sclerosis. For instance, up to 80% of the patients with Parkinson's disease suffer from OD.⁸⁻¹⁰ A stroke might result in OD when the functional connectivity of the swallowing process is disrupted, which leads to impaired activation in the damaged and undamaged hemisphere. Post-stroke recovery of swallowing function often occurs due to compensatory changes in the undamaged hemisphere. However, cortical compensation and adaption are not possible in diseases affecting the upper motor neuron of both hemispheres such as multiple sclerosis.

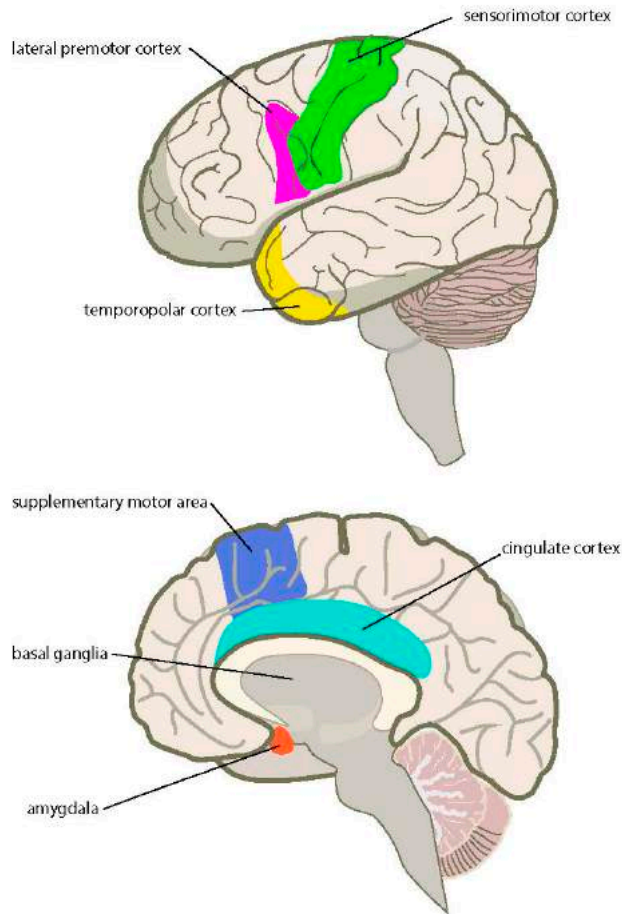


Figure 1.1

Diseases of the lower motor neuron, like spinal and bulbar muscular atrophy, lead to reorganization and increased activation, and thereby compensation, of the primary sensorimotor cortex of the upper motor neuron.⁵ In patients with Parkinson's disease, damaged motor pathways seem to be compensated by adaptive cerebral changes until the disease reaches stages at which compensation of OD is no longer possible.⁵ OD is also frequently seen in head and neck cancer patients, in whom impaired swallowing might be caused directly by the tumor or indirectly by the oncological treatment (i.e., surgery, radiation). Furthermore, OD can be caused by many other conditions such as inclusion body myositis, cervical spine abnormalities, and Zenker's diverticulum. In general, the older population is more susceptible to OD because of changes in respiratory-swallow patterns, sarcopenia of muscles involved in swallowing, reduced

tissue elasticity, changes of the cervical spine, altered oral and pharyngeal sensitivity, changes in cognitive function, diminished saliva production, reduced compensatory capacity of the brain, inadequate opening of the upper esophageal sphincter (EUS), or impaired dental status.^{5,11,12} Although an older adult's swallow is not necessarily an impaired swallow, the sensorimotor integration becomes more vulnerable with advanced age. The term *presbyphagia* is used to describe the characteristic changes in the swallowing mechanism of otherwise healthy older adults. *Presbyphagia* is increasing in the current ageing population.⁵ The nature of OD can be described using FEES (Fiberoptic Endoscopic Evaluation of Swallowing) and/or Videofluoroscopy (VFS), each considered as the gold standard in its realm. These instruments provide the clinician with information about the phenomenology or 'phenotype' of OD by measuring specific visuoperceptual, temporal, and/or spatial parameters, depending on the psychometric properties of the measurement tool. FEES allows a comprehensive assessment of pharyngeal swallowing by providing direct visualization of the larynx; it is often the first choice because of its advantages (i.e., easy to use, well-tolerated, the possibility of bedside examination, no radiation, use of real food, not expensive).^{2,13} FEES can be performed using real food or by offering a standardized protocol of colored bolus consistencies. VFS allows a comprehensive assessment of oropharyngeal swallowing by giving details on bolus flow and biomechanics at the level of the esophagus as well. VFS is usually initiated in a lateral position. Antero-posterior view is often optional, depending on the findings in the lateral view. Food and liquid mixed with barium can be given to the patient using a standardized protocol. VFS offers some additional advantages over FEES: the possibility to assess the (preparatory) oral phase of swallowing; a good view of the location of the bolus during the entire swallowing act from oral cavity to stomach; and assessment of the movement of pharynx and larynx related to other anatomical landmarks (mandible, cervical spine, etc.).² Visuoperceptual temporal, spatial, and categorical variables are used for biomechanical and symptom assessment. These instrumental swallowing assessment tools provide the clinician with information about the etiology, phenotype, and severity of OD. For several decades, awareness of OD has been rising, and the diagnostic and treatment strategies have been improving.²

Impairment of swallowing can cause severe physical complications. For example, OD is often accompanied by aspiration of food, which can lead to aspiration pneumonia or chronic pulmonary inflammation. Further, OD patients frequently have a decreased intake of food and fluids; eventually, a reduced intake of energy, water, and nutrients will result in malnutrition and dehydration. Patients might even choke on food, which can cause sudden death.^{1,2,5,7,14} OD affects the ability to eat and drink normally, which is an important part of social interaction, and can therefore have a significant impact on patients' well-being and perceived quality of life (QoL).^{7,15}

The literature suggests that OD not only has an impact on QoL but may also interfere on a mental level and might cause affective symptoms. For example, the risk of choking, severe coughing, and vomiting may cause anxiety symptoms. Moreover, lower

self-esteem, diminished social interaction, and social isolation may cause depressive symptoms.^{7,16-18} However, the literature remains unclear about whether, and if so to what extent, OD is associated with affective symptoms. Multiple locations in the brain, notably the cingulate cortex, the amygdala, and basal ganglia, are involved in emotion regulation as well as in the complex process of swallowing. However, the overlapping pathophysiological mechanisms in affective diseases and OD are not completely understood. Neurological diseases affecting these areas might lead to both OD and affective problems.¹⁸ Also, an affective state might simply amplify cognitive misattributions concerning patients' experiences of OD and swallowing. Although mental problems in OD patients seem to be common and cannot be disregarded, caregivers often don't recognize these problems and management strategies are lacking. Thus, there is an unmet clinical need to identify affective complaints such as anxious behavior.

Affective disorders

Affective disorders, also known as mood disorders, are a set of psychiatric diseases in which a disturbance in mood is the main underlying feature. Among these are depressive disorders and anxiety disorders, each of which can be divided into subtypes according to the criteria of the Diagnostic and Statistical Manual of mental disorders, fifth edition (DSM-V).¹⁹ Patients with affective disorders can present with many different symptoms and may have disturbances in emotion, ideation, cognition, and somatic functioning.¹⁹ Sometimes symptoms of anxiety and depression overlap. The overall lifetime prevalence of anxiety disorders in the Netherlands for 2011 is estimated at 19.6% (for the age group 18-65 years), based on a mental health survey.²⁰ The lifetime prevalence of a depressive disorder in the Netherlands is 13.1% for men and 24.3% for women.^{20,21} In this thesis, we focus on symptoms of anxiety and depression in patients with OD. A brief introduction to anxiety and depression in general is given below, as well as an overview of some specific psychiatric disorders within the affective spectrum.

Anxiety

The word *anxietas* was already used by the Romans to indicate a state of fearfulness. In the eighteenth century, the term anxiety was first used in medical writing with regard to mental illness. In that era anxiety was understood mainly as a state of the body, not the mind. Anxiety was seen as a physical abnormality of the nerves, or of the brain to which the nerves were connected. During the nineteenth century, anxiety was increasingly interpreted as a manifestation of psychiatric disturbances. Sigmund Freud (1856-1939) used the term *anxiety neurosis*, a description of which was first published in 1895.²² The 13 anxiety disorders listed in the DSM-IV-TR (2000) all fitted within the borders outlined by Freud's description of *anxiety neurosis*.²² Anxiety is defined as a state of high arousal that is persistent and disproportionate to actual danger and is

considered pathological if interfering with normal functioning. The exact pathophysiology of anxiety disorders is still not fully understood. In the late eighteenth century, the key loci of the central nervous system involved in anxiety were identified, including the amygdala, the nucleus of the stria terminalis, the ventral hippocampus, and the prefrontal cortex. These structures are connected by reciprocal projections, forming a macrocircuit.²³ Within this macrocircuit local pathways form a microcircuit by connecting individual nodes. It is assumed that anxiety disorders arise from disruptions in highly complex neural circuits, thereby prompting misinterpretation of threatening stimuli and in turn to inappropriate emotional and behavioral responses. To improve treatment strategies for anxiety disorders, a better understanding of the neural circuits involved in anxiety is required.²³ Anxiety disorders include generalized anxiety disorder, specific phobias, panic disorder, and anxiety disorder due to another medical condition. The various anxiety disorders differ from one another with respect to the types of objects or situations that induce fear, anxiety, or avoidance or defensive behavior. They can be differentiated on the basis of close examination by an experienced clinician.¹⁹ Anxiety disorders are pervasive and persistent conditions, and they require a comprehensive, integrated approach to treatment, especially in cases that present predominantly with somatic anxiety equivalents.²²

Generalized anxiety disorder

Patients with generalized anxiety disorder worry about many events and routine life circumstances (e.g., health, finances, children or other family members, job responsibilities, appointments). The frequency, duration, and intensity of the anxiety is out of proportion with the level of threat. It is difficult for these patients to control their worries, which typically interfere with psychosocial functioning and are often accompanied by restlessness, fatigue, irritability, and disturbed sleep. Generalized anxiety is also associated with somatic symptoms like sweating, abdominal complaints (e.g. diarrhea), dizziness, and tachycardia. Most patients with this disorder have felt anxious their whole life.¹⁹ The life-time prevalence of generalized anxiety disorder in the Netherlands is approximately 4.5%.²⁰

Panic disorder

Patients with panic disorder have recurrent panic attacks, which are characterized by intense anxiety or discomfort of sudden onset and brief duration. Patients are consistently concerned or worried about additional attacks or their consequences and/or show significant changes in behavior to avoid these attacks. The occurrence of a panic attack is not restricted to the direct physiological effects of a substance, a general medical condition, or the symptoms of another mental disorder.¹⁹

Anxiety disorder due to another medical condition

According to the recently updated DSM-V criteria, anxiety due to another medical condition is a disorder that can be best explained as a physiological effect of that condition. The judgment that anxiety symptoms can be best explained by a certain medical condition must be based on evidence (e.g., from history, laboratory findings, or physical examination). The symptoms of an anxiety disorder due to another medical condition must cause clinically significant distress or impairment in important areas of life (work, social functioning). There are many known medical conditions where anxiety can be a symptom of disease: for example, hyperthyroidism, congestive heart failure, atrial fibrillation, chronic obstructive pulmonary disease, and non-functional vestibular disorders.²⁴⁻²⁸ The course of this disorder generally follows that of the underlying medical condition, whereby the patient is distressed about its consequences or meaning. The diagnosis of an anxiety disorder due to another medical condition is not meant to include primary anxiety disorders that arise in the context of a chronic medical illness. The prevalence of anxiety disorder due to another medical condition is unknown.¹⁹

Specific phobia

Persons with a specific phobia fear a specific situation or object and desire to avoid it. Their fear is out of proportion with the actual danger it poses. Exposure to that object or situation provokes an immediate anxiety response. The anxiety, or the avoidance, causes clinically significant distress or impairment in a person's normal routine and in one's occupational or social functioning.^{19,22} When not confronted with the phobia stimulus, these persons are usually symptom-free. However, a specific phobia can interfere with one's quality of life and thus require treatment. An example is phagophobia, which means 'fear of swallowing'. The lifetime prevalence of specific phobia in the Netherlands is 7.9%.²⁰

Depression

As in anxiety disorders, somatic complaints, including functional somatic conditions, are often accompanied by mood disturbances.^{29,30} Hippocrates was the first to apply the term *melancholia*, which was derived from the Greek words *melas* (black) and *kholé* (bile); a state of decreased mood was thought to be caused by black bile. It was later characterized as being dull or stern, dejected or unreasonably torpid, without any cause.³¹ Melancholia was first described as a depressive mood disorder in the eleventh century.³² Over the past few centuries, depression has been given many different definitions, and over the last six decades different pathophysiological mechanisms have been proposed. 1) The monoamine theory states that depression is caused by dysfunction in adrenergic or serotonergic neurotransmission whereby norepinephrine, serotonin, and dopamine may play important roles in the genesis of a depressive

disorder.²¹ II) The biorhythm hypothesis postulates that depressive symptoms are caused by dysfunction of the nucleus suprachiasmaticus that affects the generation of a correct circadian rhythm.²¹ III) The neuro-endocrine hypothesis holds that depression results from dysregulation of the endocrine system, especially the hypothalamic-pituitary-adrenal axis, with an imbalance between glucocorticoid receptors and mineralocorticoid receptors, particularly in the hippocampus.²¹ IV) The neuro-immune hypothesis states that severe psychological stress produces measurable abnormalities in the immune function, which leads to the activation of macrophages and eventually results in the release of pro-inflammatory cytokines. Cytokines stimulate the production of neurotoxic substances, cause tryptophan depletion, and cause hypersecretion of cortisol. Cortisol leads to reduced production of pro-inflammatory and neurotrophic factors, which may lead to neurodegeneration, particularly in the hippocampus.²¹ V) And last, the kindling hypothesis holds that the effects of stressors may increase over time, eventually culminating in a full-blown affective episode. Thus, psychosocial stressors trigger initial episodes of depression, and with enough repetition depression may also begin to emerge spontaneously.²¹ Neuroplastic changes seem to connect all five theories in the pathogenesis of depressive disorders.²¹ From a neuroscience point of view, depression is associated with atrophy and altered connectivity of the prefrontal cortex to the limbic system, with an imbalance of excitatory and inhibitory neurotransmission. Accordingly, chronic stress and depression lead to deficits in, and dysregulation of, the gamma aminobutyric acid (GABA) neurotransmission, which is an inhibitory neurotransmitter.³³ Depressive disorders include major depressive disorder, persistent depressive disorder (dysthymia), and depressive disorder due to another medical condition. The feature common to all of these is a sad, empty, or irritable mood with cognitive, behavioral, and somatic changes. Depressive disorders have a significant effect on normal daily functioning.^{19,34}

Major depressive disorder and persistent depressive disorder (dysthymia)

A major depression is a common and serious illness that can be caused by genetic predisposition, the environment, life events, the gene-environment interaction, and personality traits or coping style. Patients with a major depression exhibit a melancholic mood and loss of interest in activities they once enjoyed. They often have weight loss and decreased appetite, sleeping problems, loss of energy, problems with concentration, and might have suicidal thoughts.¹⁹ Patients with a persistent depressive disorder have a sustained depressed mood over a two-year period or more (dysthymia). Symptoms of dysthymia are less intense than those of major depressive disorder but still affect daily life.¹⁹

Depressive disorder due to another medical condition

The criteria for a depressive disorder due to another medical condition are comparable to those of an anxiety disorder due to another medical condition; both are associated

with symptoms that are best explained by a certain medical condition and not better accounted for by another mental disorder. The patient is distressed about the consequences or meaning of the associated medical condition.¹⁹ Examples of medical conditions that can cause a depressive disorder are HIV, diabetes, cardiac diseases, and pancreatitis.³⁵⁻³⁹ The prevalence of this disorder is unknown and its course generally follows that of the underlying medical condition.¹⁹

Somatic symptom disorder

From a neuroscience perspective, functional somatic complaints without any medical or emotion-regulation cause are defined by DSM-V criteria as a somatic symptom disorder.¹⁹ Patients with a somatic symptom disorder have physical symptoms that cannot be explained by a somatic medical condition and are not attributable to another psychiatric condition. The symptoms (e.g., weakness, pain, shortness of breath) cause significant distress and affect normal functioning. The physical symptoms cause excessive feelings, behaviors, or thoughts and need to be present for at least six months. Patients with a somatic symptom disorder usually present to primary or hospital care rather than to a mental-healthcare worker. It is often difficult to convince patients that their symptoms are related to mental ill health rather than to a structural physical cause.¹⁹ The interdisciplinary medical field of psychosomatic medicine explores the relationship between psychological, social, and psychiatric factors, on the one hand, and bodily processes, on the other hand. In psychosomatic medicine, it is well established that physical illnesses and diseases are influenced by mental components.²⁹ Establishing a multidisciplinary psychosomatic approach is challenging but essential in order to better understand the pathophysiological mechanisms of psychosomatic conditions and in order to develop integrated treatment programs.

Hospital anxiety and depression scale

For caregivers, it can be very difficult to determine whether or not a patient has clinically relevant affective symptoms. Over the last several decades, various psychiatric tools and questionnaires have been developed to help clinicians identify levels of anxiety and/or depression (e.g., Hospital Anxiety and Depression Scale, Beck Depression Inventory, Trait Anxiety Inventory, Geriatric Depression Scale, Zung Depression Scale).⁴⁰⁻⁴⁷ The Hospital Anxiety and Depression Scale (HADS) is a commonly used and validated self-assessment scale for detecting states of anxiety and depression in the setting of a hospital medical outpatient clinic.⁴⁰ It was developed by Zigmund and Snait in 1982 and intended to help busy physicians determine whether patients have psychological distress that might contribute to their physical symptoms. In 2002, Bjelland et al. published a review concerning the validity of the HADS. They concluded that HADS performed well in the assessment of anxiety disorders and depression in somatic, psychiatric, and primary care patients and in the general population.⁴⁸ In this thesis, HADS was used for the screening of affective symptoms in OD patients.

Objectives and outline of this thesis

As mentioned above, OD probably interferes on a mental level and may cause psychological distress or might be worsened by affective amplification. The research underlying this thesis was seen as an opportunity to gain a better understanding of the impact of mental distress on OD, and of OD on mental distress. Ultimately, our objective was to create awareness among OD caregivers and to improve management strategies. To that end, this thesis pursues specific aims: I) to estimate the prevalence of affective symptoms and describe OD patients at risk for clinically relevant affective symptoms in order to better understand the psychological impact of OD, and vice versa; II) to give direction to OD caregivers regarding management strategies; and III) to introduce psychiatric expertise in the multidisciplinary approach of the OD patient in order to provide better management through integrated care.

As reported in the preliminary study in **chapter 2**, there is a high prevalence of clinically relevant affective symptoms in patients visiting the outpatient clinic for dysphagia, which was the reason to conduct further research on this topic. The relationship between the severity of OD symptoms as investigated with FEES, and the clinically relevant affective symptoms as rated on the Hospital Anxiety and Depression Scale, is examined in the prospective cross-sectional study described in **chapter 3**. A literature search was performed to evaluate the current evidence on affective symptoms in patients with OD, as described in the systematic review in **chapter 4**. **Chapter 5** shows the results of a cross-sectional study of patients with medically unexplained OD complaints, which was conducted to see if these symptoms are related to an affective condition or another psychiatric condition. Medically unexplained symptoms are not only present in patients with OD, but are also a common problem in ENT patients in general. **Chapter 6** investigates psychiatric comorbidity in patients with medically unexplained otorhinolaryngology symptoms (OD, dizziness, globus pharyngeus, etc.) presenting at the ENT outpatient clinic. **Chapter 7** contains the general discussion, conclusions, future perspectives, and a valorization addendum. Finally, **chapter 8** summarizes the main findings of this thesis.

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Section I

Affective symptoms and oropharyngeal dysphagia

Chapter 2

Symptoms of anxiety and depression assessed with
the hospital anxiety and depression scale in patients
with oropharyngeal dysphagia

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Abstract

Objective

The aim of the present study is to determine the presence and severity of symptoms of anxiety and depression in patients with oropharyngeal dysphagia who visit the outpatient clinic for dysphagia.

Methods

Symptoms of anxiety and depression (affective symptoms) were prospectively assessed in 96 patients using the validated Hospital Anxiety and Depression Scale. In addition, all patients underwent a standardized examination protocol used for regular healthcare in the outpatient setting for dysphagia. The protocol included the following: otorhinolaryngological examination, logopedic observation of oral intake, fiberoptic endoscopic evaluation of swallowing, video fluoroscopy of swallowing, the Functional Oral Intake Scale, a dysphagia severity scale, and the M.D. Anderson Dysphagia Inventory. Depending on the presence/absence of symptoms of anxiety and depression, several groups were distinguished. Descriptive statistics and the Mann–Whitney U test were used to test for group differences. Logistic regression models were used to identify factors associated with symptoms of anxiety and/or depression (cut-off score ≥ 8).

Results

Clinically relevant symptoms of anxiety were observed in 37% (N=34) and clinically relevant symptoms of depression in 32.6% (N=31) of the present patient population, with 21.3% having symptoms of both anxiety and depression. In total, 47.3% (N=43) of this population showed affective symptoms.

Conclusion

Given that psychological burden can enhance somatic complaints, the high number of patients suffering from affective symptoms is a relevant clinical outcome in dysphagic patients. The contribution of anxiety or depression to the development or worsening of oropharyngeal dysphagia and their role in interdisciplinary treatment strategy is warranting further research.

Introduction

Oropharyngeal dysphagia causes discomfort and loss of quality of life.^{1–8} Since oropharyngeal dysphagia is caused by numerous conditions, the exact epidemiology remains obscure.⁹ Oropharyngeal dysphagia can be observed in neurological patients i.e. stroke patients or patients suffering from a progressive neurological disorder.^{10–12} Also oropharyngeal dysphagia is seen in head and neck oncological patients due to the tumor and/or the oncological treatment.^{10,13} Severe dysphagia may lead to severe comorbidity (e.g. aspiration pneumonia, malnutrition, dehydration, and death).^{2,4,8,12} The medical, social, and emotional burden caused by dysphagia and the increased prevalence of oropharyngeal dysphagia in an aging population is reason to investigate this topic.^{14–16} Since eating and drinking form an important part of social interaction, dysphagic patients often eat in seclusion because of shame.⁸ Frequently, dysphagic patients fear they may choke on their food or develop aspiration pneumonia.¹⁷ Fear of dysphagic complications can decrease quality of life even more. Patients with oropharyngeal dysphagia may also suffer from increased psychological distress, like symptoms of anxiety and depression.^{1,3,6,7,18,19} However, studies have not specifically focused on this area using validated psychometric tools for psychiatric comorbidity and the degree of psychological distress has not been clearly identified. Additionally, it remains unclear whether these symptoms are associated with worse prognosis of dysphagia rehabilitation outcome, and increased occurrence of dysphagia comorbidity, etc. The aim of the present study was to determine the presence and severity of symptoms of anxiety and depression in patients with oropharyngeal dysphagia who visit the outpatient clinic for dysphagia at the Maastricht University Medical Center.

Method

Participants

For this study, 96 patients with dysphagic complaints were recruited from the Maastricht University Medical Center outpatient clinic for dysphagia. Patient data were collected as part of the regular healthcare program for oropharyngeal dysphagia. The oropharyngeal dysphagic complaints of the participants ranged from mild to severe. These included slow mastication and eating, oropharyngeal pooling, coughing while drinking or eating, choking on food, weight loss, etc. Patients were included if their disease was stable over a period of at least three months. There were several exclusion criteria: scoring below 23 on a Mini Mental State Examination (MMSE);²⁰ being older than 85 years (presbyphagia); not being able to swallow (aphagia); exhibiting severe dyskinesia of head and neck (resulting in problems during the examinations); suffering from severe depression or having another known psychiatric diagnosis (using antidepressant and/or anxiolytic drugs); suffering from a recent stroke (less than

3 months); having had speech therapy during the past six months (benefit of attention and rehabilitation); having no knowledge of the Dutch language; and suffering from illiteracy or blindness. At the time of examination, all head and neck oncological patients had received oncological treatment more than 6 months ago. Neurological patients had been on a stable medication program for at least three months. None of the patients was in a palliative care state of disease.

