Thesis

The diagnostical approach of globus sensation: Results from a single institution survey

A retrospective study

submitted by

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Graz, 26.04.2024

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Graz, am 26.04.2024 Lea Maria Ortner m. p.

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Dedication

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Zusammenfassung

Einführung: *Globus Pharyngeus* ist ein anhaltendes und schmerzloses Fremdkörpergefühl im Rachen. Es wird von vielen PatientInnen als unangenehm empfunden und führt zu wiederholten Vorstellungen bei HNO-FachärztInnen. Die Ursache für dieses Symptom ist häufig unklar und steht meist im Zusammenhang mit vielen anderen klinischen Erkrankungen und Symptomen. Dies erschwert die Erstellung standardisierter Untersuchungs- und Behandlungsstrategien. Ziel der vorliegenden Studie war es, die diagnostischen und therapeutischen Abläufe zu untersuchen, welche mit der Diagnose eines *Globus pharyngeus* zwischen 2014 und 2019 an der Ambulanz der klinischen Abteilung für Phoniatrie der Universitätsklinik für Hals-, Nasen-, und Ohrenheilkunde vorstellig gewesen sind.
Methodik: Es handelt sich um eine retrospektive Querschnittsstudie, in der epidemiologische Daten, diagnostische und Behandlungsverläufe sowie Überweisungsdetails von 211 Patienten gesammelt wurden. Die Identifizierung der Patienten erfolgte über das örtliche medizinische Institut für Statistik und die Datenbank "openMEDOCS". Für die Analyse kamen Microsoft Excel und deskriptive Statistik zum Einsatz, wobei die Anonymität der Patienten gewährleistet wurde.
Ergebnisse: Von den 211 PatientInnen (40,8% männlich, 59,2% weiblich; Durchschnittsalter 53,5 Jahren) berichteten 79,6% über chronische Beschwerden. Aktive Raucher wurden mit 12,3% detektiert und 26,1% hatten Allergien. Das Hauptsymptom war die Fremdkörperempfindung (64,5%), das häufigste begleitende Symptom umfasste das Halsbrennen mit Reflux (20,4%). Die Flexible Endoskopie zeigte in 31,3% der Fälle Befunde, wobei die Hyperplasie der Zungenbasis (12,8%) am häufigsten war. Zu den am häufigsten verordneten Nachuntersuchungen gehörte das Röntgen oder CT/MRT des Halses (46,4%).
Diskussion: Die erhobenen Daten wurden in Zusammenschau mit der aktuellen Studienlage zur Erstellung eines diagnostischen Algorithmus verwendet. Durch die Beachtung potenzieller Risikofaktoren (bspw. positive Raucheranamnese) und Warnsymptomen sollen unnötige Untersuchungen reduziert werden und somit sowohl der Leidensweg der PatientInnen als auch das Gesundheitssystem als Ganzes entlastet werden.

Abstract

Introduction: *Globus pharyngeus*, a persistent sensation of a painless foreign body in the throat, drives numerous visits to otorhinolaryngology clinics. The condition's unclear etiology and connections to other ailments hinder the establishment of standardized investigation and treatment approaches. This study, conducted between 2014 and 2019 at the phoniatrics outpatient ward of the University Hospital of Graz, aimed to evaluate diagnostic pathways, findings, and follow-up for patients presenting with *globus pharyngeus*.

Methods: A retrospective cross-sectional study collected epidemiological data, diagnostic and treatment pathways, and follow-up details for 211 patients identified through the local medical institute for statistics and the "openMEDOCS" database. Data analysis involved Microsoft Excel, using descriptive statistics while ensuring patient anonymity.

Results: Among the 211 participants (40.8% male, 59.2% female; mean age 53.5), 79.6% reported chronic complaints. Active smokers accounted for 12.3%, and 26.1% had allergies. The primary complaint was a sensation of a foreign body (64.5%), while the main secondary complaint was burning associated with reflux (20.4%). Flexible laryngoscopy revealed findings in 31.3% of cases, with hyperplasia at the base of the tongue (12.8%) being the most prevalent. The primary recommended post-presentation examination was X-ray or CT/MRI of the neck (46.4%).

Conclusion: The collected data were used in conjunction with the current body of research to develop a diagnostic algorithm. By considering potential risk factors (such as a positive smoking history) and warning symptoms, unnecessary examinations are intended to be reduced, thereby alleviating the suffering of patients and relieving the healthcare system as a whole.

Publications

No publications have been issued or released.

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List of Abbreviations

BMI	Body-Mass-Index
CP	Cricopharyngeal muscle
CT	Computed tomography
EERD	Extra Esophageal Reflux Disease
EGD	Esophagogastroduodenoscopy
ENT	Ear, Nose, and Throat
GERD	Gastroesophageal Reflux Disease
GETS	Glasgow-Edinburgh Throat Scale
GI	Gastrointestinal
GP	General Practitioner
HNCUP	Head and neck cancer of unknown primary
HNSCC	Head and neck squamous cell carcinoma
HPV	Human papillomavirus
HRM	High-resolution Manometry
ICD	International Classification of Diseases
LKH	Landeskrankenhaus (State Hospital)
LPR	Laryngopharyngeal Reflux
MDD	Major Depression Disorder
MLS	Micro-laryngoscopy
MPS	Micro-pharyngoscopy
MRI	Magnetic Resonance Imaging
NBI	Narrow Band Imaging
NSAID	Non-steroidal Anti-inflammatory Drug
OSAS	Obstructive Sleep Apnea Syndrome
PPI	Proton Pump Inhibitor
SCC	Squamous cell carcinoma
TIRADS	Thyroid imaging reporting and database system
TP	Thyropharyngeal muscle
UES	Upper Esophageal Sphincter
VFSS	Videofluoroscopic Swallow study

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Introduction

Classification and definition

Definition

Idiopathic *globus pharyngeus* is defined as an undesirable and intrusive feeling in the pharynx or throat without any abnormal findings or warning signs. Patients experiencing this phenomenon commonly attend otorhinolaryngology outpatient clinics. Various sensations have been reported, including tightness, itching, tickling, or burning. Patients frequently report a sensation of something lodged in their throat, along with difficulty in swallowing due to accumulated mucus. This often accompanies the habit of frequent post-swallowing. Sensations of restriction or choking are not uncommon. Nonetheless, the condition does not hinder the consumption of food itself. Patients typically experience the symptoms between meals.(1–3)

The identification of potential red flags, which can be a sign of organic cause or malignancy is crucial. These include pain, weight loss, dysphagia or odynophagia, aspiration, regurgitation, voice change/hoarseness, pain, lateralization of symptoms, tonsillar mass, cervical adenopathy and risk factors for aerodigestive malignancy (smoking, alcohol abuse). (3,4) If a patient reports any of these symptoms, it is imperative that an objective test is carried out. If idiopathic *globus pharyngeus* is suspected, a thorough investigation with laryngoscopy, endoscopy, pH-manometry, video-swallow radiography (VFSS), and reflux monitoring is performed. Without the presence of alarming symptoms, acid-suppressive therapy is typically initiated. This may be beneficial in the event of concurrent reflux symptoms. Other therapeutic options for idiopathic globus include neuromodulators and reassurance. (1)

The etiology of idiopathic *globus pharyngeus* remains unknown, owing to the dearth of scientific evidence. This translates into overtreatment, exacerbating patient anxiety and uncertainty.

Classification

Glasgow Edinburgh Throat Scale

The Glasgow-Edinburgh Throat Scale (GETS) is a questionnaire composed of ten questions that evaluate the symptoms of *globus pharyngeus*. Patients select a severity level ranging from 0 (no symptoms) to 7 (excruciating complaints). Questions 11 and 12 were included to assess the somatic burden of the patients concerning pharyngeal symptoms. The following queries are examined. (5)

- ➔ 1. Feeling of something stuck in the throat
- ➔ 2. Pain in the throat
- ➔ 3. Discomfort/irritation in the throat
- ➔ 4. Difficulty in swallowing food
- ➔ 5. Throat closing off
- ➔ 6. Swelling in the throat
- ➔ 7. Catarrh down throat
- ➔ 8. Can't empty throat when swallowing
- ➔ 9. Want to swallow all the time
- ➔ 10. Food sticking when swallowing
- ➔ 11. How much time do you spend thinking about your throat?
- ➔ 12. At present, how annoying do you find your throat sensation? (5)