Measures

All patients underwent a standardized examination protocol used for regular healthcare in the outpatient clinic for dysphagia. All measurements were performed in the same hospital by the same multidisciplinary team in order to guarantee standardized data collection. The protocol included the following: a clinical examination by a laryngologist, a clinical observation of oral intake by a speech and language pathologist, fiberoptic endoscopic evaluation of swallowing (FEES), video fluoroscopy of swallowing (VFS), the Functional Oral Intake Scale (FOIS; a dietary intake scale),²¹ body mass index (BMI) measurement, a dysphagia severity scale (DSS),⁴ the Hospital Anxiety and Depression Scale (HADS),²² and the M.D. Anderson Dysphagia Inventory (MDADI).²³

The range of scores of the FOIS is one to seven, where one corresponds with 'no oral diet, nothing by mouth' and seven with 'total oral diet, no restrictions'. The DSS is a visual analog scale (VAS), which is a psychometric response scale which can be used to measure subjective characteristics or attitudes. Dysphagic patients specify their level of agreement to a statement or question by indicating a position along a continuous line between two end-points for the DSS. The single question was: "How do you qualify your swallowing today?".⁴ The HADS questionnaire was used to score symptoms of anxiety and depression. This validated questionnaire consists of 14 items. Seven items score anxiety and 7 items depression. Both subscales have a score ranging from 0 to 21 points. A score of 8 or more has been shown to provide an optimal balance between sensitivity and specificity indicating the presence of symptoms of anxiety for the HADS-A and symptoms of depression for the HADS-D subscales.^{22,24,25} The HADS questionnaire is not a diagnostic instrument for affective disorders but rather a psychological screening instrument for symptoms of anxiety and depression in the hospital setting. The MDADI scale is a self-administered, psychometrically validated and reliable questionnaire and was used to assess the impact of dysphagia on the quality of life.²³ The MDADI consists of 20 items and has four subscales: Global (single item), Functional (5 items), Physical (8 items), and Emotional (6 items) subscale. The Global question refers to the patient's swallowing ability as it affects the overall quality of life (MDADI-G). The Functional subscale illustrates the impact of dysphagia on daily activities (MDADI-F). The Physical subscale refers to the patient's self-perception of his/her swallowing difficulty (MDADI-P). The Emotional subscale represents the patient's affective response to the dysphagia disorder, in terms of embarrassment, self-esteem, and self-consciousness (MDADI-E). All items are rated on a five-point scale (1–5) where

1 corresponds with “strongly agree” and 5 with “strongly disagree”. The maximum total score is 100 and the minimum total score is 20 (MDADI-T). A low score indicates low and a high score indicates high functioning. The MDADI is considered to have good test–retest reliability.^{4,23} The large data set from FEES and VFS assessment (1764 video recordings and 7056 measurements) derived from this patient population will be described in a subsequent paper.

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 20.0 (Armonk, NY: IBM Corp.). Descriptive data analysis was performed as presented in Table 2.1. The two-tailed Mann–Whitney U test ($p < 0.05$, 95% CI) was used to test for group differences as presented in Table 2.1. The two-tailed Spearman correlation ($p < 0.05$, 95% CI) coefficient was used to evaluate the relationship between the HADS-A and HADS-D scores. Logistic regression models were used to identify factors associated with symptoms of anxiety and/or depression (cut-off score ≥ 8). The score on the HADS-A and HADS-D (cut-off score ≥ 8) was defined as the dependent variable, and the clinical variables FOIS, DSS, MDADI-T, age, and etiology of oropharyngeal dysphagia were defined as covariates. The level of significance was set at $p < 0.05$.

Results

Patients characteristics

A total of 96 mentally competent patients with complaints of oropharyngeal dysphagia were included in this study. Of these, 39.6% ($N=38$) of the patients suffered from neurological diseases, 28.1% ($N=27$) from head and neck oncological diseases, and 32.3% ($N=31$) from miscellaneous etiologies (trauma, Zenker's diverticulum, etc.). Depending on the presence/absence of symptoms of anxiety and depression, several groups were distinguished (Table 2.1). The median age was 63.5 years and median BMI was 24.7. The male: female ratio was 67:29. No significant group differences between men and women were found using the Mann–Whitney U test as shown in Table 2.2. The HADS-A was filled out correctly by 96% ($N=92$) of the patients and the HADS-D was filled out correctly by 99% ($N=95$) of the patients. The median scores on HADS-A and HADS-D were 6 and 5 respectively. Thirty-seven percent ($N=34$) of the patients scored 8 or more points on the HADS-A scale. Thirty-two point six percent ($N=31$) of the patients scored 8 or more points on the HADS-D scale. Twenty-one point three percent ($N=20$) of the patients scored 8 or more points on both subscales. Forty-seven point three percent ($N=43$) of the total group showed affective symptoms. The correlation between the HADS-A and HADS-D subscales for the total patient group was $r=0.7$ ($p < 0.01$).

Table 2.1 Descriptive statistics and level of significance (p) for the comparison of patients with symptoms of anxiety and/or depression (cut-off score ≥ 8) and patients without affective symptoms (Mann-Whitney U test). Scores are given as median (25th, 75th percentiles).

	Descriptive group data and statistical group differences					
	No anxiety	Anxiety	No depression	Depression	Both anxiety and depression	Either anxiety or depression
	N=58 (63.0%) Median (25'; 75' perc.)	N=34 (37.0%) Median (25'; 75' perc.)	N=64 (67.4%) Median (25'; 75' perc.)	N=31 (32.6%) Median (25'; 75' perc.)	N=20 (21.3%) Median (25'; 75' perc.)	N=23 (25.3%) Median (25'; 75' perc.)
FOIS	6.0 (5.0;6.0)	6.0 (5.0;7.0)	6.0 (5.0;6.8)	5.0 (5.0;6.0) ^a	5.5 (5.0;6.8)	5.0 (5.0;6.0)
DSS	79.5 (47.3;94.0)	66.0 (32.5;85.0) ^b	72.0 (44.0;94.0)	66.0 (28.5;85)	66.0 (29.0;92.0)	67.0 (26.5;78.3)
MDADI-G	4.0 (3.0;5.0)	4.0 (2.0;5.0)	4.0 (3.0;5.0)	3.5 (1.8;5.0)	4.0 (1.5;5.0)	4.0 (2.0;4.0)
MDADI-F	21.0 (18.0;25.0)	20.0 (16.5;24.5)	21.0 (18.0;25.0)	20.0 (14.5;23.5) ^a	20.0 (16.3;24.3)	20.5 (15.0;24.8)
MDADI-P	29.0 (25.0;33.0)	29.5 (21.5;32.8)	30.0 (25.0;33.0)	26.0 (18.0;33.0)	28.0 (18.0;33.0)	26.0 (21.0;31.0)
MDADI-E	24.0 (20.0;27.5)	21.0 (17.0;23.0) ^b	23.0 (20.0;26.0)	20.0 (16.0;24.0) ^a	21.0 (16.0;26.0) ^c	20.0 (17.0;22.8)
MDADI-T	79.0 (64.0;87.0)	74.0 (61.0;85.0)	79.0 (66.8;87.5)	71.5 (52.0;85.5) ^a	74.5 (55.8;87.3)	68.0 (55.0;85.0)
HADS-A	NA	NA	5.0 (3.0;7.0)	10.0 (7.0;13.0) ^a	NA	NA
HADS-D	3.0 (1.0;6.0)	8.0 (6.0;13.5) ^b	NA	NA	NA	NA

FOIS: Functional Oral Intake Scale, DSS: Dysphagia Severity Scale, MDADI: MD Anderson Dysphagia Inventory subscales (General: MDADI-G, Functional: MDADI-F, Physical: MDADI-P, Emotional: MDADI-E), HADS: Hospital Anxiety and Depression Scale (HADS-A: Anxiety subscale, HADS-D: Depression subscale). NA=Not applicable.
^a Depression versus No depression (p<0.05). ^b Anxiety versus No anxiety (p<0.05). ^c Both Anxiety and depression versus no affective disorder (p<0.05).

The MDADI and HADS questionnaires were reviewed for possible floor and ceiling effects, noting the number of respondents who obtained the lowest or highest possible scores. No floor or ceiling effect was considered to be present because less than 8% of the respondents for MDADI and less than 3% of the respondents for HADS got the lowest or highest possible score on both questionnaires.

Table 2.2 Differences between the scores for males and females. Scores are given as median (25th, 75th percentiles). There are no significant group (gender) differences (Mann-Whitney U test).

Gender differences			
Gender	Female (N=29) Median (25';75' perc.)	Male (N=67) Median (25';75' perc.)	Total (N=96) Median (25';75' perc.)
FOIS	6.0 (5.0;6.0)	6.0 (5.0;6.5)	6.0 (5.0;6.0)
DSS	65.0 (20.5;93.5)	72.0 (46.8;90.0)	72.0 (42.0;91.0)
MDADI-G	4.0 (2.0;5.0)	4.0 (3.0;5.0)	4.0 (3.0;5.0)
MDADI-F	21.0 (16.0;24.0)	21.0 (18.0;25.0)	21.0 (17.8;25.0)
MDADI-P	27.0 (21.0;33.0)	30.0 (25.0;35.5)	29.0 (24.0;33.0)
MDADI-E	21.0 (17.8;26.0)	22.5 (20.0;26.0)	22.0 (19.0;26.0)
MDADI-T	71.5 (60.5;86.0)	79.0 (67.0;89.0)	76.0 (63.5;86.5)
HADS-A	7.0 (4.0;10.0)	6.0 (4.0;9.0)	6.0 (4.0;9.0)
HADS-D	6.0 (2.5;8.0)	5.0 (2.0;9.0)	5.0 (2.0;9.0)

FOIS: Functional Oral Intake Scale, DSS: Dysphagia Severity Scale, MDADI: MD Anderson Dysphagia Inventory subscales (General: MDADI-G, Functional: MDADI-F, Physical: MDADI-P, Emotional: MDADI-E), HADS: Hospital Anxiety and Depression Scale (HADS-A: Anxiety subscale, HADS-D: Depression subscale).

Group differences

Table 2.1 shows descriptive statistics and statistical significance tests for group differences (Mann–Whitney U test) between patients with symptoms of anxiety and/or depression and patients without. Patients with symptoms of anxiety (cut-off score ≥ 8) scored significantly lower ($p < 0.05$) on the DSS and MDADI-E compared to patients without symptoms of anxiety (Table 2.1 column 3). Patients with symptoms of depression (cut-off score ≥ 8) scored significantly lower ($p < 0.05$) on the FOIS, MDADI-F, MDADI-E, and MDADI-T compared with patients without symptoms of depression (Table 2.1 column 5). A significant group difference was found for the MDADI-E subscale between patients with symptoms for both anxiety and depression and patients without affective symptoms (Table 2.1 column 6). All other group differences were not statistically significant.

Logistic regression analyses

Symptoms of anxiety and/or depression (cut-off score ≥ 8) were defined as the dependent variable, and the clinical variables FOIS, DSS, MDADI-T, age, and etiology of oropharyngeal dysphagia were considered as independent explanatory variables in the logistic regression models. The odds ratios (ORs) of the significant covariates and their corresponding 95% confidence intervals are presented in Table 2.3. Logistic regression analyses revealed no significant association between the HADS-A (cut-off score ≥ 8) and

the MDADI-T ($p=0.166$). After adjustment for the MDADI-T in the model, no significant associations were found between the HADS-A and any of the covariates (DSS, FOIS, etiology, age). A significant negative association was found between the HADS-D (cut-off score ≥ 8) and the MDADI-T ($p=0.025$). After adjustment for the MDADI-T in the model, no significant associations were found between the HADS-D and any of the other covariates (DSS, FOIS, etiology, age). The HADS-A-and-D subscales were not significantly associated with MDADI-T ($p=0.298$). After adjustment for the MDADI-T in the model, no significant associations were found between the HADS-A-and-D and any of the covariates. A significant negative association was found between the HADS-A-or-D and the MDADI-T ($p=0.036$). After adjustment for the MDADI-T in the model, no significant associations were found between the HADS-A-or-D and any of the other covariates (DSS, FOIS, etiology, age).

Table 2.3 Estimated odds ratios (ORs) according to the fitted logistic regression models for the total patient group (N=96). Logistic regression analyses reveal some significant associations between variables.

Variables	Associations between variables OR [95% CI]; p-Value			
	HADS-A	HADS-D	HADS-A-and-D	HADS-A-or-D
MDADI-T	NS ^a	0.963 [0.93-1.00]; 0.025	NS	0.965 [0.93-1.00]; 0.036
FOIS	NS	NS	NS	NS
DSS	NS	NS	NS	NS
Age	NS	NS	NS	NS
Etiology of dysphagia	NS	NS	NS	NS

MDADI_T: MD Anderson Dysphagia Inventory Total score, FOIS; Functional Oral Intake Scale, DSS: Dysphagia Severity Scale, HADS; Hospital Anxiety and Depression Scale (HADS-A: Anxiety Subscale, HADS-D: Depression Subscale). ^a NS=Not significant.

Discussion

General aspects

This study was designed to examine the presence of clinically relevant anxiety and depression symptoms in patients who visited the Maastricht University Medical Center outpatient clinic for oropharyngeal dysphagia in daily practice. The present prospective study revealed that 37% (N=34) of this population experienced clinically relevant symptoms of anxiety and 32.6% (N=31) clinically relevant symptoms of depression. Forty-seven point three percent (N=43) of the total patient population showed clinically relevant affective symptoms. These results suggest that, almost half of this population suffers from affective complaints. Furthermore, these results indicate that dysphagic patients who have clinically relevant symptoms of anxiety and/or depression can be identified using the validated HADS questionnaire. Following this study, the majority of these patients have entered a dysphagia rehabilitation program. Information gathered by HADS-screening needs to be synthesized in forming a dysphagia management plan

for these patients. Although scientific evidence is scarce, previous research in Parkinson and in head-and-neck cancer patients for instance suggested interaction between symptoms of anxiety or depression and increased swallowing disturbances.^{7,19,26} In the study by Manor et al. the Swallowing Disturbances Questionnaire (SDQ), the Spielberger manual for the trait anxiety, and the Beck Depression Inventory (BDI) were administered to a group of patients with Parkinson's disease.¹⁹ The study demonstrates that patients with swallowing disorders experienced increased anxiety and depression compared to patients without swallowing disorders. Similar as in the current study it is not clear if there is a causal relationship between affective disorders and dysphagia. The authors concluded that the contribution of these swallowing disorders to already existing affective symptoms is very difficult to measure.

Nguyen et al. described head-and-neck cancer patients with moderate to severe dysphagia who experienced a statistically significant lower quality-of-life (University of Washington questionnaire [UW-QOL]) compared with those with no or mild dysphagia.⁷ They also had clinically relevant symptoms of anxiety and depression assessed with the HADS (severe dysphagia: HADS-A median=9; HADS-D median=10). The patient population of the outpatient clinic for oropharyngeal dysphagia under investigation in the current study also shows affective symptoms associated with a decreased quality-of-life although different validated psychometric tools to assess psychiatric comorbidity were used. Currently, there is no evidence in literature but it can be assumed that symptoms of anxiety and/or depression may be risk-factors for failure of oropharyngeal dysphagia rehabilitation. Although symptoms of anxiety and depression may occur frequently in dysphagic patients, like in other patients with complex psychiatric and somatic co-morbidity, it can be assumed that they often go undiagnosed and untreated (in case of depressive or anxiety disorders).²⁷ It is important to identify patients with these affective symptoms and to perform psychiatric assessment to diagnose and treat anxiety and/or depressive disorders in order to improve disease-specific health status and to facilitate and improve dysphagia rehabilitation outcome.

Symptoms of anxiety

Age and etiology of oropharyngeal dysphagia were not significantly associated with symptoms of anxiety. Also the FOIS (functional oral intake scale) did not show a significant association with symptoms of anxiety (cut-off score ≥ 8). Although it was expected that patients with a lower FOIS score would score higher on the HADS subscales, no significant group differences (anxiety versus no anxiety) were found (Table 2.1). An explanation for this unexpected outcome may be the skewed distribution of the FOIS levels in the current patient population. Only few patients met the criteria of level 1, 2, 3 or 4 on the FOIS scale. Furthermore, the severity of disabled dietary intake may not be a determinant of clinically relevant symptoms of anxiety. Patients with symptoms of anxiety scored significantly lower on the DSS scale compared to patients without symptoms (Table 2.1 column 3). The score on the DSS is

a patient's subjective evaluation of his/her current swallowing status. Either patients with symptoms of anxiety experience a more disabled swallowing function, or patients who experience a more disabled swallowing function are more at risk for developing symptoms of anxiety. The primary aim of the MDADI is to assess psychosocial aspects of dysphagia.²³ A lower score on the MDADI questionnaire, or one of the subscales, indicates a lower quality of life. Patients with symptoms of anxiety have a significantly lower score on the MDADI-E subscale (Table 2.1 column 3). The emotional subscale refers to the individual's affective responses to the swallowing disorder. Thus, symptoms of anxiety appear to be significantly associated with a disturbed affective response to the swallowing disorder.

Symptoms of depression

As mentioned previously the FOIS score is not normally distributed. However, patients with symptoms of depression scored significantly lower on the FOIS scale (Table 2.1 column 5). This indicates that patients with a more disabled dietary intake have a higher risk of having symptoms of depression. Whether this is a causal relationship is unclear. In the study of Han et al. the Swallowing Disturbances Questionnaire (SDQ) and the Beck Depression Inventory (BDI) questionnaire were administered to a group of patients with Parkinson's disease to investigate the relationship between depressive states and dysphagia.²⁶ Depression was significantly associated with an increased risk of dysphagia, although a causal association of depression with dysphagia could not be verified. These findings support the findings of the current study although the differences in applied assessment tools and patient populations between both studies should not be disregarded. In the study by Holland et al. the validated Sydney Swallow Questionnaire and the Geriatric Depression Scale were sent to a group of elderly people (age over 50 years).²⁸ This study found a strong and independent association between depression and dysphagia symptoms, suggesting a potential interaction. Similar to the current study no causal relationship was found.

A significant lower score for the MDADI-T, MDADI-F, and MDADI-E subscales was found in patients with depressive symptoms (cut-off score ≥ 8) compared with symptom-free patients (Table 2.1 column 5). Logistic regression analysis revealed a significant association between the MDADI-T subscale and symptoms of depression (Table 2.3). Apparently patients with oropharyngeal dysphagia and symptoms of depression have a lower quality of life. A dysphagia related lower quality of life score on the MDADI may be a possible determinant of clinically relevant symptoms of depression. The present study shows no significant association between symptoms of depression and the DSS, age or etiology of oropharyngeal dysphagia.

Limitations of the study

The present prospective study has some methodological limitations. The study revealed some interesting statistically significant preliminary data. However, the sample size may

be too small to reveal all significant associations or group differences. Heterogeneous etiology of oropharyngeal dysphagia and the small number of patients per etiological group made it impossible to compare groups for significant symptoms of anxiety or depression. Another limitation may be the cut-off value ≥ 8 that has been used for the HADS subscales in patients with oropharyngeal dysphagia in the current study. Other cut-off values, for instance >10 points, may have led to different results for clinically relevant affective symptoms in this patient population.²² The present study design adhered to the cut-off score ≥ 8 as recommended by Bjelland et al. as it has been shown to yield the most optimal balance between sensitivity and specificity.²⁵ Furthermore, there are other screening tools for symptoms of anxiety and depression available.²⁴ Another tool may have produced different results in the present study. However, the validated HADS questionnaire is a reliable and frequently used psychological measurement instrument for the screening of symptoms of anxiety and depression in the hospital setting. A further potential drawback is that healthy controls were not included. However the cut-off values for the validated HADS questionnaire as described above determined the presence of clinically relevant symptoms of anxiety and depression in the present population. Finally, three patients suffering from a known psychiatric diagnosis (phagophobia) were excluded leaving 96 subjects to be included. The inclusion of these phagophobic patients may have led to an increased frequency of affective symptoms. On the other hand, inclusion of patients treated with antidepressant and/or anxiolytic drugs may have led to decreased frequencies of affective symptoms and underestimation of the effect. However, the present study revealed affective symptoms in 47.3% (N=43) of the patients without inclusion of these subjects.

Conclusion

Clinically relevant symptoms of anxiety and/or depression are frequently present in patients who suffer from oropharyngeal dysphagia. The present data revealed significant levels of affective symptoms in patients with oropharyngeal dysphagia who visited the Maastricht University Medical Center outpatient clinic for dysphagia in daily practice. The contribution of anxiety and/or depression to the development or worsening of oropharyngeal dysphagia warrants further research, in order to investigate interdisciplinary dysphagia treatment strategies.

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Chapter 3

The relationship between fiberoptic endoscopic
evaluation of swallowing outcome and symptoms of
anxiety and depression in dysphagic patients

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Abstract

Objectives/Hypothesis

Affective complaints are involved in bothersome oropharyngeal dysphagia (OD). The aim was to determine the relationship between the severity of OD and affective symptoms.

Study Design

Prospective cohort study.

Methods

One hundred seven patients underwent a standardized examination protocol including the Hospital Anxiety and Depression Scale and fiberoptic endoscopic evaluation of swallowing (FEES). Two observers independently assessed patient performance on four ordinal FEES-variables (for thin and thick liquid consistency, blindly assessed). The relationship between FEES outcome and the presence of clinically relevant symptoms of anxiety and depression was analyzed using binary logistic regression.

Results

Significant associations were found between clinically relevant symptoms of anxiety and two variables: piecemeal deglutition (thin liquid consistency only) ($p=.026$) and postswallow vallecular pooling (thick liquid consistency only) ($p=.015$). The probability of presenting with anxiety symptoms decreased as the severity of piecemeal deglutition and postswallow vallecular pooling increased. No significant association was found between clinically relevant symptoms of depression and any specific FEES variable.

Conclusions

These data revealed few associations between anxiety symptoms and the measured FEES variables. However, the more severe the score on FEES variables, the less important the affective complaints were. Anxiety seems to play a role in OD, but no causal relationship was found, commensurate with a cross-sectional study design. The contribution of affective symptoms to the development and treatment of OD warrants longitudinal research.

Introduction

Oropharyngeal dysphagia (OD) is commonly observed at the outpatient clinic for otorhinolaryngology. The problem can be caused by various conditions (e.g., head and neck cancer and its oncological treatment; neurological diseases such as Parkinson's disease, stroke, or multiple sclerosis; Zenker's diverticulum; cervical spine degeneration).^{1–3} The epidemiology of OD is constantly changing as more diagnoses present with it. OD can have severe consequences such as aspiration pneumonia, and its possible complications can lead to malnutrition, dehydration, and sudden death.^{3–6} Furthermore, OD can lessen one's quality of life.^{6–10} Its psychosocial burden is a reason to investigate swallowing problems, as these are often associated with shame, diminished self-esteem, and embarrassment. Thereby, OD may contribute to a decreased quality of life and even social isolation.⁴ In a previous study among patients who visited the outpatient clinic for OD, 37% presented with clinically relevant symptoms of anxiety and 32.6% with depressive symptoms.¹¹ The present study investigated the relationship between the severity of OD by means of fiberoptic endoscopic evaluation of swallowing (FEES), and clinically relevant depressive and anxiety symptoms using the Hospital Anxiety and Depression Scale (HADS).

Materials and method

Participants

One hundred seven patients with OD complaints were recruited at the outpatient clinic for otorhinolaryngology and divided into three main diagnostic groups (Table 3.1). Fifty-four patients suffered from neurological diseases (e.g., Parkinson's disease, stroke), 35 patients from miscellaneous or other etiologies (e.g., Zenker's diverticulum, cervical spine degeneration), and 18 patients from head and neck oncological diseases. At the time of examination, all head and neck oncological patients had received curative oncological treatment at least 6 months prior to inclusion. All neurological patients were in a stable period of disease or on a stable medication program for at least 3 months. None of the included patients was in a stage of palliative care. Exclusion criteria were: age older than 85 years (presbyphagia), a score below 23 on the Mini Mental State Examination (MMSE),¹² severe dyskinesia of head and neck (problems during swallow examinations), recent stroke (less than 3 months prior to investigation), previously diagnosed with depression or another psychiatric disease (use of antidepressant and/or anxiolytic drugs), having had speech therapy during the past 6 months (benefit of attention and rehabilitation), not knowing the Dutch language, suffering from illiteracy or blindness. Informed consent was obtained from all patients. The medical ethics committee approved the study protocol.

Table 3.1 Characteristics of the 107 patients with oropharyngeal dysphagia.