According to Deary et al. study, approximately 70% of patients with globus did not demonstrate any swallowing difficulties. (5) Nonetheless, these patients experienced a sensation of something being lodged in their throat. Although more than 96% of globus patients reported irritation in their throat, pain was only experienced by 30% of these individuals. Ultimately, the GETS serves as a rapid and quantitative assessment tool to evaluate the severity and symptoms of *globus pharyngeus*. The throat symptoms are classified into three distinct categories, focusing on dysphagia, globus sensation, and pain/swelling in the throat. The findings of the study highlight the fact that patients with globus sensation have conspicuously higher scores on the globus scale, in comparison to the other two scales. This indicates that the GETS was found to be a reliable and valid symptom scale for assessing globus sensation. Additionally, the level of somatic distress can be assessed. (5,6)

Rome IV Criteria

During the Rome process, the Rome criteria were devised to classify functional gastrointestinal disorders objectively. The Rome IV classification created a categorization system for *globus pharyngeus.*

To fulfil the diagnostic criteria*, all of the following points must apply:

1. Persistent or intermittent, a non-painful sensation of a foreign body in the throat, with no structural lesion noted on physical examination, laryngoscopy, or endoscopy.
2. Occurrence of the sensation between meals
3. Absence of dysphagia or odynophagia
4. Absence of a gastric inlet patch in the proximal esophagus
5. Absence of evidence of gastroesophageal reflux or eosinophilic esophagus eosinophilic esophagitis is the cause of the symptom
6. Absence of severe motor disturbances of the esophagus`` (1)

*Criteria met in the last 3 months with symptom onset at least 6 months before diagnosis with a frequency of at least once a week.

``Achalasia/Esophagogastric Junction outflow obstruction, diffuse esophageal spasm, Jackhammer esophagus, absence of peristalsis.” (1)

History

The phenomenon of *globus pharyngeus* was previously thought to be associated with hysteria and uterine movement in women. However, it has since been revealed that these translations, which formed the basis of education for centuries, were incorrect. (7) Between 460 and 370 BC, during the time Hippocrates is thought to have lived, various transcripts were produced that discussed the origins of hysteria. It was associated with unfulfilled sexual desires and psychological disorders, particularly in women. The term 'globus' derives from Latin and refers to a spherical structure. (8,9) Throughout history, doctors have held the belief that hysteria is linked to sensations of a foreign object in the throat, respiratory difficulties, and discomfort while swallowing. (10) In 1707, John Purcell associated the sensation of a lump in the throat with hysterical attacks and created the term 'globus hystericus'. Purcell explained that neck strap muscle contraction leads to pressure build-up on the thyroid cartilage. In 1968, K.G. Malcomson showed that those experiencing

globus pharyngeus were not mostly female or possessed a hysterical personality. He suggested GERD as a potential origin of *globus pharyngeus.* (11)

Anatomy

Given that the *globus pharyngeus* is a symptom complex with multiple contributing factors, the subsequent discussion delves into the anatomy of the hypopharynx, larynx, cervical spine, and thyroid, all of which may play a role in the sensation of a globus.

Pharynx

The pharynx, which is responsible for the passage of air and food passage, can be thought of as a tube made up of non-keratinized squamous epithelium, muscle and connective tissue. It is divided into three parts. The most cranial section is called *pars nasalis pharyngis*, also known as the epipharynx or nasopharynx, which leads to the nasal cavity. This section is of great importance in immune defense due to the large amount of lymphatic tissue present. The *velum palatinum* (soft palate) is the caudal border. The middle part, *pars oralis pharyngis*, is also referred to as the mesopharynx or oropharynx. This component is related to the mouth. The third component is the *pars laryngea pharyngis*, hypopharynx, or laryngopharynx. It is linked to the larynx at the anterior aspect and extends towards the caudal end, connecting with the esophagus. (12–15)