Patient characteristics	No.	% or Median (range)	Mean (SD)
Gender			
Male	63	58.9%	
Female	44	41.1%	
Age, yr	107	60.0 (21–82)	58.7 (13.8)
BMI	101	25.8 (13.7–36.5)	
Etiology			
Neurology	54	50.5%	
Oncology	18	16.8%	
Other	35	32.7%	
HADS-A	105	5.0 (0–16)	
HADS-D	105	5.0 (0–19)	
DSS	105	72 (0–100)	

Median and range are given for continuous variables, whereas frequency and percentages are provided for nominal variables. BMI: body mass index; DSS: Dysphagia Severity Scale; HADS: Hospital Anxiety and Depression Scale; HADS-A: HADS Anxiety subscale; HADS-D: HADS Depression subscale; SD: standard deviation.

Examination protocol

All patients underwent a standardized examination as set forth in the protocol used in daily clinical practice at the outpatient clinic for otorhinolaryngology at the Maastricht University Medical Center. The same members of a multidisciplinary team performed all measurements. The protocol stipulated the following tests: a clinical examination by an experienced laryngologist, body mass index (BMI) measurement, MMSE, FEES examination, the Dysphagia Severity Scale (DSS), and the HADS.¹³ The DSS is a visual analogue scale (VAS) or psychometric response scale used to elicit patients' subjective evaluation of swallowing. Patients were asked to answer a question by indicating a position along a continuous line between two endpoints. The question was, "How do you assess your swallowing function today?"⁶ The HADS questionnaire is a validated tool to assess symptoms of anxiety and depression, consisting of 14 items—seven on anxiety and seven on depression. Every item is scored from 0 to 3, resulting in a range from 0 to 21 on each subscale. A score ≥ 8 on one of the subscales points to the presence of clinically relevant symptoms of anxiety or depression, indicating mood disturbances or anxiety complaints.^{13–15} All patients were given a standardized FEES examination.¹⁶ First they had to perform three swallows of 10 mL thin liquid (water) and then three swallows of 10 mL standardized applesauce (hereinafter referred to as "thick liquid"). All liquids were dyed with 5% methylene blue (10 mg/mL). A flexible fiberoptic endoscope, Pentax FNL-10RP3 (Pentax Canada Inc., Mississauga, Ontario, Canada), was used with the tip in the high position, just above the epiglottis. Thus positioned, the scope could not interfere with closure of the laryngeal vestibule.¹⁶ The FEES videos were obtained with an Alpatron Stroboscopy ACLS camera, Alpatron Light Source, and IVACX computerized video archiving system (Alpatron Medical Systems, Rotterdam, the Netherlands) and recorded on a DVD.

FEES variables

Four visuoperceptual ordinal variables (piecemeal deglutition, postswallow vallecular pooling, postswallow pyriform sinus pooling, and aspiration) (Table 3.2)¹⁷ were scored for each FEES swallow at varying speed (slow motion, normal, up to frame-by frame speed) using the software program Windows Movie Maker version 5.1 (Microsoft Corp., Redmond, WA). Before assessing the swallowing acts, two experts received consensus training for scoring these variables, as described previously.^{18–20} The judges were blinded to the identity and medical history of the patients and to each other's scores (independent rating). To determine the level of intraobserver agreement, both judges were asked to blindly assess the four FEES variables in 27 (26%) randomly selected patients (111 of the 428 videos) twice within a period of 2 weeks. To avoid observer fatigue, the measurement sessions were limited to a maximum duration of 2 hours.

Statistical analysis

Only the second swallow per consistency was taken into account in the statistical analysis. Intra- and interobserver agreement on the four FEES variables was determined with the linear weighted kappa coefficient. For each FEES variable, the assessments of the judge with the highest intraobserver agreement levels were then retained for the subsequent statistical analysis.

Results were expressed as the median (range) for continuous variables, whereas frequencies and proportions (%) were used for ordinal FEES variables. Means for age between etiological groups were compared with a one-way analysis of variance analysis. The relationship between the presence of clinically relevant symptoms of anxiety and depression (HADS score ≥ 8) and the severity of OD (assessed with FEES) was analyzed by means of the χ^2 test for contingency tables and by multiple binary logistic regression analysis. Furthermore, multiple linear regression analysis was used to study the relationship between the DSS score and the severity of OD. The measured FEES variables were considered in separate regression models because of the high degree of association between them. Calculations were always carried out on the maximum amount of data available. Missing data were not replaced. Results were considered to be significant at the 5% critical level. Statistical analyses were conducted using IBM SPSS Statistics for Windows version 21.0 (IBM Corp., Armonk, NY).

Table 3.2 Interobserver and intraobserver agreement levels per FEES variable assessed with linear weighted Kappa and 95% confidence interval.

FEES outcome variable	Definition	Ordinal scale*	Interobserver agreement Kappa (95% CI)		Intraobserver agreement Kappa (95% CI)			
			Thin liquid	Thick liquid	Observer 1	Thin liquid	Thick liquid	Observer 2
Piecemeal deglutition	Sequential swallowing on the same bolus	Five-point scale (0-4):						
		0 = no additional swallows	0.86 (0.79-0.93)	0.91 (0.86-0.96)	0.94 (0.88-0.99)	0.97 (0.93-1.00)	0.84 (0.75-0.94)	0.96 (0.91-1.00)
		1 = one additional swallow						
		2 = two additional swallows						
		3 = three additional swallows						
		4 = four or more additional swallows						
Postswallow Vascular pooling	Pooling in Valleculae After the swallow	Three-point scale (0-2):						
		0 = no pooling	0.72 (0.60-0.83)	0.78 (0.68-0.88)	0.75 (0.60-0.90)	0.85 (0.75-0.96)	0.80 (0.66-0.95)	0.85 (0.75-0.96)
		1 = filling of less than 50% of the valleculae						
		2 = filling of more than 50% of the valleculae						
Postswallow pyriform sinus pooling	Pooling in pyriform sinuses after the swallow	Three-point scale (0-2):						
		0 = no pooling	0.71 (0.58-0.83)	0.71 (0.59-0.83)	0.87 (0.76-0.98)	0.94 (0.87-1.00)	0.95 (0.88-1.00)	0.87 (0.75-0.99)
		1 = trace to moderate pooling						
		2 = severe pooling up to complete filling of the sinuses						
Aspiration	Aspiration of bolus below the vocal folds	Two-point dichotomous scale (0-1)						
		0 = no aspiration	0.83 (0.70-0.96)	0.63 (0.38-0.88)	1.00 (0.77-1.00)	0.92 (0.84-1.00)	0.94 (0.84-1.00)	0.90 (0.71-1.00)
		1 = aspiration						

Results of intraobserver agreement are given for both observers. Agreement levels are calculated on the second swallow per consistency. *Lower scores refer to normal functioning, whereas higher scores refer to more severe disability. CI: confidence interval; FEES: fiberoptic endoscopic evaluation of swallowing.

Results

Participants

A total of 107 patients who visited the outpatient clinic for OD were included. Their characteristics are described in Table 3.1. There were 44 (41.1%) females and 63 (58.9%) males with OD divided into three etiological groups, namely neurological (50.5%), head and neck oncological (16.8%), and other or miscellaneous (32.7%). Neurological etiology encompasses stroke, Parkinson's disease, and muscular dystrophies. Oncological etiology refers to a heterogeneity of tumour sites and stages in the head and neck topographical region. The category of other covers Zenker's diverticulum, cervical spine degeneration, and dysfunction of the upper esophageal sphincter. The median age in the study population was 60 years. The neurological patients were younger than the patients in the miscellaneous and oncological groups, with an average (standard deviation) of 53.4 (14.4) versus 64.1 (11.7) and 64.4 (9.2), respectively ($F(2,104) = 9.562$, $p < .0005$). The frequencies of patients per category of the different FEES variables are shown in Table 3.3, giving an indication of the average swallowing function of the study population.

Table 3.3 Frequency distribution of patients per category of the different FEES variables given as absolute numbers and percentages.

FEES Category Frequencies	Thin Liquid Consistency, N (%)	Thick Liquid Consistency, N (%)
Piecemeal deglutition		
Category 0	23 (21.5%)	10 (9.3%)
Category 1	35 (32.7%)	40 (37.4%)
Category 2	30 (28.0%)	28 (26.2%)
Category 3	8 (7.5%)	13 (12.1%)
Category 4	7 (6.5%)	15 (14.0%)
Postswallow vallecular pooling		
Category 0	36 (33.6%)	21 (19.6%)
Category 1	43 (40.2%)	37 (34.6%)
Category 2	21 (19.6%)	42 (39.3%)
Postswallow pyriform sinus pooling		
Category 0	58 (54.2%)	58 (54.2%)
Category 1	32 (29.9%)	17 (15.9%)
Category 2	12 (11.2%)	21 (19.6%)
Aspiration		
Category 0	84 (78.5%)	92 (86.0%)
Category 1	21 (19.6%)	12 (11.2%)

FEES: fiberoptic endoscopic evaluation of swallowing.

Observer agreement

Table 3.2 displays the intra- and interobserver agreement levels on each FEES variable with 95% confidence intervals (CIs) for thin and thick liquids separately. The agreement levels were sufficient for all measured FEES variables. The lowest intraobserver

agreement level was 0.75 (95% CI: 0.60-0.90) for postswallow vallecular pooling in thin liquid consistency (observer 1), whereas the lowest interobserver agreement level was 0.63 (95% CI: 0.38-0.88) for aspiration of thick liquid.

Descriptive data of the HADS questionnaire

The HADS-Anxiety (A) and HADS-Depression (D) subscales were filled out completely by 98.1% of the patients. The median score on HADS-A was 5.0 (range, 3.5–9.0); the median score on HADS-D was 5.0 (range, 2.0–8.0). Clinically relevant symptoms of anxiety or depression were present in 46 (43.0%) patients. Thirty-seven (35%) patients showed symptoms of anxiety, 31 (29%) patients showed symptoms of depression. No floor or ceiling effect was observed because less than 5% of the patients had the lowest or highest possible score on the HADS questionnaire.

HADS questionnaire and FEES

Depression subscale

Results from the logistic regression analyses for the presence of clinically relevant depressive symptoms as a function of OD severity (category or severity level of the ordinal FEES variable) are given in Table 3.4. There was no significant association between clinically relevant symptoms of depression and any specific FEES variable (or level of its ordinal scale) for either consistency. However, a significant association was found between HADS-D and age, representing the probability of depressive symptoms rising with age (odds ratio: 1.06, 95% CI: 1.01-1.10). A significant association was also found between the presence of clinically relevant depressive symptoms and OD etiology, representing the probability of higher depressive symptoms in neurology and head and neck oncology patients as compared to patients in the miscellaneous category. The odds ratios are 8.7 (95% CI: 2.08-36.4) for neurological patients and 7.6 (95% CI: 2.04-28.2) for oncological patients. The results of the χ^2 test were consistent with the findings. Moreover, analysis of the third swallow per consistency led to the same results.

Anxiety subscale

The results for clinically relevant anxiety symptoms are given in Table 3.5. For thin liquid consistency, there was a significant association between piecemeal deglutition and the presence of clinically relevant anxiety symptoms ($p=.026$). The probability of presenting with anxiety symptoms decreased with a rising severity of piecemeal deglutition. For thick liquid consistency, there was a significant association between postswallow vallecular pooling and the presence of clinically relevant anxiety symptoms ($p=.015$). The probability of anxiety symptoms was higher in category 1 of postswallow vallecular pooling compared to category 0 (no pooling) and category 2 (severe pooling).

All other results were not statistically significant. The results of the χ^2 test were consistent with the findings. Moreover, analysis of the third swallow per consistency led to the same results.

Table 3.4 Logistic regression analyses of the presence of HADS-D clinical symptoms for thin and thick liquid consistency.

	Liquid Consistency			
	Thin		Thick	
	Estimate (SE)	p value	Estimate (SE)	p value
Model 1				
Intercept	-3.07 (1.31)	.019	-3.49 (1.45)	.016
Piecemeal deglutition		.14		.20
Category 1*	-1.27 (0.66)	.055	-0.60 (0.81)	.46
Category 2	-0.79 (0.65)	.23	-0.19 (0.87)	.83
Category 3	0.37 (0.94)	.70	1.06 (0.96)	.27
Category 4	-1.91 (1.28)	.14	-0.93 (1.03)	.37
Age, yr	0.06 (0.02)	.010	0.06 (0.02)	.013
Etiology		<.0001		<.0001
Oncology	0.31 (0.68)	.65	0.34 (0.66)	.61
Other	-2.23 (0.72)	.002	-2.11 (0.70)	.003
Model 2				
Intercept	-3.71 (1.28)	.004	-3.29 (1.25)	.009
Postswallow vallecular pooling		.77		.27
Category 1*	0.15 (0.53)	.78	0.51 (0.62)	.41
Category 2	-0.33 (0.66)	.62	-0.54 (0.61)	.38
Age, yr	0.06 (0.02)	.007	0.05 (0.02)	.016
Etiology		.001		.001
Oncology	0.12 (0.60)	.85	0.13 (0.62)	.83
Other	-2.03 (0.67)	.002	-2.14 (0.70)	.002
Model 3				
Intercept	-3.54 (1.22)	.004	-3.33 (1.23)	.007
Postswallow pyriform sinus pooling		.89		.19
Category 1*	-0.20 (0.55)	.72	-0.74 (0.72)	.30
Category 2	-0.30 (0.73)	.68	-1.04 (0.65)	.11
Age, yr	0.05 (0.02)	.008	0.05 (0.02)	.009
Etiology		.001		<.0001
Oncology	0.14 (0.61)	.82	0.10 (0.63)	.87
Other	-2.09 (0.68)	.002	-2.18 (0.69)	.001
Model 4				
Intercept	-3.48 (1.23)	.005	-3.64 (1.26)	.004
Aspiration				
Category 1*	-1.07 (0.68)	.11	-1.52 (0.91)	.095
Age, yr	0.06 (0.02)	.008	0.06 (0.02)	.009
Etiology		<.0001		<.0001
Oncology	0.03 (0.61)	.96	0.53 (0.64)	.41
Other	-2.23 (0.69)	.001	-3.64 (1.26)	.004

Category 0 is the reference category for all FEES variables. Neurology is the reference category for etiology.

* Lower categories refer to normal functioning, whereas higher categories refer to more severe disability.

HADS-D: Hospital Anxiety and Depression Scale-Depression; SE: standard error.

Table 3.5 Logistic regression analyses of the presence of HADS-A clinical symptoms for thin and thick liquid consistency.

	Liquid consistency			
	Thin		Thick	
	Estimate (SE)	p value	Estimate (SE)	p value
Model 1				
Intercept	0.37 (0.43)	.40	-0.98 (0.68)	.15
Piecemeal deglutition		.026		.35
Category 1*	-1.15 (0.57)	.043	0.51 (0.75)	.50
Category 2	-1.17 (0.59)	.048	0.55 (0.78)	.48
Category 3 + 4	-2.24 (0.88)	.010		
Category 3			0.82 (0.88)	.35
Category 4			-0.81 (1.02)	.43
Model 2				
Intercept	-0.49 (0.32)	.14	-0.92 (0.42)	.028
Postswallow vallecular pooling		.88		.015
Category 1*	-0.21 (0.46)	.65	1.09 (0.54)	.043
Category 2	-0.21 (0.56)	.71	-0.25 (0.55)	.66
Model 3				
Intercept	-0.64 (0.27)	.017	-0.39 (0.25)	.12
Postswallow pyriform sinus pooling		.95		.32
Category 1*	0.13 (0.45)	.77	-0.48 (0.59)	.41
Category 2	-0.05 (0.67)	.94	-0.77 (0.57)	.18
Model 4				
Intercept	-0.40 (0.23)	.079	-0.64 (0.22)	.004
Aspiration				
Category 1*	-1.05 (0.60)	.079	-0.05 (0.65)	.94

Category 0 is the reference category for all FEES variables. * Lower categories refer to normal functioning, whereas higher categories refer to more severe disability. HADS-A: Hospital Anxiety and Depression Scale-Anxiety; SE: standard error.

DSS score and FEES

Table 3.6 shows the results of linear regression analyses of the FEES variables, age, BMI, and OD etiology on the DSS score (patients' subjective evaluation of their own swallowing function). A significant association was found between DSS and postswallow pyriform sinus pooling for thick liquid consistency. The highest DSS scores (higher score = better swallowing perception) fall into the lower categories of the postswallow pyriform sinus pooling scale (lower category = better swallowing function). All other results were not statistically significant.

Table 3.6 Results of the linear regression analysis for the dysphagia severity scale for thin and thick liquid consistency.

	DSS score (Thin)		DSS score (Thick)	
	Estimate (SE)	p value	Estimate (SE)	p value
Model 1				
Intercept	80.5 (12.4)	<.0001	90.0 (13.32)	<.0001
Piecemeal deglutition		.89		.061
Category 1*	1.21 (6.61)	.85	-14.4 (8.40)	.089
Category 2	-4.12 (6.92)	.55	-9.81 (8.87)	.27
Category 3	-6.00 (11.2)	.59	-30.9 (10.6)	.004
Category 4	-4.92 (11.3)	.66	-15.0 (10.1)	.14
Age, yr	-0.069 (0.20)	.73	-0.043 (0.20)	.83
Etiology		.011		.013
Oncology	-23.6 (7.84)	.003	-22.1 (7.40)	.004
Other	-11.2 (6.11)	.069	-9.20 (5.85)	.12
Model 2				
Intercept	83.1 (11.5)	<.0001	80.4 (11.6)	<.0001
Postswallow vallecular pooling		.30		.56
Category 1*	-8.36 (5.53)	.13	-7.05 (6.53)	.28
Category 2	-6.58 (6.78)	.33	-4.72 (6.30)	.46
Age, yr	-0.056 (0.20)	.78	-0.022 (0.20)	.91
Etiology		.004		.006
Oncology	-24.5(7.27)	.001	-23.8 (7.30)	.002
Other	-11.1 (5.93)	.064	-10.5 (5.98)	.081
Model 3				
Intercept	76.7 (11.3)	<.0001	73.5 (10.8)	<.0001
Postswallow pyriform sinus pooling		.91		.046
Category 1*	1.95 (5.80)	.74	16.4 (6.95)	.021
Category 2	-1.60 (8.23)	.85	8.65 (6.26)	.17
Age, yr	-0.037 (0.20)	.85	-0.062 (0.19)	.75
Etiology		.007		.010
Oncology	-23.7 (7.40)	.002	-22.2 (7.18)	.003
Other	-10.8 (6.19)	.083	-9.12 (5.89)	.13
Model 4				
Intercept	76.7 (11.2)	<.0001	76.3 (11.2)	<.0001
Aspiration				
Category 1*	7.29 (6.41)	.26	5.99 (7.99)	.46
Age, yr	-0.056 (0.20)	.78	-0.037 (0.20)	.86
Etiology		.006		.004
Oncology	-23.7 (7.27)	.002	-25.9 (7.56)	.001
Other	-11.1 (6.09)	.072	-10.5 (6.10)	.087

Category 0 is the reference category for all FEES variables. Neurology is the reference category for etiology.

* Lower categories refer to normal functioning, whereas higher categories refer to more severe disability.

SE: standard error

Discussion

The present study revealed a high prevalence (43%) of clinically relevant affective symptoms in patients with OD. Little is known about the pathways by which psychiatric

comorbidity may be involved in OD. This is the first study to investigate whether there is a relationship between the severity of affective complaints and the severity of OD as measured by FEES.

Our investigation did not demonstrate a significant association between clinically relevant depressive symptoms and the FEES outcome variables. This suggests that there may be no relationship between a depressive state and the severity of OD. However, our study did find a significant association between clinically relevant anxiety symptoms and the FEES variable piecemeal deglutition (for thin liquid consistency), with a higher probability of anxiety symptoms in the lower ordinal categories of the piecemeal deglutition scale. Furthermore, a significant association was found for clinically relevant symptoms of anxiety and the FEES variable postswallow vallecular pooling (for thick liquid consistency). There, the probability of anxiety symptoms was higher in the postswallow vallecular pooling category 1 compared to category 0 and category 2. Apparently, severe OD did not result in a higher probability of having affective complaints. These findings may indicate that less severe or medically unexplained subjective OD complaints could be a manifestation of an anxious and somatically hyperaroused state. Such a state is characterized by somatic anxiety equivalents due to either psychiatric disorders or early stages of somatic diseases.^{21,22} Another possible explanation may be that patients with more severe chronic OD often had a long history of disease. They may have already adapted to their physical limitations, unlike patients with mild OD in the early stages or acute onset of disease. Regarding Parkinson's disease, for instance, the prevalence of depression peaks at the beginning of the disease and again in its latter stages; in between, the prevalence of affective complaints is lower.²³ Moreover, all head and neck oncological patients in this study were not in a palliative stage of care, meaning that they were cancer survivors. Head and neck oncological patients often show improvement in their psychological and psychiatric functioning during follow-up, whereas the severity of the disease or functional disability remains stable or even deteriorates. These patients successfully adjust to living with their physical problems; as time passes, their fear of recurrence and death is likely to decline.^{24–26}

This study showed a relationship between the patients' subjective evaluation of their own swallowing as measured with a VAS (DSS) on the one hand, and the FEES variable postswallow pyriform sinus pooling (for thick liquid consistency) on the other. For the rest of the FEES variables, no significant association with the DSS was found. Given these results, no relation is apparent between the measured severity of OD and the patients' subjective evaluation of their own swallowing. Some patients with a nearly normal swallowing function considered their swallowing to be very impaired, whereas some patients with severe OD considered it normal, though acknowledging that they were not always aware of their diminished swallowing function. For example silent aspiration, a severe swallowing abnormality, can occur without subjectively suffering from it.^{27,28} Moreover, several patient groups (neurodegeneration, stroke, head and neck oncology post-radiation and post-surgery) tend to have sensory deficits that may

contribute to inaccurate judgment.^{29–35} Inaccuracy of perceptual judgment (underestimation of the problem) may manifest itself in fewer subjective complaints.²⁷ This could explain why the present study found very few significant associations between the DSS and the severity of OD as measured with FEES. Another explanation may be that higher anxiety levels influenced the patients' experience, in terms of suffering without severe OD. A previous study in the present patient population showed a significant association between DSS and symptoms of anxiety.¹¹ That finding indicated that a patient's subjective evaluation of swallowing probably is a better indicator of affective symptoms than the FEES outcome. These findings are in accordance with the literature on medically unexplained physical symptoms.^{21,22} Recognizing that affective symptoms are common in OD patients¹¹ and assuming that these problems are not solely dependent on the severity of OD could lead to new directions for future research. These insights could also serve as grounds for a clinically relevant implementation of affective symptom screening in dysphagia management. Such screening could extend diagnostic skills throughout the field while preventing under detection of relevant psychiatric comorbidities.^{11,36} Although OD intervention has already been organized as a multidisciplinary field in the Netherlands, psychiatric and psychological expertise has not yet been routinely integrated in the approach.^{22,37}

Limitations of the study

Head and neck cancer and neurological diseases, regardless of OD, are associated with symptoms of anxiety and depression. In the current study it is difficult to define what affective symptoms can be purely attributed to OD. However, previous studies in post-treatment head and neck cancer patients and post-stroke patients showed a lower prevalence of symptoms of anxiety and depression compared to our study population (15%–24% vs. 29% for depression and 14%–21% vs. 35% for anxiety).^{38–43} This may indicate a contributing effect of OD on affective symptoms. Moreover, only a few associations have been shown between the FEES outcome and symptoms of anxiety. The sample size was too small to yield additional significant results. Because of the heterogeneity of the study population and the small size of the etiological subgroups, no further statistical analyses of group differences could be performed. Furthermore, FEES was used as a diagnostic tool to measure the severity of swallowing dysfunction. The question remains whether other diagnostic tools (such as videofluoroscopy, manometry, or electromyography) would have provided different results. On the other hand, FEES is commonly used in the evaluation of OD worldwide. Finally, several disorders may be accompanied by cognitive impairment (e.g., Parkinson's disease, stroke). Several patients with severe OD were excluded from this study because of a MMSE below 23; their exclusion might have affected the frequencies of affective symptoms.

Conclusion

Affective symptoms were observed in almost half of the patients with OD. Clinically relevant symptoms of anxiety were significantly associated with some FEES variables (piecemeal deglutition and postswallow vallecular pooling). However, the more severe the score on piecemeal deglutition and postswallow vallecular pooling, the less important the affective complaints were. Thus, anxiety seems to play a role in OD, particularly in the early stages of neurological or oncological disorders or in medically unexplained subjective OD complaints.^{21,22} Given the cross-sectional study design, no causal relationship was found. Therefore, further investigation of the contribution of affective symptoms to the development and treatment of OD would warrant longitudinal research.

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Chapter 4

Affective symptoms in patients with oropharyngeal
dysphagia: A systematic review

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Abstract

Objective

Affective disorders are prevalent in different somatic conditions and influence somatic symptom bother and quality of life. Mood and anxiety disorders impact patients' compliance and adherence to treatment. This systematic review summarizes published studies on affective complaints in patients with oropharyngeal dysphagia (OD) in order to determine the quality of studies concerning any association of OD with symptoms of depression and/or anxiety.

Methods

A literature search was carried out using electronic databases Embase, Medline, Web-of-science, PsycINFO, Cochrane Library, and Google scholar. Two reviewers made the preselecting cut by screening all articles on title and abstract and independently screened the full texts of this initial set of articles. Methodological quality of the studies that met the inclusion criteria was assessed independently.

Results

Twenty-four articles were included in the analysis after full-text screening and by applying the inclusion and exclusion criteria. All studies concluded that symptoms of depression were associated with impaired swallowing function, and 9 out of 12 studies concluded that symptoms of anxiety were associated with functional impairment of swallowing. The reviewers found heterogeneous outcomes and methodological limitations, which prevented data from pooling.

Conclusion

Although no meta-analytic conclusions can be drawn, it appears that symptoms of anxiety and depression are common in OD. Caregivers have to be aware of this in order to detect affective comorbidity. Given that affective conditions influence patients' treatment adherence and compliance, integrated care approaches should be advocated in case of comorbidity. Studies on treatment effect are lacking and well-designed prospective research is needed.

Introduction

Oropharyngeal dysphagia (OD) is commonly seen in the otorhinolaryngology outpatient clinic, and is defined as 'difficulty to transport bolus from the mouth, via the pharynx, to the entrance of the esophagus'.¹ The etiology of OD is diverse: stroke; chronic neurological diseases (e.g., multiple sclerosis, Parkinson's disease, myasthenia gravis); head and neck cancer or its oncological treatment effects (e.g., surgery, radiation); inclusion body myositis; Zenker's diverticulum; cervical spine abnormalities (e.g., degenerative, osteophytes); rising age (presbyphagia), etc.¹⁻³ The prevalence of OD is high. For instance, it affects > 30% of patients who had a stroke, and 52%-82% of patients with Parkinson's disease. The prevalence of OD is increasing with age, and up to 40% of the elderly aged 65 years and older have OD. This frequency is even higher in institutionalized elderly.⁴ It is estimated that OD affects 40 million people in Europe.⁵ The complications of OD can be severe: aspiration pneumonia; dehydration; malnutrition; or even sudden death.^{1,6-8} Furthermore, it affects health-related quality of life. Patients with OD often have feelings of shame, embarrassment, and social isolation.⁷⁻¹¹ Because of the complexity of the etiology, and a high incidence of mental health related comorbidity, a multidisciplinary strategy including mental health care is essential.^{12,13} In general, psychiatric symptoms of anxiety and depression are common in patients with chronic conditions (chronic obstructive pulmonary disease (COPD), diabetes mellitus (DM), irritable bowel syndrome (IBS), overactive bladder (OAB) etc.),¹⁴⁻¹⁹ and OD is also associated with clinically relevant affective complaints.²⁰ However, little is known about the strength and the direction of this association and investigations on the pathophysiology, risk factors, and treatment effect are scarce. The aim of this systematic review is to summarize published studies on affective symptoms in patients with OD and to analyze the quality of the literature. The broader objective was to elucidate how affective comorbidities may impact on symptom bother and treatment compliance in order to advocate integrated or collaborative care approaches.

Method

Identification and selection of studies This review was conducted by following the Cochrane Collaboration criteria for systematic reviews. One of the authors and an experienced university library information specialist carried out a literature search using the electronic biomedical databases Embase, Medline, Web-of-Science, PsycINFO, Cochrane Library, and Google scholar. Search terms were related to dysphagia and to affective conditions (see Table 4.1 for the complete syntax). The entire search was performed on the 1st of June 2016. Two independent reviewers made the first preselecting cut by screening all articles on title and abstract. Then they independently screened full texts of this initial set of articles. Furthermore, the reference lists of the

selected articles were screened for additional literature. If an article was not electronically available, the authors were contacted to obtain the full text. All studies that examined swallowing function and affective conditions were included. However, reviews, studies without use of validated assessment tools on affective symptoms, expert opinions, conference papers, studies with a sample size below 10, and studies in patients with eating disorders or other psychiatric disorders (not being affective conditions) were excluded.

Table 4.1 Literature search.

Embase	(dysphagia/de OR (dysphag* OR ((swallow* OR deglutit*) NEAR/3 (disorder* OR problem*))) :ab,ti) AND (psychiatry/exp OR psychiatrist/de OR 'psychiatric diagnosis'/de OR 'mood disorder'/exp OR 'anxietydisorder'/exp OR 'mental patient'/exp OR (psychiatr* OR depressi* OR ((mood OR anxi* OR Affective) NEAR/3 disorder*) OR neuropsych*) :ab,ti) NOT ([Conference Abstract]/lim OR [Letter]/lim OR [Note]/lim OR [Conference Paper]/lim OR [Editorial]/lim)
Medline	(Deglutition Disorders/ OR (dysphag* OR ((swallow* OR deglutit*) ADJ3 (disorder* OR problem*))) :ab,ti.) AND (exp psychiatry/ OR exp mood disorders/ OR exp anxiety disorders/ OR Mentally Ill Persons/ OR (psychiatr* OR depressi* OR ((mood OR anxi* OR Affective) ADJ3 disorder*) OR neuropsych*) :ab,ti.) NOT (letter OR news OR comment OR editorial OR congresses OR abstracts).pt.
Web-of-science	TS=((dysphag* OR ((swallow* OR deglutit*) NEAR/3 (disorder* OR problem*))) AND ((psychiatr* OR depressi* OR ((mood OR anxi* OR Affective) NEAR/3 disorder*) OR neuropsych*))) AND DT=(Article)
PsycINFO	(Dysphagia/ OR (dysphag* OR ((swallow* OR deglutit*) ADJ3 (disorder* OR problem*))) :ab,ti.) AND (exp psychiatry/ OR exp Affective Disorders/ OR exp anxiety disorders/ OR (psychiatr* OR depressi* OR ((mood OR anxi* OR Affective) ADJ3 disorder*) OR neuropsych*) :ab,ti.) NOT (letter OR news OR comment OR editorial OR congresses OR abstracts).pt.
Cochrane	((dysphag* OR ((swallow* OR deglutit*) NEAR/3 (disorder* OR problem*))) :ab,ti) AND ((psychiatr* OR depressi* OR ((mood OR anxi* OR Affective) NEAR/3 disorder*) OR neuropsych*) :ab,ti)
Google scholar	Dysphagia "swallowing deglutition disorder disorders problem problems" psychiatry psychiatrist psychiatric "mood affective anxiety disorders" depression depressive

Data analysis and assessment of study quality

The included studies were assessed for methodological quality using a 12-item critical appraisal tool derived from the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) (Table 4.2). The QUADAS is a tool to assess the diagnostic accuracy of studies included in systematic reviews.²¹ Two independent reviewers used its critical appraisal criteria to analyze all included articles, scoring each criterion with a 'yes', 'no', or 'unclear'. Internal validity was rated with items 3, 4, 5, 6, 9, 10, 11, and 12, and external validity with items 1, 2, 7, and 8. The reviewers resolved any differences between assigned scores through discussion.

Table 4.2 Criteria for quality assessment.

1.	Was the spectrum of patients representative of the patients who will receive the test in practice?
2.	Were the selection criteria clearly described?
3.	Was the diagnostic swallowing tool (e.g. questionnaire, FEES) likely to correctly classify the swallowing condition?
4.	Was the psychiatric screening tool a validated screening tool?
5.	Is the time period between the diagnostic swallowing test and the psychiatric screening test short enough to be reasonably sure that the target conditions did not change between the two tests?
6.	Did all patients receive the same diagnostic tests?
7.	Was the execution of the swallowing test described in sufficient detail to permit replication of the test?
8.	Was the execution of the psychiatric test described in sufficient detail to permit replication of the test?
9.	Were the psychiatric test results interpreted without knowledge of the results of the swallowing test?
10.	Were the swallowing test results interpreted without knowledge of the results of the psychiatric test?
11.	Were withdrawals from the study explained?
12.	Method of data analyses. Were appropriate statistical methods applied?

Results

A total of 3586 articles were identified, and 2528 remained after removing duplicates. All articles were screened for title and abstract, which left 60 potentially eligible for inclusion. The level of agreement between the two reviewers for this first selection was 91%. The level of agreement between the two reviewers for eligibility after full text screening was 75%. After discussion full consensus was achieved. Finally 24 articles were included in the analysis after full-text screening and by applying the inclusion and exclusion criteria.^{9–11,20,22–41} All of the articles included were written in English (see Figure 4.1 for the flowchart of the literature search process). Fifteen articles reported on cross-sectional studies,^{9,10,20,23–28,30–33,36,41} 5 on prospective cohort studies,^{22,29,37,39,40} 2 on retrospective cohort studies,^{11,38} and 2 on case-control studies.^{34,35} The studies were too heterogeneous in outcome and not of sufficient quality to carry out a meta-analysis. Instead, a qualitative analysis was performed. Table 4.3 provides an overview of the included articles, summarizing study design, sample size, population characteristics, and measurement tools. The included articles are segregated by type of assessment tools used for OD (single swallowing questions, clinical evaluation of swallowing, swallowing-related questionnaires, videofluoroscopic swallowing studies and fiberoptic endoscopic evaluation of swallowing), and discussed below.

Quality of studies

The quality assessment is presented in Table 4.4. The level of agreement between the two reviewers for quality assessment was 91.3% (263 of the 288 QUADAS items). After discussion full consensus was achieved. Thirteen of the included studies met all criteria for external validity,^{20,22,24,29–31,33,34,36,37,39–41} whereas none met all criteria for internal validity. Eight studies fulfilled 6 out of 8 criteria for internal validity.^{9,11,23,26,30,31,35,36} Twenty-three studies were rated ‘unclear’ on items 9 and 10, as the article did not

reveal whether results of the swallowing test were interpreted without knowledge of the psychiatric assessment and vice versa.^{9,10,20,22–41}

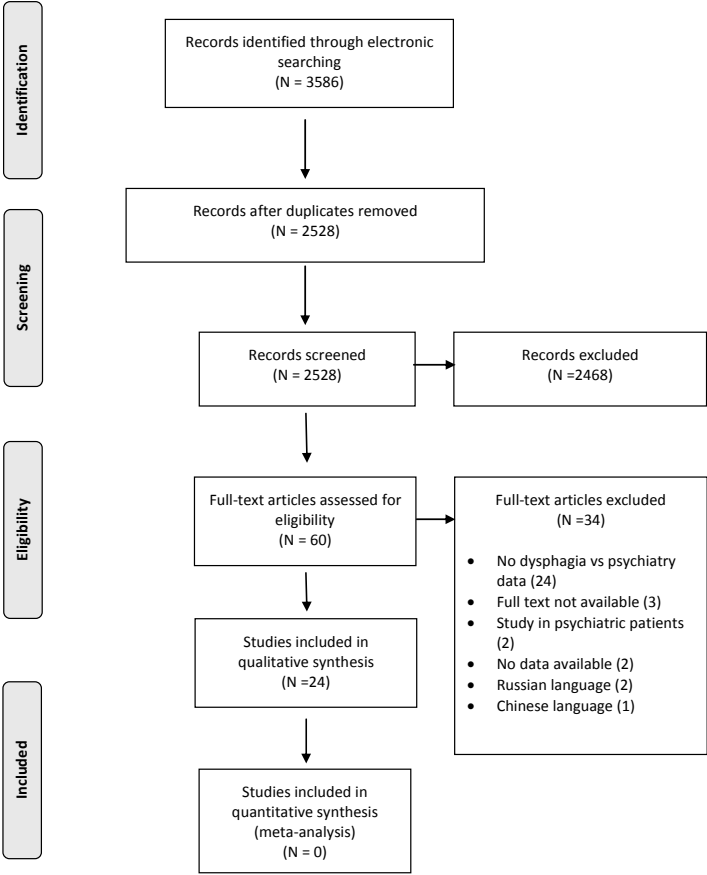


Figure 4.1 Flowchart of the literature process.

Assessment tools

Various assessment tools for swallowing function and affective symptoms were used. In order to assess swallowing function, most studies used self-reporting questionnaires or rating scales.^{9,20,22–27,29,32,33,35} With regard to the assessment of affective symptoms, most studies^{11,20,24,26,33,34,37,38,41} used the Hospital Anxiety and Depression Scale (HADS). In 19 studies the swallowing assessment and the assessment of depression and/or anxiety symptoms were performed on the same day.^{9–11,20,22–24,26,28–31,34–37,39–41} In 5 studies time points of the assessments were unclear. See Table 4.3 for a complete overview of the assessment tools used for swallowing function and affective symptoms.

Table 4.3 Overview of the included articles.

Author	N/pop/etiology	Measurement tool for dysphagia	Measurement tool for affective symptoms	Design	Results
Nguyen et al. ¹¹	N=104 Patient treated for head and neck cancer	Videofluoroscopy of Swallowing	Hospital Anxiety and Depression Scale ⁴⁶	Retrospective cohort study	Hospital Anxiety (OR 0.23; 95% CI 0.07–0.69; $p=0.005$) and Depression (OR 0.15; 95% CI 0.04–0.45; $p=0.0001$) scores were greater in moderate-to-severe dysphagia compared to absent or mild dysphagia.
Nguyen et al. ³⁸	N=101 Head and neck cancer patients	Videofluoroscopy of Swallowing	Hospital Anxiety and Depression Scale ⁴⁶	Retrospective cohort study	Hospital Anxiety ($p=0.001$) and Depression ($p=0.0001$) scores were greater in patients with post-treatment dysphagia.
Kang et al. ⁴⁰	N=50 Stroke patients	1. Videofluoroscopy of Swallowing 2. Physical examination	Beck Depression Inventory ^{47,50}	Non-randomized controlled trial	Significant improvement in swallowing function and depression symptom scores ($p<0.05$) in experimental group compared to control group.
Manor et al. ¹⁰	N=69 Patients with Parkinson's disease	1. The Swallowing Disturbance Questionnaire ⁴³ Clinical swallowing evaluation 2. Fiber-optic Endoscopic Evaluation of Swallowing Fiber-optic Endoscopic Evaluation of Swallowing	Trait Anxiety Inventory ⁵¹ Beck Depression Inventory ^{47,50}	Cross-sectional study	Correlation between Swallowing Disturbance Questionnaire and scores of anxiety ($r=0.472$, $p<0.000$) and depression ($r=0.357$, $p<0.003$).
Verdonschot et al. ⁴¹	N=107 Patients with complaints of oropharyngeal dysphagia		Hospital Anxiety and Depression Scale ⁴⁶	Cross-sectional study	High prevalence (43%) of anxiety and depression symptoms. Significant association between anxiety symptoms and piecemeal deglutition ($p=0.026$) and postswallow vallecular pooling ($p=0.015$).
Lin et al. ³⁰	N=513 Elderly	1. Self-reported 2. A 16-item swallowing questionnaire 3. Neurological examination designed to detect symptoms and signs of impaired swallowing 4. A timed swallowing test (90 ml cold water)	Geriatric Depression Scale ⁵²	Cross-sectional study	Elderly with depression symptoms had significantly greater impaired swallowing compared to elderly without symptoms ($\chi^2=15.34$, $p<0.001$).

Table 4.3 (continued)

Author	N/pop/etiology	Measurement tool for dysphagia	Measurement tool for affective symptoms	Design	Results
Miller et al. ³¹	N=137 Patients with Parkinson's disease	150 ml water swallowing test	Geriatric Depression Scale ⁵²	Cross-sectional study	Patients unable to complete 150 ml swallowing test had significantly greater depression symptoms ($p=0.01$) compared to patients able to complete 150 ml swallowing test.
Thomas et al. ³⁴	N=79 Patients with Multiple Sclerosis	150 ml water swallowing test	Hospital Anxiety and Depression Scale ⁴⁶	Case-control study	Abnormal swallowing was associated with higher depression symptom scores ($p<0.001$).
Zhang et al. ³⁹	N=59 Tongue cancer patients	Water swallowing test	Zung Depression Scale ⁵³	Prospective cohort study	Lower levels of the water swallowing test were associated with lower depression symptom scores.
Yang et al. ²⁸	N=415 Elderly (age >65), living in a single typical South Korean city	Standardized swallowing assessment	Diagnosed according to the DSM-IV criteria ⁵⁴	Population-based cross-sectional study (part of a longitudinal study)	Major depressive disorder was significantly associated with dysphagia. (OR 3.0; $p=0.022$).
Verdonschot et al. ²⁰	N=96 Patients with complaints of oropharyngeal dysphagia	1. MD Anderson Dysphagia Inventory ⁵⁵ 2. Visual Analogue Scale (Dysphagia Severity Scale) ⁷	Hospital Anxiety and Depression Scale ⁴⁶	Cross-sectional study	High prevalence of affective symptoms (43.7%). MD Anderson Dysphagia Inventory scores were significantly associated with symptoms of depression ($p=0.05$).
Cnossen et al. ³⁷	N=67 Head and neck cancer patients	EORTC QLQ-H&N35 swallowing subscale ⁵⁶	Hospital Anxiety and Depression Scale ⁴⁶	Prospective cohort study	Swallowing problems were associated with anxiety and depression symptom scores at time of diagnosis ($r=0.52$; $p=0.00$) and at time of follow up ($r=0.46$; $p=0.00$).
Holland et al. ²⁷	N=634 Healthy elderly in residences in the North of England	Sydney Swallow Questionnaire ⁵⁷	Geriatric Depression Scale ⁵²	Population-based cross-sectional study	Regression analysis revealed that depression symptoms significantly affect dysphagia scores ($F=9.5$; $p=0.00$).

Table 4.3 (continued)

Author	N/pop/etiology	Measurement tool for dysphagia	Measurement tool for affective symptoms	Design	Results
Mentz et al. ³²	N=634 Healthy elderly	Sydney Swallow Questionnaire ⁵⁷	Geriatric Depression Scale ⁵²	Cross-sectional study	Depression symptom scores were significantly related to the total swallowing scores ($r=0.133$; $p<0.00$).
Nogueira et al. ³⁶	N=266 Nursing home residents	1. Dysphagia Self-Test ⁵⁸ 2. 3 ounce water swallowing test	Geriatric Depression Scale ⁵²	Cross-sectional study	Depression symptom scores had significant effect on the Dysphagia Self-Test scores ($p=0.05$).
Han et al. ²³	N=127 Patients with Parkinson's disease	Swallowing Disturbances Questionnaire ⁴³	Beck Depression Inventory II ⁴⁷⁻⁵⁰	Cross-sectional study	Odds Ratio's (95% CI) of dysphagia on different depression symptom levels were: 3.28 (0.93-11.55) for mild; 13.44 (3.10-58.16) for moderate; 30.35 (5.65-162.97) for severe, suggesting a strong relationship between depression symptoms and dysphagia.
Lin et al. ²⁹	N=46 Post-treatment head and neck cancer patients	1. MD Anderson Dysphagia Inventory ⁵⁵ 2. 'Question 5' from the University of Washington Quality of Life scale	Beck Depression Inventory-Fast Screen ⁴⁷⁻⁵⁰	Prospective cohort	Logistic regression analysis revealed associations between symptoms of depression and MD Anderson Dysphagia Inventory scores ($\beta=-21.8$, $p=0.038$) and symptoms of depression and a swallowing related question ($\beta=-23.9$, $p=0.035$).
Chan et al. ³⁵	N=77 Head and neck cancer patients	MD Anderson Dysphagia Inventory ⁵⁵	Beck Depression Inventory Fast Screen ⁴⁷⁻⁵⁰	Case-control study	Depression symptom scores were significantly associated with the functional ($\beta=17.31$; $p=0.009$), physical ($\beta=14.99$; $p=0.032$) and emotional ($\beta=11.60$; $p=0.049$) domains of the MD Anderson Dysphagia Inventory.

Table 4.3 (continued)

Author	N/pop/etiology	Measurement tool for dysphagia	Measurement tool for affective symptoms	Design	Results
MacLean et al. ⁹	N=110 Patients after total laryngectomy	Self-designed Demographic Questionnaire including items on swallowing: - Any difficulty in swallowing? (yes/no) - Changes to their diet texture? (yes/no) - Patients had to list any foods avoided and state why. Those respondents with reported dysphagia were then asked to provide further specific information about their swallowing difficulties	Depression Anxiety Stress Score ⁵⁹	Cross-sectional study	Patients with dysphagia had significantly higher levels of symptoms of depression ($z=-2.58$; $p=0.010$) and anxiety ($z=-2.94$; $p=0.003$).
Perez-Lloret et al. ²⁴	N=419 Patients with Parkinson's disease	'Item 7' from the Unified Parkinson's Disease Rating Scale ⁶⁰	Hospital Anxiety and Depression Scale ⁴⁶	Cross-sectional study	Dysphagia was related to higher depression symptom scores ($p=0.001$).
Walker et al. ²⁶	N=75 Patients with Parkinson's disease	1. 'Item 7' from the Unified Parkinson's Disease Rating Scale ⁶⁰ 2. Two questions: Do you have difficulty swallowing food or liquid or tablets? Do you cough after eating/drinking	Hospital Anxiety and Depression Scale ⁴⁶	Cross-sectional study	Swallowing problems were significantly correlated with anxiety ($r=0.249$; $p=0.033$) and depression symptom scores ($r=0.281$, $p=0.016$).
Althaus et al. ²⁵	N=220 Patients with Parkinson's disease	'Item 7' from the Unified Parkinson's Disease Rating Scale ⁶⁰	Montgomery Asberg Depression Rating Scale ⁶¹	Cross-sectional study	Dysphagia was a significant predictor for depression symptoms ($R^2=0.289$).

Table 4.3 (continued)

Author	N/pop/etiology	Measurement tool for dysphagia	Measurement tool for affective symptoms	Design	Results
Kang et al. ²²	N=72 Patients with degenerative disc disease of the cervical spine	Bazaz– Yoo dysphagia scale. Four grades (None, Mild, Moderate, Severe) based on subjective symptoms	Zung Depression Scale ⁵³ Zung Anxiety Scale ⁶²	Prospective cohort study	The presence of psychiatric symptoms ($p=0.005$) was the only significant predictor of the presence of chronic dysphagia.
Airolidi et al. ³³	N=36 Patients treated for carcinoma of the oral cavity	1. Dische morbidity recording scheme evaluation ⁶³ 2. Visual Analogue Scale: from 0 (no impairment) to 10 (maximum impairment)	Hospital Anxiety and Depression Scale ⁴⁶	Cross-sectional study	Patients with severe dysphagia showed higher symptom levels of anxiety and depression ($p<0.001$) compared with patients with no/slight dysphagia.

Table 4.4 Quality assessment.

	1. Was the spectrum of patients representative of the patients who will receive the test in practice?	2. Were selection criteria clearly described?	3. Was the diagnostic swallowing questionnaire , FEES) likely to correctly classify the swallowing condition?	4. Was the psychiatric screening tool a validated screening tool?	5. Is the time period between the diagnostic swallowing test and the psychiatric screening test short enough to be reasonably sure that the target conditions did not change between the two tests?	6. Did all patients receive the same diagnostic tests?	7. Was the execution of the swallowing test described in sufficient detail to permit replication of the test?	8. Was the execution of the psychiatric test described in sufficient detail to permit replication of the test?	9. Were the psychiatric test results interpreted without knowledge of the results of the swallowing test?	10. Were the swallowing test results interpreted without knowledge of the results of the psychiatric test?	11. Were withdrawals from the study explained?	12. Method of data analyses. Were appropriate statistical methods applied?
Nguyen et al. ¹¹	YES	NO	YES	YES	YES	YES	YES	YES	NO	YES	NO	YES
Nguyen et al. ³⁸	YES	NO	YES	UNCLEAR	UNCLEAR	YES	NO	YES	UNCLEAR	UNCLEAR	NO	UNCLEAR
Kang et al. ⁴⁰	YES	YES	YES	YES	YES	YES	YES	YES	UNCLEAR	UNCLEAR	NO	YES
Manor et al. ¹⁰	YES	NO	YES	YES	YES	YES	YES	YES	UNCLEAR	UNCLEAR	NO	YES
Verdonschot et al. ⁴¹	YES	YES	YES	YES	YES	YES	YES	YES	UNCLEAR	UNCLEAR	YES	YES
Lin et al. ³⁰	YES	YES	YES	YES	YES	YES	YES	YES	UNCLEAR	UNCLEAR	YES	YES
Miller et al. ³¹	YES	YES	YES	YES	YES	YES	YES	YES	UNCLEAR	UNCLEAR	YES	YES
Thomas et al. ³⁴	YES	YES	YES	YES	YES	YES	YES	YES	UNCLEAR	UNCLEAR	NO	YES
Zhang et al. ³⁹	YES	YES	YES	YES	YES	YES	YES	YES	UNCLEAR	UNCLEAR	NO	NO
Yang et al. ²⁸	YES	NO	YES	YES	YES	YES	YES	YES	UNCLEAR	UNCLEAR	YES	YES
Verdonschot et al. ²⁰	YES	YES	YES	YES	YES	YES	YES	YES	UNCLEAR	UNCLEAR	NO	YES
Crossen et al. ³⁷	YES	YES	YES	YES	YES	YES	YES	YES	UNCLEAR	UNCLEAR	NO	YES
Holland et al. ²⁷	YES	NO	YES	UNCLEAR	UNCLEAR	YES	YES	YES	UNCLEAR	UNCLEAR	YES	YES
Mentz et al. ³²	NO	NO	YES	UNCLEAR	UNCLEAR	YES	YES	YES	UNCLEAR	UNCLEAR	NO	YES
Nogueira et al. ³⁶	YES	YES	YES	YES	YES	YES	YES	YES	UNCLEAR	UNCLEAR	YES	YES
Han et al. ²³	YES	UNCLEAR	YES	YES	YES	YES	YES	YES	UNCLEAR	UNCLEAR	YES	YES
Lin et al. ²⁹	YES	YES	YES	YES	YES	YES	YES	YES	UNCLEAR	UNCLEAR	NO	YES
Chan et al. ³⁵	YES	NO	YES	YES	YES	YES	YES	YES	UNCLEAR	UNCLEAR	YES	YES
MacLean et al. ⁹	YES	NO	YES	YES	YES	YES	NO	YES	UNCLEAR	UNCLEAR	YES	YES
Perez-Lloret et al. ²⁴	YES	YES	NO	YES	YES	YES	YES	YES	UNCLEAR	UNCLEAR	YES	YES
Walker et al. ²⁶	YES	NO	YES	YES	YES	YES	YES	YES	UNCLEAR	UNCLEAR	YES	YES
Althaus et al. ²⁵	YES	NO	NO	UNCLEAR	UNCLEAR	YES	YES	YES	UNCLEAR	UNCLEAR	NO	YES
Kang et al. ²²	YES	YES	NO	YES	YES	YES	YES	YES	UNCLEAR	UNCLEAR	NO	YES
Airolidi et al. ³³	YES	YES	UNCLEAR	UNCLEAR	UNCLEAR	YES	YES	YES	UNCLEAR	UNCLEAR	YES	YES

Videofluoroscopic swallowing study and fiber-optic endoscopic evaluation of swallowing

Nguyen et al.¹¹ performed a study to evaluate OD in patients treated for head and neck cancer. One hundred and four patients treated for head and neck cancer (e.g. surgery, radiotherapy, chemoradiotherapy, or postoperative radiotherapy), with different disease sites and stages, were retrospectively analyzed. Patients with complaints of dysphagia (N=73) underwent a VFSS to assess its severity (mild, moderate, severe). The control group (N=31) had no complaints. The HADS scores were significantly elevated in the dysphagic group. Scores on anxiety and depression symptoms were significantly higher in moderate and severe OD categories compared to mild OD. In addition, Nguyen et al.³⁸ compared head and neck cancer patients retrospectively who had received chemoradiation (N=101) with patients who had received postoperative radiation. They did not find any difference in symptoms of anxiety or depression between these 2 treatment groups. However, post-radiation patients who developed complications, of which OD was the most common, reported symptoms of anxiety and depression significantly more often. Kang et al.⁴⁰ conducted a non-randomized controlled trial in 50 stroke patients with OD as confirmed by VFSS. A control group of 25 patients received a conventional swallowing therapy (tactile-thermal stimulation, 5 days per week for 2 months). The experimental group of 25 patients received the same conventional therapy but also bedside training, which consisted of oral, pharyngeal, laryngeal, and respiratory exercises (1 h per day for 2 months). Before and after therapy, all 50 patients underwent a VFSS and filled out the BDI. The experimental group showed a significantly better swallowing function and lower levels of depressive symptoms than the control group. In the study of Manor et al.,¹⁰ 69 patients with Parkinson's disease underwent a clinical observation of swallowing by a speech and language pathologist who reported how the patient manipulated food in the mouth, the oral transit time, the presence of a swallowing reflex, and signs of aspiration (e.g., coughing, choking, change in vocal quality). If there were signs of reduced swallowing function, patients were referred for a FEES examination. Patients with swallowing disturbances showed significantly higher scores of anxiety and depressive symptoms than patients without swallowing disturbances. Verdonshot et al.⁴¹ performed a study in 107 patients with OD of various etiologies. Patients' performances on four FEES-variables were assessed by two independent observers and then compared with the results of the HADS questionnaire. Although clinically relevant symptoms of anxiety and depression were present in 46 (43%) patients, the data revealed only few significant associations between anxiety symptoms and the FEES-variables. The more severe the dysphagia, the less important the affective complaints were.

Clinical evaluation of swallowing

Several studies used a water-swallowing test as a measurement tool for OD. Lin et al.³⁰ investigated swallowing function in institutionalized elderly. Elderly with symptoms of

depression showed a higher frequency of impaired swallowing compared to elderly without symptoms of depression. Miller et al.³¹ found an increased frequency of depressive symptoms related to a poorer outcome of the swallowing tests in Parkinson's patients. Thomas et al.³⁴ and Zhang et al.³⁹ found a significant positive association between impaired swallowing and depressive symptoms in patients with multiple sclerosis and tongue cancer, respectively. Yang et al.²⁸ performed a population-based study among 415 elderly. A clinical observation of swallowing was performed using water-swallowing tests and, if no dysfunction was noted, a meal observation was subsequently performed. Patients diagnosed with a major depressive disorder had dysphagia more often and major depression was an independent risk factor for dysphagia.

Swallowing-related questionnaires

Various questionnaires were used to assess swallowing and to record affective symptoms. Verdonschot et al.²⁰ performed swallowing assessment in 96 patients with OD of various etiologies. A high prevalence of symptoms of anxiety and depression in the total population was found. Cnossen et al.³⁷ found that OD was significantly and positively associated with symptoms of anxiety and depression in head and neck cancer patients. Holland et al.²⁷ and Mentz et al.³² studied dysphagia in otherwise healthy elderly. Both study populations consisted of individuals who represented the surviving members of the University of Manchester Longitudinal Study of Cognition in Normal Healthy Old Age.⁴² They found significant associations between impaired swallowing scores and symptoms of depression. Han et al.²³ used the Swallowing Disturbances Questionnaire⁴³ and found a positive association between lower swallowing scores and symptoms of depression in Parkinson patients. For a complete overview of all included articles, see Table 4.3.

Single swallowing questions

The following studies used a single item or question to determine swallowing function. Perez-Lloret et al.,²⁴ Walker et al.,²⁶ and Althaus et al.²⁵ studied Parkinson and showed a significant positive association between OD and depressive symptoms. The study of Walker et al.²⁶ also showed an association of OD with symptoms of anxiety. Kang et al.²² concluded that the presence of symptoms of anxiety and/or depression was a predictor for the presence of chronic dysphagia in patients who underwent surgery for degenerative disc disease of the cervical spine. Airolidi et al.³³ described a high prevalence of symptoms of anxiety and depression in oral cancer patients with severe OD after surgical flap reconstruction and postoperative radiotherapy.

Discussion

This systematic review is the first to summarize and evaluate the evidence of an association between affective symptoms and oropharyngeal dysphagia. It consists of 24 articles that reported on swallowing function and affective complaints in different populations. Data pooling was prevented by heterogeneity of assessment tools, diversity of study populations, and poor methodological quality. Although no meta-analytic conclusions can be drawn from the included articles, symptoms of anxiety and depression appear to be common in dysphagic patients.

All studies concluded that symptoms of depression were significantly and positively associated with impaired swallowing function. Twelve studies investigated symptoms of anxiety as well, and 9 studies found a significant association with dysphagia too. Quality of the included studies varied. Thirteen of the included studies met all criteria for external validity,^{20,22,24,29–31,33,34,36,37,39–41} whereas none met all criteria for internal validity. Little is known about the relationship between the severity of OD and affective symptoms. Nguyen et al.¹¹ concluded that anxiety and depressive symptoms scored higher in patients with moderate and severe OD compared to patients with mild OD, while the study of Verdonchot et al.⁴¹ concluded that affective symptoms were common in OD patients, but patients with severe OD did not have a higher probability of affective complaints. Moreover, having affective symptoms might be a predictor of subjectively experienced dysphagia severity.⁴¹ It remains unclear what the exact mechanism behind the association of OD with affective states is. However, in patients with medically unexplained otorhinolaryngological symptoms (MUORLS), including dysphagia, affective conditions are common.¹² This could be a reflection of a state of dysphagia amplification⁴¹ which is comparable to the sensitization and alarm falsification process known from other functional somatic conditions.⁴⁴ Anxiety and depressive disorders might influence the perception of swallowing by influencing an 'alarm' set point to a dysfunctional state experienced as OD. From a neurobiological perspective, cerebral motor cortex areas may be related to the neural stress connectome in anxiety and depression.⁴⁵ Further research on this topic is needed.

The results of the current review should be seen in the light of several limitations. The search strategy used MeSH terms and a limited number of free-text terms. Nonetheless, all of the included studies investigated symptoms of anxiety and/or depression. A broader search strategy could have generated different search results. Due to an assessable stratum, we decided to focus on specific symptomatology rather than on a wide range of sub-threshold psychological complaints. The search was conducted with an experienced university library information specialist, and together it was decided to not include "gray literature" in the search strategy. Moreover, a 12-item critical appraisal tool, as derived from the QUADAS, was used for quality assessment. It is possible that a different tool would have led to a different assessment of the included studies. Overall, it was difficult to compare the results of the 24 studies for several reasons. First of all, despite the focus on affective complaints, the studies were

considerably heterogeneous regarding patient populations and outcome parameters. The study populations consisted of stroke patients, head and neck oncology patients, the elderly, and others. Furthermore, the studies applied a wide range of assessment tools for affective symptoms or conditions and swallowing function. Second, most articles had methodological limitations (e.g., no clear description of the selection criteria; little or incomplete information about diagnostic tools and procedures; no information about test result interpretation; and no explanation of withdrawals) (Table 4.4), which made it impossible to carry out data pooling and meta-analysis. Moreover, most studies used only 1 tool to assess swallowing, while a multidimensional approach is recommended for the diagnosis of OD and assessment of OD severity. A broader protocol should include a structured interview, a clinical observation of oral intake by a speech and language pathologist, and a FEES and/or VFSS.¹³ In addition, almost all studies used questionnaires that can only be applied as screening tools for symptoms of anxiety and depression. These tests are not suitable to come to a diagnosis of affective disorders. Although self-assessment questionnaires give an indication of patients' depressive or anxiety state, a consultation by an experienced psychiatrist or psychologist should be included in order to get a valid diagnosis.¹² Given that the use of psychotropic drugs may have led to an underestimation of affective states, reporting about psycho-pharmacy is essential in cohort studies as well. However, several articles did not mention the use of any psychotropic medication. In 19 articles it remained unclear whether drugs were used or not.^{9–11,22,26–29,31–40} Further, affective symptoms could be related to the underlying disease state instead of OD. It is unclear how well the studies controlled or adjusted for the underlying diseases.

Overall, the question remains unsolved whether there is a causal relationship between affective symptoms and swallowing problems in OD patients. Therefore, future studies investigating this topic should use instrumental measurement tools for OD (e.g. FEES, VFSS) and psychiatric assessment should be done by a psychiatrist as a gold standard instead of self-reporting questionnaires. It is important that the execution of the swallowing test is standardized in every included patient. Moreover, the time period between swallowing assessment and psychiatric assessment should be short in order to assure that the conditions of OD and the affective state do not change between the two tests. Nevertheless, it is clear that affective symptoms are common in patients with OD. Screening for affective symptoms could be helpful for caregivers who are not familiar with psychiatric symptomatology in order to estimate influences on possible treatment refractoriness. To date, few treatment-effect studies have been conducted in OD patients with psychiatric comorbidity. Moreover, psychiatric symptoms or diagnoses other than anxiety disorders and depression might be prevalent in OD patients too. However, very few studies have been published on this topic. At least in complex patients with affective comorbidity, the management of OD requires a multidimensional approach to enable patients to adhere to swallowing rehabilitation. For that reason, psychological or psychiatric expertise should be integrated in future

multidimensional OD approaches, which might contribute to the treatment satisfaction in OD.

Conclusion

The current literature revealed that affective symptoms in patients with OD are common. Screening for affective symptoms in patients with OD is clinically relevant and may help caregivers who are not aware of psychiatric comorbidity to detect cases. Although the likelihood of psychiatric comorbidity in OD patients seems obvious, therapy-effect studies to document effect of integrated care are scarce. As the present review of the literature demonstrates, there is a need for well-designed prospective research to investigate the possible benefit of integrated medical psychiatric care in patients with OD and affective comorbidity.

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Section II

Medically unexplained symptoms

Chapter 5

Medically unexplained oropharyngeal dysphagia at the
University Hospital ENT outpatient clinic for dysphagia
– a cross-sectional cohort study

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Abstract

Background

Medically unexplained oropharyngeal dysphagia (MUNOD) is a rare condition. It presents without demonstrable abnormalities in the anatomy of the upper aero-digestive tract and/or swallowing physiology. This study investigates whether MUNOD is related to affective or other psychiatric conditions.

Methods

The study included patients with dysphagic complaints who had no detectable structural or physiological abnormalities upon swallowing examination. Patients with any underlying disease or disorder that could explain the oropharyngeal dysphagia were excluded. All patients underwent a standardized examination protocol, with FEES examination, the Hospital Anxiety and Depression Scale (HADS), and the Dysphagia Severity Scale (DSS). Two blinded judges scored five different FEES variables.

Results

None of the 14 patients included in this study showed any structural or physiological abnormalities during FEES examination. However, the majority did show abnormal piecemeal deglutition, which could be a symptom of MUNOD. Six patients (42.8%) had clinically relevant symptoms of anxiety and/or depression. The DSS scores did not differ significantly between patients with and without affective symptoms.

Conclusion

Affective symptoms are common in patients with MUNOD, and their psychiatric conditions could possibly be related to their swallowing problems. Therefore, consultation of a psychiatrist and multidisciplinary integrated care are recommended for patients with MUNOD.

Introduction

Patients with swallowing problems are commonly seen at the otorhinolaryngology outpatient clinic. Their oropharyngeal dysphagia (OD) may be attributed to somatic etiologies such as head and neck cancer, progressive neurological disorders, or stroke.¹⁻³ These disorders may change the normal anatomy and/or disturb normal function of the upper aero-digestive tract and thereby hamper normal swallowing. Rarely, OD occurs without demonstrable abnormalities in the anatomy of the upper aero-digestive tract and/or swallowing physiology, prompting a diagnosis of medically unexplained oropharyngeal dysphagia (MUNOD).⁴ In the literature, this condition is known by various names: functional dysphagia, swallowing phobia, psychogenic dysphagia, or phagophobia.⁴ A functional somatic disorder is defined as physical complaints or symptoms impairing normal function of the bodily process that are not attributable to an underlying structural disease.⁵ Functional somatic disorders and comorbid anxiety and depression are both associated with increased severity of symptoms and greater illness burden.⁶ Medical specialties tend to apply their own diagnostic labels to functional somatic disorders. Psychiatry uses the term somatic symptom disorder, while other specialties make their own specific diagnosis (e.g. irritable bowel syndrome (IBS), fibromyalgia (FM), functional dyspepsia (FD)).⁵⁻⁷ In the field of mental health, patients with MUNOD are frequently diagnosed with a functional somatic disorder or rarely with phagophobia (fear of swallowing). According to the DSM-V classification, phagophobia belongs to the category of 'specific phobias'⁷ whereby exposure to the phobic stimulus provokes an immediate anxiety response. The phobic situation is avoided or endured with intense distress. Also, the specific phobia interferes with a patient's normal routine, functioning, or social activities. Phagophobia can only be diagnosed if other psychiatric or somatic conditions are excluded as a possible cause for the dysphagia and accompanying emotional and bodily distress.⁷ Patients with phagophobia experience an abnormal sensation during swallowing, sometimes accompanied by behavioral abnormalities during swallowing examination.⁷ In the literature, phagophobia is often described in children,^{8,9} but little is known about this condition in adults. Given the strong association of medically unexplained symptoms with affective conditions, it is advisable to use the broader term 'MUNOD' (instead of 'phagophobia'). It may be a symptom within other psychiatric conditions like obsessive-compulsive disorder, panic disorder, post-traumatic stress disorder (PTSD), social phobia, or depression.¹⁰ In patients with persistent complaints of MUNOD who do not show detectable abnormalities upon swallowing examination performed with fiberoptic endoscopic evaluation of swallowing (FEES) or videofluoroscopic swallowing study (VFSS), and who do not present with an underlying somatic disease, a possible cause of the complaints should be sought in a psychiatric condition (e.g., somatic symptom disorder, phagophobia, affective disorder, PTSD)^{3,4,11,12} In most complex and high-utilizing patients with OD, affective or somatoform comorbidity should therefore be considered.^{13,14}

Aim

So far, no other studies have investigated whether patients with MUNOD have clinically relevant symptoms of anxiety and depression. This study is the first to inquire whether MUNOD is related to an affective condition or presents as a symptom within another psychiatric condition. The aim of this study is to better understand the psychiatric symptoms in patients with MUNOD and to provide guidance for integrated (otorhinolaryngological and psychiatric) management strategies in the context of best clinical practice.

Materials and methods

Patients

Patients with OD complaints (usually choking) who were referred to the outpatient clinic for dysphagia of the Maastricht University Medical Center (MUMC+) between July 2011 and April 2016, without detectable abnormalities in swallowing examination, were included in the study. The following exclusion criteria were applied: age younger than 18, age older than 85 (presbyphagia), complaints of esophageal dysphagia (e.g. swallowing-related chest pain, esophageal regurgitation, history of esophageal dysphagia), history of head and neck cancer, evidence or suspicion of neurodegenerative disease (e.g. Myasthenia Gravis, multiple sclerosis, Parkinson's disease), stroke patients, patients with a Zenker's diverticulum or cervical spine abnormalities, patients with any other somatic disease or disorder that could explain the OD complaints, a score below 23 on the Mini Mental State Examination (MMSE),¹⁵ or not knowing the Dutch language. Informed consent was obtained from all patients.

Examination protocol

All patients underwent a standardized examination protocol (prospectively collected data) used in daily clinical practice at the outpatient clinic for dysphagia. This protocol comprises a structured interview, standardized otorhinolaryngology examination, a standardized FEES examination,¹⁶ the Hospital Anxiety and Depression Scale (HADS),¹⁷ a dysphagia severity scale (DSS),^{18,24} Body Mass Index (BMI) measurement, and the MMSE.¹⁵ The FEES-examinations were carried out by an experienced laryngologist together with the speech therapist. First, patients had to perform three swallows of 10 cc thin liquid (water), then three swallows of 10 cc standardized applesauce (One 2 fruit[®]) (hereafter 'thick liquid'), and then one bite-sized cracker (80 gr Delhaize Mini Toast[®]). All liquids were dyed with 5% methylene blue (10 mg/ml). A flexible fiberoptic endoscope, Pentax FNL-10RP3 (Pentax Canada Inc., Mississauga, Ontario, Canada), was used during the FEES examination. The tip of the endoscope was in 'high position', just above the epiglottis, so the scope could not interfere with closure of the laryngeal

vestibule.¹⁶ The FEES videos were obtained with the Xion SD camera, Xion EndoSTROBE camera control unit (PAL 25 fps), and Matrix DS data station with DIVAS software (Xion Medical, Berlin, Germany) and recorded on a DVD. Second, the investigators administered the HADS, a validated tool to assess clinically relevant symptoms of anxiety and/or depression. It consists of 14 items: seven on the anxiety subscale and seven on the depression subscale. Each single item is scored from 0 to 3, resulting in a minimum of 0 and a maximum of 21 points on each subscale. A higher score indicates more anxiety or depression symptoms. A score of ≥ 8 on a subscale implies the presence of clinically relevant anxiety or depression symptoms, which is an indicator of an anxiety disorder or depression.^{17,19,20} Third, a patient's subjective swallowing assessment was measured with the DSS, a visual analog scale (VAS); this instrument is a psychometric response scale for measuring subjective characteristics or attitudes.^{14,18} Dysphagic patients specify their level of agreement with a statement or question by indicating a position along a continuous line between two end-points for the DSS. The single question was, "How do you rate your swallowing today?" A score of 100 (maximum) indicates normal swallowing. The MMSE is a tool to screen patient's cognitive status. A score below 23 is interpreted as mild cognitive impairment for which a formal cognitive assessment to determine the pattern and extent of deficits is recommended. Therefore, to reduce possible bias in the HADS and DSS outcomes due to cognitive dysfunctions in the present study, patients with an MMSE below 23 were excluded.

FEES variables

To be sure that none of the selected patients had severe abnormalities during FEES examination (e.g. severe pooling, deep penetration, aspiration), suggesting a possible underlying somatic cause, five visuoperceptual ordinal variables (piecemeal deglutition, postswallow vallecular pooling, postswallow pyriform sinus pooling, laryngeal penetration, and aspiration) were scored by two independent judges.^{13,21-26} All of these variables were scored for every FEES swallow at varying speed. The judges underwent consensus training for these measurements, as described previously.^{13,21-26} Both judges were blinded to the patients' identity and medical history. The judges were also blinded to each other's scores. To determine intraobserver agreement, 30 (29%) of the FEES swallows were rated twice (repeated measurements). These FEES swallows were randomly selected and again blinded for both judges. Fatigue-related observer bias was avoided by limiting the judge's rating task to two hours per session.

Statistical analysis

Levels of interobserver and intraobserver agreement were measured for each variable by the linear weighted kappa coefficient. Results were expressed as the median (range) for continuous variables, while frequencies and proportions (%) were used for ordinal FEES variables. The Mann-Whitney U test and the Chi-squared test were used for group

comparisons. Spearman's rho was used for correlations between continuous variables. All statistical analyses were performed with IBM SPSS Statistics for Mac, version 22.0 (Armonk, NY: IBM Corp.).

Results

Participants

Approximately 120 patients per year visited the outpatient clinic for dysphagia. Patients were referred by general practitioners, otorhinolaryngologists, or other specialists such as a neurologist or pulmonologist. The main reason for referral was to exclude pathology of the upper aero-digestive tract as a cause for OD. Fourteen patients met the criteria for MUNOD and were included in the study. The median age was 52 (19-68). In total seven of the participants (50%) were female. See Table 5.1 for general patients' characteristics.

Table 5.1 Patients' characteristics.

Subject	Age	Gender	BMI	MMSE-score	Psychiatric History	Psychiatric Medication	Referred by	No. of visits otorhinolaryngology outpatient clinic MUMC ⁺
1	56	Female	29	30	-	-	GP	6
2	27	Male	17	30	Pervasive developmental disorder – not otherwise specified	-	Internist	1
3	43	Male	17	25	Cluster B personality disorder	Temazepam, Oxazepam	GP	2
4	41	Female	21	23	Panic disorder	Citalopram	Otorhinolaryngologist	3
5	51	Male	23	30	-	-	MV	1
6	68	Male	25	29	-	-	GP	1
7	26	Male	MV	23	-	-	GP	9
8	53	Male	MV	23	-	-	Otorhinolaryngologist	3
9	63	Female	MV	26	-	-	GP	1
10	19	Female	16	23	-	-	GP	1
11	60	Female	37	29	Psychotic depression	Quetiapine	Neurologist	1
12	61	Female	34	29	-	-	Internist	1
13	34	Female	20	30	-	-	GP	2
14	66	Male	25	30	-	-	Pulmonologist	2

BMI: Body Mass Index; MMSE: Mini Mental State Examination; GP: General Practitioner; MV: missing value; MUMC+: Maastricht University Medical Center

Observer agreement

Table 5.2 shows levels of inter- and intraobserver agreement for all FEES-variables with 95% confidence interval. Intraobserver agreement levels are shown for both raters separately. All levels of agreement were almost perfect ($\text{Kappa} > 0.9$). The lowest level of interobserver agreement was 0.95 (CI 95% 0.89-1.00) for postswallow pyriform sinus pooling. The lowest level of intraobserver agreement was 0.90 (CI 95% 0.80-1.00) for postswallow vallecular pooling. The prevalence of impairment was very low for all variables.

Table 5.2 Interobserver and intraobserver agreement levels per FEES variable assessed with linear weighted Kappa and 95% confidence interval.

FEES outcome variable	Definition	Ordinal scale ^a	Interobserver agreement (95% CI)	Intraobserver agreement (95% CI)	
				Observer 1	Observer 2
Piecemeal deglutition	Sequential swallowing on the same bolus	Five-point scale (0-4) 0 = no additional swallows 1 = one additional swallow 2 = two additional swallows 3 = three additional swallows 4 = four additional swallows	0.99 ^b (0.97-1.00)	0.93 (0.84-1.00)	0.93 (0.84-1.00)
Postswallow vallecular pooling	Pooling in valleculae after the swallow	Three-point scale (0-2) 0 = no pooling 1 = filling of less than 50% of the valleculae 2 = filling of more than 50% of the valleculae	0.95 (0.91-1.00)	0.96 (0.89-1.00)	0.90 (0.80-1.00)
Postswallow pyriform sinus pooling	Pooling in pyriform sinuses after the swallow	Three-point scale (0-2) 0 = no pooling 1 = trace to moderate pooling 2 = severe pooling up to complete filling of the sinuses	0.95 (0.89-1.00)	1.00	1.00
Penetration and aspiration	Penetration of bolus in the laryngeal vestibule, above the vocal folds Aspiration of bolus below the vocal folds	Three-point scale (0-2) 0 = no penetration 1 = penetration 2 = aspiration	0.98 (0.96-1.00)	0.97 (0.90-1.00)	0.97 (0.90-1.00)

Results of intraobserver agreement are given for both observers. ^a Lower scores refer to normal functioning whereas higher scores refer to more severe disability. ^b Kappa values: <0: less than chance agreement, 1: perfect agreement.

FEES-variables

Descriptive data of the FEES-variables are displayed in Table 5.3. Piecemeal deglutition was rated as normal (category 0) in 31.0% (N=13), 16.7% (N=7), and 7.1% (N=1) of the swallows for thin liquid consistency, thick liquid consistency, and bite-sized cracker, respectively. In five patients postswallow vallecular pooling was rated as mild (14.3% and 7.1% of the swallows for thin liquid and thick liquid consistency, respectively), but in none of these patients was pooling observed in all seven recorded swallows. All five patients showed at least one normal swallow without vallecular pooling. None of the swallows was rated as severe vallecular pooling (category 2). Penetration was observed in two patients. The first patient showed a trace of methylene blue on the laryngeal side of the epiglottis during the first thin liquid swallow. The second patient showed deeper penetration, near the vocal folds, in multiple swallows and was therefore excluded because an underlying somatic cause of OD could not be excluded. None of the patients showed aspiration or pyriform sinus pooling during the swallowing examination. The study population was too small to perform further statistical analyses.

Table 5.3 Frequency distribution of swallows per category of the different FEES variables.

FEES category frequencies			
	Thin liquid consistency N (%) N=42	Thick liquid consistency N (%) N=42	Bite-sized cracker N (%) N=14
Piecemeal deglutition			
Category 0	13 (31.0)	7 (16.7)	1 (7.1)
Category 1	10 (23.8)	15 (35.7)	2 (14.3)
Category 2	13 (30.9)	10 (23.8)	2 (14.3)
Category 3	1 (2.4)	3 (7.1)	2 (14.3)
Category 4	5 (11.9)	6 (14.3)	6 (42.9)
MV ^a	0	1 (2.4)	1 (7.1)
Postswallow vallecular pooling			
Category 0	35 (83.3)	36 (85.7)	12 (85.7)
Category 1	6 (14.3)	3 (7.1)	0
Category 2	0	0	0
MV	1 (2.4)	3 (7.1)	2 (14.3)
Postswallow pyriform sinus pooling			
Category 0	41 (97.6)	40 (95.2)	12 (85.7)
Category 1	0	0	0
Category 2	0	0	0
MV	1 (2.4)	2 (4.8)	2 (14.3)
Penetration/aspiration			
Category 0	40 (95.2)	41 (97.6)	12 (85.7)
Category 1	1 (2.4)	0	0
Category 2	0	0	0
MV	1 (2.4)	1 (2.4)	2 (14.3)

^a Missing value; FEES variable could not be rated.

HADS

Six of the 14 participants (42.8%) showed clinically relevant symptoms of anxiety (score ≥ 8 on the anxiety subscale). Three of the 14 (21.4%) showed clinically relevant symptoms of depression (score ≥ 8 on the depression subscale). These three also had a score ≥ 8 on the anxiety subscale. Thus, 42.8% (N=6) of the participants had clinically relevant symptoms of anxiety and/or depression. The Chi-squared test showed no gender differences between patients with and without clinically relevant symptoms of anxiety ($p=0.28$) or depression ($p=0.51$). The Mann-Whitney U test showed no age differences between patients with and without clinically relevant symptoms of anxiety ($p=1.00$) or depression ($p=0.76$).

DSS

The median score for the DSS was 66.0 (18-100). Spearman's rho revealed no significant correlation between age and DSS. The DSS was not significantly different for patients with clinically relevant symptoms of anxiety or depression compared to patients without symptoms of anxiety or depression. Males scored significant higher on the DSS compared to females. See Table 5.4 for the results of the Mann-Whitney U tests for group comparison.

Table 5.4 Comparison of DSS between patients with clinically relevant symptoms of anxiety or depression and patients without symptoms of anxiety or depression.

	N	DSS score ^a Median (range)	Level of significance p-value
HADS-D ^b ≥ 8	N=3	85.0 (18-100)	$p=0.659$
HADS-D < 8	N=11	57.0 (31-98)	
HADS-A ^c ≥ 8	N=6	76.0 (18-100)	
HADS-A < 8	N=8	55.5 (31-98)	$p=0.662$
Male	N=7	85.0 (44-100)	
Female	N=7	54.0 (18-77)	

^a Dysphagia Severity Score; ^b Depression subscale of the Hospital Anxiety and Depression Scale; ^c Anxiety subscale of the Hospital Anxiety and Depression Scale ^d Statistically significant.

Discussion

This is the first study that investigates swallowing function in relation to symptoms of anxiety and depression in patients with MUNOD. All 14 included patients presented with complaints of OD, and none showed structural abnormalities during FEES examination. However, the majority showed abnormal piecemeal deglutition, which could be an early symptom of an underlying somatic disorder impairing normal swallowing physiology. However, it is conceivable that abnormal piecemeal deglutition is a clinically relevant symptom of MUNOD. Since these patients are often anxious about swallowing, multiple swallows of smaller fragments of the same bolus may offer

them a sense of safety or control. In these patients, piecemeal deglutition seems to be a habitual coping strategy rather than a subclinical neurogenic impaired swallowing pattern. Nevertheless, follow-up for a possible progressive neurologic disease is recommended. It is assumed that swallowing physiology in patients with MUNOD is normal. However, an interesting question is whether MUNOD could disturb normal swallowing physiology. Roland et al. evaluated the incidence of esophageal contractility disturbances in psychiatric patients.²⁷ Manometry showed a high percentage of functional motor impairment in patients with complaints of anxiety and/or depression, while endoscopy in these patients showed no structural abnormalities.²⁷ In a large prospective population-based study, Koloski et al. showed that anxiety is an independent predictor for new onset functional gastrointestinal disorders like irritable bowel syndrome, suggesting that affective disorders can underlie physical symptoms.²⁸ The bladder-gut-brain axis is an interesting framework. It suggests a bidirectional pathway between brain and body, assuming that both functional and affective disorders are stress related and that functional symptoms are a sensitized response to earlier threats. This sensitization might mediate false-alarm signals (alarm falsification as a defense system). That, in turn, could provoke emotional and physical distress, resulting in psychiatric conditions and functional disorders like MUNOD.^{6,28} A study by Dum et al. raised the possibility that motor areas of the cerebral cortex are important in the stress and depression connectome,²⁹ and Grillon et al. suggested that anxiety increases motor response inhibition.³⁰ These studies indicate a relationship between affective function and motor function and thus strengthen the assumption that functional complaints might be part of a hypersensitivity or alarm-falsification disorder.⁶ By implication, MUNOD and functional motor impairment may be interrelated too, causing disturbances of the normal swallowing physiology (such as increased piecemeal deglutition). So far, no studies have been published on this subject. However, the assumption that patients with MUNOD must have a normal swallowing function might be incorrect. Through this bidirectional pathway, a psychiatric problem can have sensorimotor effects on the swallowing function without there being any other cause of dysphagia, such as a chronic neurological disorder. Then, it would be plausible that OD can be caused by affective disorders or psychiatric conditions, even when the swallowing physiology is disturbed. In this study, none of the participants had symptoms indicating an underlying somatic disease, and none showed other abnormalities during structured interviews or general otorhinolaryngology examination (normal cranial nerve integrity, speech, etc.). Although a somatic cause of dysphagia might seem unlikely, MUNOD should always be a diagnosis of exclusion. Previous research showed a high prevalence of clinically relevant affective symptoms in OD patients.^{13,14,31} The present study underpins these data. It also shows a high prevalence (42.8%) of clinically relevant affective symptoms, which indicates that MUNOD seems to be related to affective conditions in more than 40% of the cases. Four of the participants (28.5%) had already been diagnosed with a psychiatric condition (psychotic depression, panic disorder, pervasive developmental disorder –

not otherwise specified, cluster B personality disorder). The patient with cluster B personality disorder showed clinically relevant symptoms of anxiety and depression, and the patient with panic disorder exhibited clinically relevant symptoms of anxiety. In these patients MUNOD and affective symptoms are likely to be part of their psychiatric disorder.

The DSS scores were not significantly different between patients with and without clinically relevant affective symptoms. Apparently, clinically relevant symptoms of anxiety and depression are not related to the severity of MUNOD symptoms. A psychological screening questionnaire, like the HADS, is a simple tool for the preliminary assessment of the affective state of a patient. However, the expertise of a psychiatrist is essential to a definitive diagnosis and treatment of any psychiatric condition, including phagophobia or other anxiety disorders, and depression. It might be helpful to draw upon the patient's psychiatric history and to involve his or her own psychiatrist when preparing a multidisciplinary treatment strategy. Involvement of a psychiatrist would obviously be necessary. However, the patient must be willing to cooperate and accept that a psychiatric problem might be the cause of the swallowing problems. In this study, only four patients could be convinced to visit a psychiatrist after visiting the outpatient clinic for dysphagia. Following referral to the psychiatrist, one patient was diagnosed with an anxiety disorder and one patient was diagnosed with an identity disorder. Two of the referred patients were already known with a psychiatric disorder (panic disorder and psychotic depression), see Table 5.1. Early recognition of MUNOD and a motivational trajectory towards integrated care are necessary to develop effective treatment strategies, to reduce health care consumption and health care costs, to decrease the risk of iatrogenic damage arising from continuous diagnostic intervention, and to prevent frustration in the interaction between physician and patient.¹¹ Almost all of the participants had already consulted multiple specialists or had made recurrent visits to outpatient clinics all over the Netherlands. Consultation of a psychiatrist must be considered as an early option in the diagnostic strategy of MUNOD instead of the 'last resort' after unsuccessful treatment. Diagnosis and treatment of an underlying psychiatric disease may improve the swallowing problems. It is important to realize that affective symptoms are frequently present in patients with MUNOD. Assuming a bidirectional pathway between brain and body, MUNOD could be understood as a symptom of physical distress or part of an alarm falsification and defense reaction as seen in other functional syndromes. In patients with prolonged dysphagic complaints, with no indication of a somatic disease or abnormality, psychiatric conditions must be considered as a possible cause of OD. Validated psychological screening questionnaires could be helpful in the detection of affective conditions but also of other psychiatric conditions. Involvement of a psychiatrist and/or psychologist is recommended.

Limitations of the study

This investigation has some limitations. First, since MUNOD is a rare condition, the number of patients included in the study is small, so only a limited statistical analysis could be performed. Second, the HADS questionnaire was used for screening of anxiety and depression symptoms. Possibly, a different screening tool or multiple screening tools would have led to different results. Third, three of the participants were taking psychiatric medication (see Table 5.1), which could have a negative effect on swallowing.^{32,33} Furthermore, the use of psychiatric medication could have led to an underestimation of the HADS scores. Furthermore, this investigation used a cross-sectional study design and was not intended as a therapy-effect study; the effect of different treatment options could be examined in future research, which could also specify treatment strategies in patients with MUNOD and psychiatric comorbidity.

Conclusion

MUNOD is a rare condition that is difficult to diagnose. We hope to help dysphagia caregivers by sharing our results and experiences. Patients deserve a professional approach, particularly because their diagnostic trajectory has often been long and inconclusive. Affective symptoms are common in these patients. MUNOD could be a symptom of a psychiatric condition or part of the alarm falsification defense system, suggesting that physical symptoms and affective disorders are stress-related and a response to earlier threats. Consultation of a psychiatrist for patients with MUNOD is recommended as part of a pathway toward multidisciplinary integrated care.

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Chapter 6

Medically unexplained otorhinolaryngological
symptoms: towards integrated psychiatric care

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Abstract

Objective

To evaluate the presence of medically unexplained otorhinolaryngological symptoms in a patient cohort and propose an interdisciplinary approach for their care.

Methods

This prospective cohort study describes a population of patients presenting at the Department of Otorhinolaryngology at the Maastricht University Medical Center (MUMC). Patients with symptoms that did not meet clear “medical” criteria and were associated with psychological distress and high healthcare utilization were enrolled in the study by two experienced otorhinolaryngologists following informed consent. The aim of the study is 1) to specify the presence of medically unexplained otorhinolaryngological symptoms (MUORLS) and 2) to evaluate the integration of otorhinolaryngological and psychiatric treatment in an interdisciplinary approach in order to help otorhinolaryngologists improve patient care.

Results

Of the 102 patients included, 41% (N=42) did not have a proven somatic otorhinolaryngological diagnosis. For only 10.8% (N=4) of the latter, no psychiatric diagnosis had been established. Overall, 78% of the study population (N=80) was diagnosed with psychiatric morbidity/comorbidity, as defined in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-4-TR).

Conclusion

The preliminary data suggest that the majority of patients with these unexplained complaints may suffer from under- or undiagnosed psychiatric morbidity. Therefore, easy access to integrated interdisciplinary care (otorhinolaryngology and psychiatry) should be offered to patients with MUORLS after detailed information is made available to them about the pathogenesis of the complaints and the foreseen psychosomatic approach.

Introduction

Medically unexplained otorhinolaryngological symptoms (MUORLS) are common in tertiary care settings, although exact prevalence rates are unknown.¹ In general, medically unexplained symptoms frequently accompany psychiatric disorders.² Nonetheless, psychiatric morbidity/co-morbidity is consistently underrecognized, which precludes effective treatment.² Given that MUORLS are associated with high impairment, healthcare costs, risk of iatrogenic damage, and frustration among both physician and patient, it is critical to improve early detection.^{3,4} The first step is to identify the underlying disorder, which might be psychiatric, through a diagnostic process that could be lengthy due to the somatic focus of the physician and, therefore, delay successfully targeted interventions.^{5,6} For some otorhinolaryngological (ORL) subcategories, such as oropharyngeal dysphagia, benign paroxysmal positional vertigo, and tinnitus, affective symptomatology such as depression, phobia or anxiety has been reported.^{7,8} However, the Dutch evidence-based guidelines on various ORL pathologies/complaints still do not help the physician to recognize and label MUORLS because these guidelines do not cover integrated care. Notably, consultation-liaison (CL) psychiatry and psychosomatics are not part of that recommendation.^{9,10}

The current study investigates presentation with MUORLS in a patient cohort and, if present, proposes an integrated interdisciplinary approach (ORL and psychiatry) for their care. Ultimately, this could yield guidelines for multidisciplinary diagnosis to be followed by otorhinolaryngologists. Successful diagnosis may not only help control healthcare costs but may also improve patient care because MUORLS are associated with significant impairment, especially in patients with psychiatric comorbidity.

Materials and methods

Data collection

Participants. Patients with MUORLS were recruited from the Department of Otorhinolaryngology at the Maastricht University Medical Center (MUMC). Their complaints were heterogeneous: dizziness, postnasal drip, nasal airway obstruction, pharyngeal Globus sensation, upper airway distress, gagging while eating, tinnitus, and so forth. There were several exclusion criteria: not willing to cooperate with an integrated interdisciplinary approach; suffering from severe depression with suicidal behavior or already having a known psychiatric diagnosis or using antidepressant and/or anxiolytic drugs; not being able to understand the integrated interdisciplinary advice due to cognitive impairment; being under 18 years; and not adequately understanding the Dutch language. None of the patients was in a palliative state of disease. Informed consent was obtained from all patients.

Study design and setting

Patients with no clear “medical” explanation for their symptoms who had associated psychological distress and/or high healthcare utilization were enrolled in the study by two experienced otorhinolaryngologists (L.W.J. B and R. vd B) from December 2011 till December 2013. These somatic specialists served a gate-keeping function and as a last resort. Patients were referred by general practitioners (GP), ORL specialists from other hospitals, or medical practitioners from other healthcare facilities. By their very nature, unexplained symptoms are vague or difficult to characterize, which hampers differential diagnosis. Therefore, all patients underwent a structured interview, a standardized clinical ORL examination, and additional diagnostics (instrumental examinations, imaging, etc.), depending on the kind of symptoms and the Dutch evidence-based guidelines on the various ORL pathologies/complaints.^{9,10} Examinations such as computed tomography scanning of paranasal sinuses, endoscopy of the upper aerodigestive tract, videofluoroscopy of swallowing, electronystagmography with caloric and rotatory testing, and magnetic resonance imaging scanning of the brain were performed to detect and/or rule out somatic causes of the complaints. These examinations were often performed before the patients met our two last-resort otorhinolaryngologists. The included patients had complaints in the ORL topographic region without a somatic substrate in the end-organ or with a somatic ORL diagnosis that did not fit the subjective complaints. This means that subjective complaints showed a discrepancy with the outcome of clinical and instrumental examinations. Patients were acquainted with the psychiatrist during a joint consultation in the ORL outpatient clinic. Following this first informative and motivational consultation, patients with a psychiatric diagnosis or lack of coping skills were invited to visit the outpatient clinic for hospital psychiatry and medical psychology at the MUMC in order to undergo further structured clinical psychiatric investigation. Depending on the diagnosis (anxiety disorder, depressive disorder, somatoform disorder, etc.) mental healthcare took place as indicated.¹¹

Given the patients’ fear of stigmatization, the otorhinolaryngologists were not able to convince all patients with confirmed MUORLS of the benefits of an integrated interdisciplinary approach that draws upon an experienced psychiatrist at the same hospital. In patients diagnosed with psychiatric comorbidity and who consented to accept psychiatric treatment (i.e., pharmacological intervention and/or psychotherapy), follow-up took place either in the integrated ORL-psychiatry setting (in cases of somatic and psychiatric co-morbidity) or in the hospital psychiatry and medical psychology outpatient setting alone (in cases of medically unexplained symptoms and psychiatric morbidity).

Data analysis

Variables of interest. Diverse variables were analyzed for the current study. These were selected to reflect the burden on the patient and the health care system. They also

indirectly reflect the delay in care due to a difficult differential diagnosis and to multiple diagnostic examinations or visits to exclude somatic causes for the complaints. The variables include the number of visits to the ORL outpatient clinic or other departments, number of additional (instrumental) examinations, number of surgical interventions, and so forth (Table 6.1).

Table 6.1 Variables of interest associated with medically unexplained otorhinolaryngological symptoms.

Variable	Definition
1 ORL ^a complaint	Nature or topography of the subjective ORL complaint
2 ORL somatic diagnosis (if present)	Established or proven somatic ORL diagnosis
3 Other somatic diagnosis (if present)	Established or proven somatic diagnosis outside ORL
4 Number of disciplines for ORL complaint	Number of medical disciplines and health professions involved in care for specific ORL complaint
5 Number of disciplines for other complaints	Number of medical disciplines and health professions involved in care for other (non-ORL) complaints
6 Number of visits to ORL outpatient clinic	Number of visits to the ORL outpatient clinic for the specific subjective ORL complaint
7 Number of instrumental examinations	Number of instrumental examinations for the specific subjective ORL complaint
8 Number of ORL surgical interventions	Number of surgical interventions for the specific subjective ORL complaint
9 Number of other surgical interventions	Number of surgical interventions for other (non-ORL) complaints
10 ORL treatment	ORL treatment for the specific subjective complaint
11 Psychiatric diagnosis	Final psychiatric diagnosis underlying the specific subjective ORL complaint
12 Psychiatric treatment	Final psychiatric treatment to manage the specific subjective ORL complaint

^a ORL: otorhinolaryngological.

Statistical analysis

Descriptive statistical data are presented in Table 6.2, 6.3, 6.4, 6.5, 6.6, and 6.7.

Results

Characteristics of participants

One hundred and two patients with MUORLS were included (total N=102; 58 females and 44 males). They were receptive to an integrated multidisciplinary approach (ORL& psychiatry) in order to screen for or diagnose psychiatric morbidity/co-morbidity. Their median age was 60 years (25th, 75th percentile: 49; 68 years).

Results of the descriptive statistics

Table 6.2 presents the frequency distribution of the various subjective ORL complaints for the study population. Fifty-three percent of the patients (N=53) reported dizziness, and the second-largest group mentioned pharyngeal Globus sensation (N=14; 14.0%).

Table 6.2 Frequency distribution of the otorhinolaryngological complaints in the study population (N=102).

ORL ^a complaint	N (%)
Dizziness/vertigo	53 (53.0)
Pharyngeal globus	14 (14.0)
Dysphagia	8 (8.0)
Nasal obstruction	6 (6.0)
Dysphonia	5 (5.0)
Choking	4 (4.0)
Tinnitus	4 (4.0)
Discomfort tracheostomy	2 (2.0)
Stridor breathing sounds	1 (1.0)
Snoring with fatigue	1 (1.0)
Postnasal drip	1 (1.0)
Tubair catarrh sensation	1 (1.0)
Missing values	2 (2.0)

^a ORL: otorhinolaryngological.

Table 6.3 shows the frequency distribution of the ORL somatic diagnoses for the total study population. Forty-one percent of the patients (N=42) did not have a proven somatic ORL diagnosis. Out of this share, 10.8% (N=4) did not have an established psychiatric diagnosis.

Table 6.3 Frequency distribution of the otorhinolaryngological somatic diagnoses in the study population (N=102).

ORL ^a somatic diagnosis (if present)	N (%)
No somatic diagnosis	42 (41.2)
Vestibulopathy (vestibular migraine, Menière's disease, BPPV ^b , utricular dysfunction etc.)	34 (33.3)
Otopathy (hearing loss, recurrent otitis, myringosclerosis etc.)	7 (6.9)
Head and neck cancer with various stages, locations etc.	7 (6.9)
Chronic rhinopathy (polyps, rhino sinusitis, maxillary sinus cyst etc.)	5 (4.9)
Obstructive sleep apnea syndrome	4 (3.9)
Benign vocal fold pathology (paralysis, polyps, cysts etc.)	3 (2.9)
Missing values	0 (0)

^a ORL: otorhinolaryngological. ^b BPPV: benign paroxysmal positional vertigo.

Table 6.4 shows the data on healthcare consumption in the present population. The number of disciplines involved, visits to the outpatient clinics, and (instrumental) examinations for the ORL complaint and other (non-ORL) complaints were reported. Furthermore, ORL surgery in the topographic area of complaint and interventions for other (non-ORL) disorders/complaints were registered (ventilation tubes, nasal septum

correction, microlaryngeal surgery, etc.). The median number of visits to the ORL outpatient clinic was six, and the median number of additional (instrumental) examinations was four.

Table 6.4 Descriptive data of healthcare consumption for the study population (N=102).

Variable	Median (25th perc; 75th perc)	Range (min-max)
1 Number of other somatic (non-ORL ^a) diagnoses	2 (0; 4)	0-13
2 Number of involved disciplines for the specific subjective ORL complaint	1 (1; 1)	0-3
3 Number of involved disciplines for other (non-ORL) complaints	0 (0; 1)	0-9
4 Number of visits to the ORL outpatient clinic	6 (4; 10)	1-92
5 Number of additional (instrumental) examinations	4 (2; 9)	0-57
6 Number of ORL surgical interventions	0 (0; 0)	0-3
7 Number of other surgical interventions	0 (0; 0)	0-4

^a ORL: otorhinolaryngological.

Table 6.5 shows the frequency distribution of the ORL treatment that was given to the patients for their unexplained complaints. More than half of the patients did not receive an ORL treatment (N=68; 68.0%). Twenty-four patients (24.0%) received a non-psychotropic drug treatment for the complaints (topical nasal steroids, systemic steroids, antibiotics, etc.).

Table 6.5 Frequency distribution of otorhinolaryngological treatment in the study population (N=102).

Variable ORL ^a treatment	N (%)
No ORL treatment	68 (68.0)
Drug/pharmacological treatment	24 (24.0)
Surgical treatment ^b	5 (5.0)
Outpatient follow-up	3 (3.0)
Missing values	2 (2.0)

^a ORL= otorhinolaryngological. ^b Some patients underwent more than one surgical intervention (ventilation tubes in tympanic membrane, microlaryngoscopy for benign vocal fold lesions, nasal septum correction, rhinoplasty, etc.).

Table 6.6 represents the frequency distribution of the psychiatric diagnoses. Seventy-eight percent of the study population (N=80) was diagnosed with a psychiatric morbidity/co-morbidity based on the definitions of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-4-TR)¹². The most frequent diagnosis was anxiety disorder (N=31; 35.2%). Furthermore, depressive disorder and undifferentiated somatoform disorders were common, N=20 (22.7%) for both. Only 9.1% (N=8) of the patients were not diagnosed with a psychiatric disorder. Among the patients with an ORL somatic diagnosis (N=60) fifteen (29.4%) were diagnosed with an anxiety disorder and sixteen (31.4%) with an undifferentiated somatoform disorder.

Table 6.6 Frequency distribution of psychiatric diagnoses in the study population (N=102) and according to the presence or absence of an ORL^a diagnosis.

	ORL diagnosis		
	Yes (N=60)	No (N=42)	Total (N=102)
Psychiatric diagnosis	N (%)	N (%)	N (%)
Anxiety disorder	15 (29.4)	16 (43.2)	31 (35.2)
Undifferentiated somatoform disorder	16 (31.4)	4 (10.8)	20 (22.7)
Depressive disorder	11 (21.6)	9 (24.3)	20 (22.7)
No psychiatric diagnosis	4 (7.8)	4 (10.8)	8 (9.1)
Adaptation disorder	3 (5.9)	1 (2.7)	4 (4.5)
Grief bereavement	0 (0.0)	1 (2.7)	1 (1.1)
PTSD ^b	0 (0.0)	1 (2.7)	1 (1.1)
Mild cognitive impairment	0 (0.0)	1 (2.7)	1 (1.1)
Eating disorder	1 (2.0)	0 (0.0)	1 (1.1)
Bipolar disorder	1 (2.0)	0 (0.0)	1 (1.1)
Missing values	9 (15.0)	5 (12.0)	14 (13.7)

^a ORL: otorhinolaryngological. ^b PTSD: Posttraumatic Stress Disorder.

Table 6.7 gives the frequency distribution of the received psychiatric treatment (selective serotonin reuptake inhibitors, psychotherapy, etc.).

Table 6.7 Frequency distribution of psychiatric treatment in the study population (N=102).

Variable psychiatric treatment	N (%)
Psychotherapy	38 (42.7)
Psychotropic drugs	27 (30.3)
No treatment	14 (15.7)
Psychotropic drugs and psychotherapy	6 (6.7)
Outpatient follow-up (psychiatry)	4 (4.4)
Missing values	13 (12.8)

Some observations included in Table 6.2, 6.5, 6.6, 6.7 had to be scored as missing values because of incomplete reporting of data in the patients' medical files.

Discussion

To our knowledge, this is the first study investigating MUORLS at an integrated ORL-psychiatry outpatient setting of a university medical center. MUORLS has become a topic of considerable interest, given the growing population of these patients and the increasing concern about quality of life, healthcare costs, risk of iatrogenic damage, and healthcare trajectories that are unsatisfactory to both the patients and their physicians.^{3-6,13,14} An important outcome of this study is insight into the existence of this patient population and the detour they take to obtain appropriate treatment in daily clinical ORL practice. Among their medically unexplained physical symptoms, our

patient cohort had a high prevalence of psychiatric comorbidity.^{3,15} Ultimately, this investigation may inform efforts to develop an integrated interdisciplinary treatment plan and thus to decrease the risks and medical costs of MUORLS. Quite often a diagnosis of MUORLS is made by exclusion. Uncertainty as to the cause of the symptoms can make physicians uneasy; as they weigh the need to rule out serious illness and increasing chronicity against the cost, distress, and damage of extensive clinical testing.^{16,17} It may be the fear of missing a “serious diagnosis” that underlies physicians’ emphasis on the physical side of the symptoms. Queries about psychological distress are therefore subordinated to an examination of physical aspects or even forgotten during consultations.^{5,16} The present study revealed that the majority of the patients suffering from MUORLS were diagnosed with a psychiatric disorder (N=80, 78%). A final psychiatric diagnosis was often delayed by requiring additional (instrumental) examinations to exclude a somatic disorder or serious illness. Some of the patients visited the ORL outpatient clinic many times (up to 92) or received care in many different disciplines for diverse medical complaints, thereby raising both the costs of healthcare and the risk to the patient. Thirty-two percent of the patients had received some ORL treatment (N=32) without improvement of complaints before they visited our two ORL experts. Seventy-eight percent (N=80) of the study population was diagnosed with a psychiatric morbidity/co-morbidity. However, the determination of a psychiatric diagnosis in MUORLS patients with an established somatic ORL diagnosis should not be disregarded (N=47; 92%). The presence of a somatic ORL diagnosis has often delayed referral to the integrated ORL-psychiatry care setting. Among MUORLS patients without a somatic ORL diagnosis, 90% (N=38) were diagnosed with a psychiatric comorbidity. Given the underdetection of psychiatric morbidity along a non-integrated trajectory, evidence-based treatment was implemented right from the start of our multidisciplinary outpatient clinic approach.² Thus, in patients with expected multi-morbidity, screening for psychiatric morbidity makes sense.¹⁸ Consequently, an integrated approach is deemed necessary, as it gets patients motivated for and referred to psychosomatic care. Eventually, structured clinical diagnostics may lead to evidence-based treatment for psychiatric morbidity/co-morbidity.

Limitations of the study

This prospective investigation has methodological limitations. Although the study yielded some interesting preliminary data, the study population is too small to reveal significant group differences. The heterogeneous etiology of MUORLS and the small number of patients per complaint or somatic diagnostic group prevented the comparison of groups for significant differences. Furthermore, selection bias may have occurred due to patients’ fear of stigmatization or other patient-related reasons (e.g., only willing patients were included, patients were referred to a tertiary university medical center), so it is impossible to generalize. Still, the enrollment reflected the theoretical population of patients with MUORLS who consult the otorhinolaryngologist

for diagnosis and treatment at the university medical center. One potential drawback is the absence of controls, although finding and including patients with similar somatic ORL diagnosis without MUORLS would have introduced selection bias as well. Furthermore, although the study design was prospective, the search for patient data in the medical files may have been incomplete. It is possible that some information was missed despite extensive and careful searching, and patients may have visited other hospitals for the same complaints without reporting it. This may have led to an underestimation of the results in the current study; an overestimation is very unlikely. Finally, patients suffering from a known psychiatric disorder were excluded. Their inclusion would have led to a higher frequency of MUORLS. On the other hand, inclusion of patients treated with antidepressant and/or anxiolytic drugs would have led to lower frequencies of MUORLS and underestimation of its presence.

Conclusion

Findings from the present cohort study suggest that the majority of patients with MUORLS suffer from under- or undiagnosed psychiatric morbidity. Patients suffering from MUORLS deserve easy access to integrated interdisciplinary care (ORL and psychiatry) followed by detailed psycho-education about the pathogenesis of their complaints and the future psychosomatic approach. Further research should focus on the development of effective methods to ensure that patients with MUORLS will be identified and treated (in a multidisciplinary approach) accordingly.

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Section III

Chapter 7

General discussion, future perspectives, and
valorization addendum

General discussion, future perspectives, and valorization addendum

This chapter offers a general discussion to integrate material from the previous chapters and then draws some conclusions from the results presented there. Some recommendations for future research are made at the end of this chapter, followed by a valorization addendum.

Oropharyngeal dysphagia (OD) is a complex medical problem; due to its complexity, it is often under-recognized in a clinical setting. Underdiagnosis is likely, and delay in treatment can lead to severe complications or sudden death.¹⁻⁴ It is therefore important for healthcare professionals to recognize OD; the awareness of OD has increased over the past decades and empirical research has been conducted in this field.¹ Although patients with OD often have decreased quality of life and psychological distress, their mental health issues are underexposed in the literature.⁴⁻⁸ In response to the absence of uniform diagnostic and treatment strategies for OD in the Netherlands, a multidisciplinary, evidence-based, national guideline was published in 2017.⁹ Although this guideline underlines the importance of psychosocial management, evidence regarding the implementation of psychosocial management in the multidisciplinary teams is lacking, indicating that a holistic psychosomatic approach is sparsely implemented.

Affective symptoms in OD patients

This thesis has described the high prevalence of clinically relevant affective symptoms (anxiety and depression) in OD patients (see chapters 2, 3, and 4)¹⁰⁻¹² and identified some key contributing factors. First, eating and drinking are necessities of life. Obviously, an impairment affecting one of the most fundamental daily requirements, namely nutrition, has an effect on psychological well-being. Moreover, patients who fear aspiration and choking will eat more slowly than their tablemates and may modify their food and eating behaviors to decrease the risk of complications. Furthermore, eating and drinking form an important aspect of social interaction. Drip feeding, but also drooling and spilling of food are not socially desirable table habits. Sensing ostracism, OD patients tend to be ashamed, fear social berating, decrease their social activities, and frequently even end up in social isolation, which may enhance the risk of psychiatric comorbidity.^{2,4} Accordingly, many patients have difficulty accepting their condition and coping with OD.

In chapter 2, we reported a prevalence of 47.3% of clinically relevant affective symptoms in patients with OD.¹⁰ These results were confirmed by the systematic literature review presented in chapter 4. In all included studies, OD and depressive symptoms were significantly associated, and 9 out of 12 studies revealed a significant association between OD and anxiety symptoms.¹¹ However, many studies were of poor methodological quality, and in most studies it remained unclear how OD was

diagnosed. It is therefore essential to implement a standardized diagnostic protocol, including fiberoptic endoscopic evaluation of swallowing (FEES) and/or videofluoroscopy of swallowing (VFS), before drawing any conclusions about whether a patient has OD or not. This protocol would provide the physician with information about the severity and pathophysiological mechanism of OD. As shown in chapter 3, the severity of OD, as measured by a standardized FEES examination, did not appear to be a good indicator for the presence and severity of affective symptoms, nor for the subjectively experienced severity of OD.¹² According to that examination, patients with more severe swallowing problems did not have a higher probability of presenting affective symptoms, which seems contra intuitive. An explanation could be that less-severe swallowing problems are a manifestation of an anxious and somatically hyperaroused state, which is characterized by somatic anxiety equivalents. The hyperarousal might be caused by a psychiatric disorder but could also represent an early stage of somatic disease. This interpretation is new and has not been advanced previously in the dysphagia literature.¹²⁻¹⁸ Another possible explanation for this paradox is that patients with severe or chronic OD often have a longer history of disease, implying that they have found ways to cope with their symptoms, in turn leading to an improvement of their psychological well-being. This reasoning is in line with previous literature on patients with Parkinson's disease (PD) and oncological disorders. Regarding PD, the associated depressive symptoms arise mainly at the beginning of the disease, after which the symptoms of depression decrease and then increase in the latter stages.¹⁹ However, the overall relationship between the severity of PD and depression remains poorly understood; depression in PD is most likely multifactorial (e.g., psychological, environmental, and disease-specific factors).²⁰ Mental health and depressive symptoms often improve in oncological patients over the course of the disease, even when their functional disability remains stable or deteriorates.²¹⁻²³ The fact that severity of OD is not a good indicator for the presence of affective symptoms underscores the complexity of the problem and the difficulty of detecting comorbidity in a clinical setting. Additionally, the patients' own evaluation of swallowing function (as measured with the Dysphagia Severity Scale - DSS) did not correspond with the severity of OD as assessed by FEES.¹² This incongruity of perceptual judgment is explained by the decreased sensation due to the underlying disease (e.g., Parkinson's disease, myotonic dystrophy type 1, head and neck cancer).²⁴ However, the patients' own evaluation of swallowing was associated with anxiety symptoms, suggesting that higher anxiety levels might amplify the individual experience of suffering, regardless of the severity of OD. On the other hand, the experience of OD may lead to increased anxiety symptoms as well, suggesting that the association between OD and affective complaints might be bidirectional.

Medically unexplained symptoms

Our studies, as described in chapters 2 and 3 of this thesis, only included patients with a proven somatic disease (neurological, oncological). That underlying somatic disease could, at least partly, explain their OD. However, patients with medically unexplained oropharyngeal dysphagia (MUNOD) are often referred to the ear-nose-throat (ENT) outpatient clinic for dysphagia as well.^{25,26} Medically unexplained symptoms are seen not only in patients with OD but also in other ENT patients (with vertigo, tinnitus, etc.).^{27,28} Patients with medically unexplained otorhinolaryngology symptoms (MUORLS) form a challenging patient group. Caregivers struggle with these patients and treatment strategies are often unsuccessful, which leads to frustration in caregivers and patients, multiple visits to outpatient clinics, invasive diagnostics, unnecessary treatment, and increasing healthcare costs.²⁹⁻³² Therefore, we conducted a more specific investigation, studying 14 patients with MUNOD presenting at the ENT outpatient clinic who had no clear explanation for their swallowing complaints and showed no detectable abnormalities during a standardized swallowing examination. It was determined that the medically unexplained OD was frequently accompanied by symptoms of anxiety and depression, suggesting that these patients were in a somatic hyperaroused state (as mentioned above). MUNOD might be caused by underlying disturbances (e.g., a psychiatric disorder) or be part of an early state of the somatic disease. An increasing body of evidence points to a bidirectional pathway between brain and body.¹²⁻¹⁸ In this neurobiological framework, somatic symptoms, functional disorders, and psychiatric conditions are the result of a sensitized response to earlier threats. This false-alarm signaling results in emotional and physical distress, in turn inducing psychiatric symptoms (such as anxiety and depression) and somatic symptoms (such as OD). Comparable results are seen in patients with dyspepsia, irritable bowel syndrome, and overactive bladder.^{13,14,16,17} Alarm falsification as part of a patient's defense system may worsen the somatic symptoms in patients who already have OD that was caused by an early stage of somatic disease. But this defense might also cause or increase OD symptoms in medically unexplained oropharyngeal dysphagia (MUNOD). Taking the argument a step further, the effects of psychiatric diseases on swallowing not only influence swallowing perception but may also affect the normal swallowing physiology with complications like prolonged mealtime, gagging, or piecemeal deglutition.

OD patients are not the only ones with medically unexplained symptoms; these also occur in many other subcategories of the ENT population. The study described in chapter 6 is the first to investigate the presentation of patients with MUORLS at an integrated ENT-psychiatry outpatient clinic.²⁷ All patients had subjective complaints that showed discrepancies with the outcome of clinical and instrumental examinations, and all had psychological distress or high healthcare utilization. The most common otorhinolaryngological complaints were vertigo, pharyngeal globus, OD, and nasal obstruction. Forty-one percent of the patients did not have a proven ENT diagnosis, and the other 59% had an ENT diagnosis that could not explain the subjective complaints.

The included patients received a joint consultation with an otorhinolaryngologist and a psychiatrist. The majority (78%) appeared to have a psychiatric disorder, according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-4-TR). In patients without an ENT diagnosis this share was even higher (90%). Diagnosis of the psychiatric illness was often delayed because patients usually take a detour, seeking ‘appropriate somatic treatment’ for their complaints. The patients in the study group underwent repeated somatic examinations and treatments to exclude an underlying somatic disease, sometimes in different disciplines and even for diverse complaints. Referral of MUORLS patients with a proven ENT diagnosis is often delayed because caregivers focus exclusively on that somatic diagnosis. The MUORLS patients in the study group visited the outpatient clinic multiple times (up to 92 visits) and even underwent unnecessary treatment and interventions, which may have led to higher healthcare costs and unnecessary risks for the patient. Overall, in 32% of the patients ENT treatment did not alleviate their complaints.

Limitations

The studies described in this thesis had some methodological limitations. First of all, the sample sizes of the studies in chapters 2, 3, 5, and 6 might have been too small to reveal significant associations or group differences. Because of the heterogeneity of the study populations, in combination with the small size of the etiological subgroups, no further statistical analyses of group differences or statistical stratification could be performed in chapters 2 and 3. Furthermore, HADS was used to screen for symptoms of anxiety and depression. HADS is a reliable and frequently used instrument that is validated for the outpatient clinic; nonetheless, using a different or multiple screening tools could have produced different results. FEES was used as a diagnostic tool to measure severity of swallowing dysfunction in chapter 3. Perhaps another diagnostic tool (such as videofluoroscopy, manometry, or electromyography) would have provided different results. Also, it remains difficult to define which affective symptoms can be attributed purely to OD, and it is hard to determine if there is a causal relationship.

Clinical practice

Although the pathophysiological mechanisms of psychiatric symptoms in patients with swallowing problems are not yet understood, this thesis shows that affective problems in OD patients are highly prevalent. The contribution of swallowing disorders to affective symptoms, or vice versa, is difficult to assess, and it remains unclear if there is a causal relationship.^{6,10,12} The literature suggests that somatic and psychiatric complaints might be interconnected; by implication, somatic patients with psychiatric comorbidity may benefit from an integrated approach, including mental healthcare. However, the evidence remains sparse.^{13,14,18,33-35} Integrated somatic and psychiatric care is still not part of current clinical practice, which implies that affective symptoms in OD patients, like in other patients with somatic and psychiatric comorbidity, often

remain undiagnosed and thus untreated.^{10,12,34} Psychological distress might negatively affect swallowing rehabilitation. Effective treatment for anxiety and depression symptoms might allow patients to be more capable of putting effort into their OD rehabilitation, compared to patients suffering from untreated affective symptoms.³⁶ Improvement of the psychiatric condition or psychological well-being might also lead to a decreased experience of OD. Thus, it is important to recognize affective symptoms early by performing a psychiatric assessment in order to diagnose and treat the affective condition. This could improve the patients' disease-specific health status and may improve their OD rehabilitation outcome. The current Dutch evidence-based guidelines on various ENT pathologies/complaints do not help the clinician to recognize and manage mental health issues and MUORLS in the ENT population, and discipline-overarching guidelines on integrated care are needed.⁹ Mental distress is often underexposed during consultation, and queries on mental health are mostly subordinated to the examination of physical aspects, perhaps forgotten or completely avoided.^{37,38} The ENT specialist needs to be prepared for psychiatric comorbidity in the ENT population in general and specifically in OD patients. In patients with expected multi-morbidity (abnormal behavior, failure of treatment, high healthcare utilization, medically unexplained symptoms, repeated referrals, frustration between caregiver and patient etc.) screening for psychiatric comorbidity is warranted. Screening tools like the Hospital Anxiety and Depression Scale (HADS) can be helpful. A monodisciplinary approach is, in our opinion, obsolete; instead, these patients need early implementation of an integrated multidisciplinary psychosomatic strategy. Furthermore, it is assumed that integrated care makes mental health issues easier to discuss and gets patients motivated for referral to psychiatric care.^{13,35} Combining knowledge from different disciplines might decrease misdiagnosis and inappropriate treatment, and a multidisciplinary approach may lead to a decrease in healthcare costs and to improvement of patients' satisfaction and safety.³⁹

Future perspectives

This thesis shows that there is a high coincidence between OD and affective symptoms. However, more research on this topic is needed. First of all, little is known about the pathophysiological mechanisms of affective symptoms in these patients. The neurobiological framework of the above-mentioned bidirectional pathway between brain and body, the body-brain axis, is the basis for an interesting 'alarm-falsification theory'. However, that theory needs further investigation to provide better understanding of OD as a 'false-alarm symptom'.^{13,14} Second, longitudinal studies and therapy-effect studies are needed to investigate the effect of integrated care and psychiatric treatment on swallowing rehabilitation outcome. Third, more prospective and longitudinal studies investigating psychiatric morbidity in other specific MUORLS phenotypes (vertigo, globus pharyngeus, tinnitus etc.) are needed.

Last but not least, to generate a more etiology-driven nosology of functional ENT disorders it is necessary to apply a momentary assessment methodology. By measuring complaints in patients' daily life, symptom formation will better be understood. In other words, symptoms impacting on symptoms and interacting with context should be assessed repeatedly and randomly in order to understand how complaints arise.⁴⁰

Valorization addendum

The studies presented in this thesis were designed to provide insight in psychiatric (co)morbidity in patients with OD and to provide guidance for OD caregivers. OD, which basically means the inability to eat and drink normally, affects over 40 million people in Europe.⁴¹ The financial impact of OD is substantial.^{42,43} OD has various underlying etiologies, including stroke, progressive degenerative neurological diseases, and oncological diseases, and may cause severe complications.^{1-4,44} In recent decades, this problem has been gaining attention worldwide and high-quality research has been done, mainly concerning the diagnostic trajectory and treatment strategies for OD patients. Although the literature suggests a high impact on OD patients' health-related quality of life, knowledge about mental distress in OD patients is scarce and discussions of the psychological burden remain speculative.

The recommended integrated approach to the OD patient is a multidisciplinary one, involving different caregivers including medical specialists (otorhinolaryngologists, neurologists, psychiatrists, radiologists, oncologists, etc.) and allied health professionals (speech-language pathologists, dieticians, nurses, etc.). In this thesis, we propose developing an integrated psychosomatic approach by adding a staff-guided mental-healthcare worker to this multidisciplinary team. To that end, the results of this thesis are not only of relevance for ENT specialists and psychiatrists but for all professionals involved in the long-lasting trajectory of OD care.

This thesis offers deeper insight into the high prevalence of mental health issues in OD patients, but it also draws attention to psychiatric problems in patients with various ENT complaints. However, prospective longitudinal studies are needed to understand mental distress in the ENT population more fully. Better understanding must underpin efforts to improve patients' healthcare status and rehabilitation outcome, which will in turn lead to decreased healthcare utilization and costs. Unfortunately, financial resources and grants are scarce in this field; consequently, little fundamental research or research of clinical relevance has been done. We hope that this thesis will lead to greater awareness among caregivers of the mental health issues that accompany OD, to more research in this field, and to better management strategies, all in order to better help this complex category of patients. Future models of integrated OD care certainly deserve to be considered for research grants.

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Summary

Summary

This thesis reports our research on clinically relevant affective symptoms in patients with oropharyngeal dysphagia (OD), and it consists of two sections. Chapters 2, 3, and 4 discuss clinically relevant affective symptoms in dysphagic patients with an underlying somatic disease. Chapters 5 and 6 discuss psychiatric comorbidities in patients with medically unexplained oropharyngeal and otorhinolaryngological symptoms.

Prevalence of affective symptoms in patients with OD

Patients with somatic disease often suffer from psychiatric problems. For example, affective symptoms are common in cardiac patients, patients with chronic obstructive pulmonary disease, and patients with diabetes. The prevalence of clinically relevant affective symptoms varies with the etiology of the somatic disease. Before starting on this thesis, we knew little about affective symptoms and psychiatric comorbidity in patients with OD. However, these patients often exhibited a depressed mood during their outpatient clinic visit or behaved anxiously during the interview and physical examination.

The goal of the first study, as presented in **Chapter 2**, was to determine the prevalence of clinically relevant affective symptoms in the population of outpatient clinic patients with OD. All of the 96 included patients had OD, as assessed with Fiberoptic Endoscopic Evaluation of Swallowing (FEES) and Videofluoroscopy of Swallowing (VFS), and were diagnosed with an underlying somatic cause of OD (Parkinson's disease, head and neck cancer, myotonic dystrophy, etc.). The Hospital Anxiety and Depression Scale (HADS) was used for measuring clinically relevant symptoms of anxiety and depression. This validated questionnaire consists of 14 items: 7 on the anxiety subscale and 7 on the depression subscale. Every item is scored from 0 to 3, resulting in a range from 0 to 21 on each subscale. Symptoms of anxiety or depression were defined as clinically relevant when they received a score of 8 or more. In addition, the study used a visual analogue scale (VAS), namely the simple and highly subjective Dysphagia Severity Scale (DSS), to elicit a patient's own evaluation of the current swallowing status. This study showed a prevalence of 47.3% (N=43) of clinically relevant affective symptoms in OD patients, which was in line with many other outpatient populations and underlined the significant psychological burden of OD. Furthermore, patients with clinically relevant symptoms of anxiety scored significantly lower on the DSS compared to patients without symptoms of anxiety. This indicated either that symptoms of anxiety might lead to more subjective dysphagic complaints, or that OD might be a risk factor for having clinically relevant symptoms of anxiety. No significant association was found between the DSS scores and clinically relevant symptoms of depression.

Severity of OD and affective symptoms

As mentioned above, clinically relevant affective symptoms are frequently present in patients with OD. We expected to find that patients with severe OD had a higher risk of exhibiting clinically relevant affective symptoms compared to patients with mild or moderate OD.

In **chapter 3** the relationship between the severity of OD and clinically relevant affective symptoms was investigated. In total 107 patients with OD were included in the study, all of whom were diagnosed with an underlying somatic cause of OD. They underwent a standardized FEES examination whereby the severity of OD was measured using four visuoperceptual FEES variables, which were scored by two independent consultants. These judges were blinded for each other's ratings and for the patients' history. For measurement of clinically relevant anxiety and depression symptoms, the patients had to fill out the HADS. The DSS was used for the patient's own evaluation of their swallowing status. Although a positive association between HADS scores and FEES outcome variables was expected, no such relationship was found. For some FEES variables, a negative association was found. Apparently, patients with more severe OD did not exhibit clinically relevant affective symptoms more often. Hence, the presence of clinically relevant affective symptoms in OD patients cannot be inferred from the severity of the swallowing impairment as measured with FEES. Moreover, the DSS result was not associated with any of the FEES outcome variables, meaning no relationship was found between the measured severity of OD and the patients' own subjective evaluation of swallowing impairment. Sensory deficits in patients with a neurological disease, and thereby presumably with a less accurate perception of swallowing problems, might be an explanation (severe OD, but few complaints). In **chapter 2** we already reported that the DSS outcome was associated with clinically relevant symptoms of anxiety. Perhaps higher levels of anxiety (and possibly also depression) might influence the perception of swallowing impairment, leading the patients to overestimate their swallowing problem. In other words, anxiety may amplify the subjective perception of swallowing problems (i.e., alarm falsification).

Evaluation of affective symptoms in OD

Chapter 4 presented an overview of the published literature on anxiety and depression in OD patients based on a systematic literature review. After a structured database search in Embase, Medline, Web-of-Science, PsycINFO, Cochrane Library, and Google Scholar, 24 articles were included for analysis. The included studies were assessed for methodological quality using a 12-item critical appraisal tool with which two independent reviewers evaluated the internal and external validity. None of the studies fulfilled all the criteria for methodological quality. Because of the heterogeneous outcomes and methodological limitations, data could not be pooled. Although no meta-analytic conclusions could be drawn, some trends were observed. All 24 studies concluded that depression was significantly and positively associated with impaired

swallowing function. Nine out of the 12 studies investigating anxiety concluded that clinically relevant anxiety symptoms were positively associated with swallowing problems. However, it remained unclear if there is a causal relationship. Therefore, future cohort studies should use standardized instrumental measurement tools for OD, and psychiatric assessment should be done by a psychiatrist as a gold standard instead of relying on self-reporting questionnaires in order to diagnose the presence and severity of the affective condition. Just 5 of the included studies used FEES or VFS to measure OD, and our own study (**chapter 3**) was the only one among these that described the measured outcome variables.

Medically unexplained OD

Sometimes, though rarely, patients have complaints of OD without demonstrable abnormalities in the anatomy of the upper aero-digestive tract and/or swallowing physiology. This medically unexplained oropharyngeal dysphagia (MUNOD) is a difficult problem for healthcare professionals.

The study in **chapter 5** investigated clinically relevant affective symptoms in 14 patients with MUNOD. The HADS was used to measure the presence of clinically relevant affective symptoms, and the DSS was used for the patient's own evaluation of swallowing. None of the included patients showed any structural and/or physiological abnormalities or any significant swallowing problems during a standardized FEES examination. Five visuoperceptual FEES variables were scored by two independent judges. Most patients showed abnormal piecemeal deglutition (sequential swallowing on the same bolus). This could be a MUNOD symptom because multiple swallows of smaller fragments of the bolus as part of a behavioral adaptation might give the patient a sense of security and control in an aroused status of anxiety. More patients (42.8%, N=6) showed clinically relevant symptoms of anxiety than of depression (21.4%, N=3). No significant differences were found in DSS scores between patients with and without clinically relevant affective symptoms. An interesting question is whether OD complaints could be caused by an affective state. One theory is drawn from the bladder-gut-brain axis, which is a bidirectional pathway between brain and body. According to that theory, functional disorders and somatic symptoms are sensitized responses to earlier threats (alarm falsification). MUNOD could be such false-alarm behavior. In patients with prolonged unexplained complaints of OD, psychiatric conditions must be considered as a possible cause and a psychiatrist should be involved.

Medically unexplained otorhinolaryngology symptoms

Medically unexplained symptoms are seen not only in patients with OD but also in many other patients at the otorhinolaryngological (ORL) outpatient clinic. Medically unexplained otorhinolaryngology symptoms (MUORLS) are associated with increased healthcare costs, risk of iatrogenic damage, and frustration among patients and

healthcare workers. A psychiatric disorder might be the underlying cause and its identification is often delayed, partly due to the somatic focus of the physician and the patient.

Chapter 6 investigated patients with MUORLS and proposed an integrated multidisciplinary approach that would involve consulting a psychiatrist. In total 102 patients with ORL complaints were included. Their most common complaints were dizziness, pharyngeal globus, OD, dysphonia, and nasal obstruction. All patients had subjective complaints that showed a discrepancy with the clinical examination (no ORL diagnosis or an ORL diagnosis that did not fit the complaints). Included patients had a joint interview with an otorhinolaryngologist and a psychiatrist at the ORL outpatient clinic. If indicated, patients were subsequently invited to visit the hospital psychiatry outpatient clinic. Of all included patients, 78% (N=80) appeared to have a psychiatric diagnosis according to the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-4-TR). Psychiatric diagnosis was often delayed by additional examinations that were performed to exclude somatic disorders. Many patients visited the outpatient clinic on numerous occasions (up to 92 times). Thirty-two percent (N=32) of the patients underwent some type of treatment for a somatic diagnosis without any improvement of their complaints. Thus, patients with MUORLS often suffered from psychiatric (co)morbidity, which probably contributed to their ORL complaints.

General discussion

Although psychological distress, including affective symptoms, is common in OD patients, this problem is often under-recognized. Eating and drinking are fundamental daily requirements and an important part of social interaction. OD patients often are ashamed and have decreased social activities, implying that swallowing problems have an effect on psychological well-being. The severity of OD does not seem to be a good indicator for the presence of clinically relevant affective symptoms, which underscores the complexity of the problem. In addition, patients with medically unexplained symptoms, who constitute a challenging category of patients, often suffer from clinically relevant affective symptoms. An interesting theory in this matter is drawn from the bladder-gut-brain axis, which states that body and brain are interconnected and that psychiatric disorders, but also early stages of a somatic disease, might coincidentally induce psychological and somatic symptoms. This behavior of alarm falsification within the body's defense system may worsen the somatic symptoms in OD patients with an underlying somatic disease, but it might also cause medically unexplained symptoms. There is increasing evidence that psychological and somatic symptoms are interconnected. Patients with both somatic and psychological symptoms may benefit from an interdisciplinary approach that includes mental healthcare. It is assumed that integrated care makes it easier to discuss psychological distress and gets patients motivated for referral to psychological and psychiatric care. The studies described in this thesis had a cross-sectional design, meaning no causal relationship

between affective symptoms and OD could be demonstrated. Therefore, to better understand the nature and direction of the relationship between psychiatric symptoms and OD, longitudinal cohort studies should be conducted in the future.

Samenvatting

Samenvatting

Dit proefschrift bevat studies naar affectieve symptomen bij patiënten met orofaryngeale dysfagie (OD), en kan worden verdeeld in twee secties; hoofdstukken 2, 3, en 4 hebben betrekking op affectieve symptomen bij patiënten met OD, bij wie er sprake is van een onderliggende somatische ziekte of aandoening. Hoofdstuk 5 en 6 hebben betrekking op patiënten met medisch onbegrepen klachten.

Prevalentie van angst- en depressieve symptomen bij patiënten met OD

Bij patiënten met een somatische ziekte of aandoening is er vaak sprake van psychische problemen. Zo worden bijvoorbeeld affectieve symptomen vaak gezien bij patiënten met cardiale problemen, patiënten met chronisch obstructieve longziekten (COPD) of patiënten met suikerziekte. De prevalentie van affectieve symptomen is afhankelijk van de etiologie van het somatische ziektebeeld. Voorafgaand aan dit proefschrift was er slechts weinig bekend over affectieve symptomen en psychiatrische co-morbiditeit bij patiënten met OD. Echter, deze patiënten maakten tijdens hun poliklinische bezoeken vaak een depressieve indruk of gedroegen zich angstig tijdens het slikonderzoek.

Het doel van de eerste studie uit dit proefschrift (**hoofdstuk 2**) was om de prevalentie van angst- en depressieve symptomen (affectieve symptomen) bij patiënten met OD, die zich op de dysfagie polikliniek presenteerden, vast te stellen. Zesennegentig patiënten met OD, zoals vastgesteld door middel van Fiberoptic Endoscopic Evaluation of Swallowing (FEES) en Videofluoroscopisch Slikonderzoek (VFS), werden geïnccludeerd. Alle patiënten hadden een onderliggende somatische ziekte als verklaring voor de OD (ziekte van Parkinson, hoofd-halskanker, myotone dystrofie, etc.). Voor het meten van klinisch relevante angst- en depressieve symptomen werd in deze studie gebruik gemaakt van de Hospital Anxiety and Depression Scale (HADS). Deze gevalideerde vragenlijst bestaat uit 14 onderdelen; 7 vragen hebben betrekking op angstsymptomen (angst subschaal) en 7 vragen op depressieve symptomen (depressie subschaal). Aan iedere vraag kunnen 0 tot 3 punten worden toegekend. De totale score ligt dan tussen de 0 en 21 punten voor beide subschalen. Klinisch relevante angst- of depressieve symptomen zijn gedefinieerd als een score van 8 of hoger of een van de beide subschalen. Ook werd bij patiënten de Dysphagia Severity Scale (DSS) afgenomen. Deze visueel analoge schaal (VAS) is een makkelijke en subjectieve beoordeling van de actuele slikfunctie door de patiënt zelf. Een lage DSS-score betekent dat de patiënt de slikfunctie als slecht beoordeelt. Een hoge DSS-score betekent dat de patiënt de slikfunctie als goed beoordeelt. Deze studie toont een hoge prevalentie (N=43; 47.3%) van klinisch relevante affectieve symptomen hetgeen overeenkomt met andere poliklinische patiënten populaties. Patiënten met klinisch relevante angstsymptomen hadden een lagere DSS-score in vergelijking met patiënten zonder angstsymptomen. Dit kan betekenen dat ofwel angstsymptomen leiden tot meer subjectieve klachten van OD ofwel klachten van OD een risicofactor zijn voor klinisch relevante angstsymptomen. Er

werd geen verband gevonden tussen de DSS-score en klinisch relevante depressieve symptomen.

Ernst van OD en affectieve symptomen

Zoals hierboven besproken komen affectieve symptomen vaak voor bij patiënten met OD. Onze verwachting was dat patiënten met ernstige OD een hoger risico zouden hebben op affectieve symptomen in vergelijking met patiënten met een milde OD.

In **hoofdstuk 3** onderzochten wij of er een verband bestaat tussen de ernst van de OD en het hebben van affectieve symptomen. Er werden in totaal 107 patiënten met OD geïnccludeerd in deze studie. Alle geïnccludeerde patiënten waren gediagnosticeerd met een onderliggende somatische ziekte of aandoening en ondergingen een gestandaardiseerd FEES-onderzoek. De ernst van de OD werd bepaald aan de hand van 4 visuoperceptieve FEES-variabelen welke werden beoordeeld door twee onafhankelijke en geblindeerde beoordelaars. Voor het meten van klinisch relevante angst- en depressieve symptomen werd de HADS-vragenlijst gebruikt. De DSS werd gebruikt als subjectieve beoordeling van de slikfunctie door de patiënt zelf. Deze studie toont geen positieve correlatie tussen affectieve symptomen en de ernst van de OD. Blijkbaar kunnen affectieve symptomen bij dysfagie-patiënten niet worden voorspeld aan de hand van de ernst van OD zoals gemeten met FEES. Ook werd geen correlatie gevonden tussen de DSS-score en de verschillende FEES-variabelen. Er blijkt dus geen verband te zijn tussen de ernst van de OD en de subjectieve beoordeling van de slikfunctie door de patiënt zelf. Een toenemend verlies van sensorische functie en daardoor een minder nauwkeurige waarneming van slikproblemen zou een verklaring hiervoor kunnen zijn. In **hoofdstuk 2** werd wel associatie gevonden tussen de DSS-score en klinisch relevante angstsymptomen. Wellicht hebben angstsymptomen (en mogelijk ook depressieve symptomen) invloed op de 'slikperceptie' en is er bijvoorbeeld een overschatting van het slikprobleem.

Evaluatie van affectieve symptomen bij OD

Hoofdstuk 4 bevat een systematische literatuur review en geeft een overzicht van de gepubliceerde literatuur over angst- en depressieve symptomen bij patiënten met OD. Na een gestructureerd database onderzoek in Embase, Medline, Web-of-Science, PsychINFO, Cochrane Library en Google scholar werden 24 artikelen geïnccludeerd voor beoordeling. De geïnccludeerde studies werden beoordeeld op methodologische kwaliteit door twee onafhankelijke beoordelaars met behulp van een 12-punts kritisch beoordelingsinstrument voor de evaluatie van de interne en externe validiteit. Geen van de geïnccludeerde studies voldeed aan alle criteria voor methodologische kwaliteit. Vanwege de methodologische beperkingen en de heterogene uitkomstmaten kon de data van de verschillende studies niet worden samengevoegd. Ondanks het feit dat er geen meta-analyse kon worden verricht, werden wel enkele trends gezien. Alle 24 studies concludeerden dat depressieve symptomen positief geassocieerd zijn met OD.

Negen van de 12 studies waarbij werd gekeken naar angstsymptomen concludeerden dat angstsymptomen positief zijn geassocieerd met OD. Echter, een causaal verband tussen affectieve symptomen en OD kon niet worden aangetoond. Longitudinaal cohortonderzoek is nodig om het verband tussen OD en affectieve symptomen beter te begrijpen. Er dient dan gebruik gemaakt te worden van gestandaardiseerde meetinstrumenten om OD te beoordelen. Ook dient bij voorkeur psychiatrisch onderzoek te worden verricht door een psychiater in plaats van vragenlijsten voor de screening naar affectieve symptomen. Slechts 5 studies gebruikten FEES of VFS om OD te meten en in slechts 1 studie (onze eigen studie, **hoofdstuk 3**) werden de uitkomstvariabelen voor FEES en VFS beschreven.

Medisch onbegrepen klachten van OD

Soms hebben patiënten klachten van OD zonder aantoonbare afwijkingen van de anatomie van de bovenste aerodigestieve tractus en/of aantoonbare afwijkingen van de slikfysiologie. Deze medisch onbegrepen orofaryngeale dysfagie (MUNOD) is een ingewikkeld probleem voor zorgverleners.

In de studie van **hoofdstuk 5** werd bij 14 patiënten met MUNOD onderzocht of er sprake was van klinisch relevante affectieve symptomen. De HADS werd gebruikt om klinisch relevante angst- en depressieve symptomen te meten en de DSS werd gebruikt voor de subjectieve beoordeling van de slikfunctie door de patiënt zelf. De geïncludeerde patiënten hadden geen structurele afwijkingen of ernstige slikproblemen tijdens FEES-onderzoek. Vijf visuoperceptieve FEES-variabelen werden beoordeeld door twee onafhankelijke beoordelaars. De meeste patiënten hadden een afwijkende variabele 'piecemeal deglutition' (het aantal slikacts dat de patiënt nodig heeft om 1 bolus te verwerken). Een afwijkende 'piecemeal deglutition' zou een symptoom van MUNOD kunnen zijn, aangezien meerdere slikacts van kleinere porties van eenzelfde bolus een gevoel van zekerheid en controle kunnen geven. Tweeënvijftig procent (N=6) van de patiënten had klinisch relevante angstsymptomen en 21.3% (N=3) van de patiënten had klinisch relevante depressieve symptomen. Er waren geen significante verschillen in DSS-scores tussen patiënten met en zonder affectieve symptomen. Zou OD veroorzaakt kunnen worden door een affectieve stoornis? Eén theorie is de 'bladder-gut-brain-axis'; een bi-directioneel *pathway* tussen lichaam en brein. Deze theorie stelt dat functionele aandoeningen en somatische symptomen, en de daarbij behorende affectieve problemen, het resultaat zijn van een gesensitiseerde respons op eerdere bedreigingen die de patiënt heeft ervaren ('vals alarm' of 'alarmfalsificatie'). MUNOD kan een dergelijk symptoom zijn. Bij patiënten met aanhoudende onbegrepen klachten van OD moet een onderliggende psychiatrische aandoening als oorzaak van deze klachten worden overwogen en een psychiater worden betrokken in de zorg.

Medisch onbegrepen keel-, neus- en oorklachten

Medisch onbegrepen klachten worden niet alleen gezien bij patiënten met OD maar ook bij veel andere patiënten op de polikliniek Keel-, Neus- en Oorheelkunde (KNO). Medisch onbegrepen KNO-klachten (MUORLS) zijn geassocieerd met hogere zorgkosten, risico op iatrogeen letsel en frustratie tussen patiënt en zorgverleners. Een psychiatrisch ziektebeeld kan de onderliggende oorzaak zijn echter wordt dit meestal pas laat herkend doordat zorgverleners en patiënten zich focussen op de somatiek.

In de studie van **Hoofdstuk 6** werden patiënten met MUORLS integraal multidisciplinair benaderd inclusief een beoordeling door een psychiater. In totaal werden 102 patiënten met MUORLS geïncludeerd. De meest voorkomende klachten waren duizeligheid, globusgevoel, OD, dysfonie en nasale obstructie. Alle patiënten hadden subjectieve klachten die niet in verhouding stonden met het klinisch onderzoek (geen KNO-diagnose of een KNO-diagnose die niet paste bij de klachten). Patiënten werden gezien op de polikliniek KNO in een gezamenlijk consult met een KNO-arts en een psychiater. Indien geïndiceerd, kregen patiënten een uitnodiging op de polikliniek psychiatrie. Van alle geïncludeerde patiënten bleek 78% (N=80) een psychiatrisch ziektebeeld te hebben. Deze diagnose werd vaak vertraagd door herhaaldelijk en veelvuldig onderzoek om een somatische aandoening uit te sluiten. Veel patiënten bezochten de polikliniek veelvuldig (tot wel 92 keer). Tweeëndertig procent (N=32) van de patiënten onderging een somatische behandeling zonder verbetering van de klachten. Patiënten met MUORLS hebben vaak psychiatrische (co)morbiditeit welke waarschijnlijk bijdraagt aan hun KNO-klachten.

Algemene discussie

Ondanks dat een groot deel van de patiënten met OD last heeft van affectieve symptomen wordt dit probleem vaak niet herkend. Eten en drinken behoren tot de primaire levensbehoeften en zijn daarnaast een belangrijk onderdeel van sociale interactie. Patiënten met OD schamen zich vaak en hebben daardoor minder sociale activiteiten. Een verminderde slikfunctie heeft daardoor effect op het psychosociale welbevinden van de patiënt. De ernst van OD lijkt geen goede voorspeller te zijn voor het al dan niet aanwezig zijn van affectieve symptomen, wat de complexiteit van dit probleem alleen maar meer onderstreept. Ook patiënten met medisch onbegrepen OD, een uitdagende patiëntencategorie, hebben vaak last van affectieve symptomen. Een interessante theorie hierbij is de 'bladder-gut-brain axis', die stelt dat lichaam en brein verbonden zijn en psychiatrische ziekten, maar ook somatische aandoeningen, psychologische en somatische symptomen kunnen veroorzaken. Dit 'vals alarm' afweersysteem kan somatische symptomen bij patiënten met een somatisch verklaarde OD verergeren en medisch onbegrepen symptomen veroorzaken. Steeds meer literatuur suggereert dat psychologische en somatische symptomen elkaar beïnvloeden. Patiënten met somatische symptomen en psychologische co-morbiditeit kunnen voordeel hebben van een interdisciplinaire benadering inclusief een psychiater

of psycholoog. Tijdens integrale zorg kunnen psychologische problemen makkelijker bespreekbaar worden gemaakt en kunnen patiënten eerder gemotiveerd zijn om verwezen te worden voor psychologische of psychiatrische hulp. Aangezien de studies in dit proefschrift cross-sectionele onderzoeken zijn, kon geen causaal verband tussen affectieve symptomen en OD worden aangetoond. Toekomstige longitudinale cohortstudies zijn nodig om de aard en de richting van de relatie tussen psychiatrische symptomen en OD te bepalen.

Dankwoord

Dankwoord

Het proefschrift is eindelijk af! Het tot stand komen van dit proefschrift zou absoluut onmogelijk zijn geweest zonder de steun en hulp van velen. Via dit dankwoord wil ik iedereen bedanken die mij de afgelopen bijna zes jaar heeft gesteund. Graag richt ik het woord tot een aantal mensen in het bijzonder.

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List of publications

List of publications

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Curriculum Vitae

Curriculum Vitae

Rob Johannes Carel Gerardus Verdonschot is geboren op 25 februari 1988 te Hapert. In 2006 behaalde hij zijn Gymnasiumdiploma aan het Pius-X college te Bladel en startte hij met de opleiding Geneeskunde aan de Universiteit Maastricht. Na het behalen van zijn Bachelor geneeskunde heeft hij in het collegejaar 2009-2010 een fulltime bestuursfunctie bekleed bij studentenvereniging KoKo. Tijdens zijn coschappen was hij werkzaam in diverse ziekenhuizen in Limburg en Noord-Brabant. Zijn coschap kindergeneeskunde deed hij in Pretoria, Zuid-Afrika. Gezien zijn interesse in de Keel-, Neus- en Oorheelkunde heeft hij in het laatste studiejaar van zijn opleiding geneeskunde een klinische- en wetenschapsstage gedaan bij de afdeling Keel-, Neus- en Oorheelkunde en Hoofd-Halschirurgie van het Academisch Ziekenhuis Maastricht (MUMC+), alwaar hij sindsdien betrokken is bij onderzoek naar patiënten met orofaryngeale dysfagie. In 2013 behaalde hij zijn Master Geneeskunde en startte hij met zijn promotieonderzoek bij de vakgroep KNO van het MUMC+. Later dat jaar ging hij aan het werk als arts-assistent op de spoedeisende hulp van het Erasmus Medisch Centrum in Rotterdam (Erasmus MC). In januari 2016 startte hij in het Erasmus MC met de opleiding tot spoedeisende hulp arts. Rob zal deze opleiding naar verwachting in december 2018 afronden. Sinds 2016 is hij lid van de wetenschapscommissie van de Nederlandse Vereniging van Spoedeisende Hulp Artsen, waar hij zich inzet om wetenschappelijk onderzoek binnen de spoedeisende geneeskunde te bevorderen. Gedurende zijn werk als arts-assistent in Rotterdam heeft hij zijn werkzaamheden als promovendus in Maastricht voortgezet, met dit proefschrift als eindresultaat. Rob woont samen met zijn vriendin Tosca van Halsema te Rotterdam.