Two distinct muscle groups are mainly required for the pharyngeal phase of the swallowing process. The first of these are the ring-shaped pharyngeal constrictor muscles. The second is the pharyngeal elevators, which develop from the inner longitudinal layer of muscles. (15)

The swallowing process involves three distinct phases, which require precise coordination from various muscles. Food is broken down into smaller pieces and combined with saliva during the oral phase. The so-called bolus is then pushed by the muscles of the floor of the mouth along the palate towards the *isthmus faucium*, supported by the hyoglossus and styloglossus muscles. This phase builds substantial pressure within the mouth, facilitating the entry of food into the pharynx, thereby initiating the pharyngeal phase. The *musculi tensor* and *levator veli palatini*

contract, resulting in the elevation of the soft palate. The palate is then pressed against Passavant's ridge, formed by the *musculus constrictor pharyngis superior*, which in turn closes the epipharynx, thus preventing the regurgitation of food. The upper sphincter system, composed of the *musculi palatoglossi*, prevents food from refluxing while the movement of the tongue body aids in this process. During the oral phase, the floor of the mouth is raised by the suprahyoid muscles and the larynx is elevated by the *musculus thyrohyoideus*, and this contraction causes the hyoid bone and larynx, which are located under the base of the tongue, to move up and forward. Consequently, the epiglottis covers the *aditus laryngis*, thereby reflexively shutting the glottis and impeding the respiratory muscles. Through contraction and elevation of the pharynx by the corresponding muscles, the bolus passes through the pharynx and finally reaches the esophagus and the last phase of the swallowing act is initiated. The peristaltic contractions then push the food bolus along the esophagus. (14) The piriform sinus, also known as the piriform recess, is located at the level between the thyroid cartilage and the aryepiglottic fold. Due to its location, it is susceptible to obstructions from foreign bodies. Mechanical obstruction is capable of eliciting both a cough reflex and a globus sensation. (14,16)

Larynx

The larynx is a segment of the respiratory tract located in the anterior neck. It is composed of various cartilages, muscles, membranes, and ligaments. It connects the lower sections of the pharynx, hypopharynx, and trachea. It contains specialized muscles that allow the vocal folds to adjust their position, thereby narrowing or widening the glottis. These muscles are also integral to the movement of the various cartilage parts. The larynx plays an important role not only in respiration but also in phonation. The framework comprises cartilage structures, specifically the thyroid and cricoid cartilage, which form the basic framework. The *cartilago aerytaenoidea* acts as a movable suspension of the vocal folds. Positioned at the summit of the arytenoid cartilage is the *cartilago corniculata*, commonly known as Santorini’s cartilage in honor of Italian anatomist, Giovanni Domenico Santorini. (12–14) The laryngeal membranes and ligaments maintain the different positions of the cartilage and allow complex movements. Of particular significance in this process are the vocal folds as they constitute the glottis, which is crucial in voice production. (12–

14) The glottis, positioned between the supra and subglottic spaces in the middle of the larynx, forms the basis for phonation.

Cervical spine

The spinal column comprises mobile constituents, which encompass vertebrae, intervertebral discs, and the musculoligamentous parts. The structure constitutes a relatively robust and steady framework. Bones can be connected continuously through synarthroses, also known as pseudo-joints, or discontinuously through diarthroses. Synarthroses can be categorized into three groups: ligamentous connection with *junctura fibrosa*, cartilaginous connection with *junctura cartilagine*a, and bony connection with *junctura ossea.* The synarthroses of the spine consist mainly of the intervertebral joints, where the intervertebral discs are situated, along with the uncovertebral joints, a cervical spine-specific occurrence. The limitation of movement in any individual component is achieved through stable fixation. The 23 individual vertebrae that make up the spinal column provide the body with a high degree of mobility and, at the same time, maximum stability. A significant number of patients reported experiencing problems with their cervical spine, with tension being a frequent cause. Consequently, it was postulated that such tension extends to the muscles located at the front of the neck and the larynx. These tensions might cause the sensation of a foreign object in the throat, leading to the *globus pharyngeus.* (12–14,17)

Thyroid gland

The thyroid gland is an endocrine organ that synthesizes calcitonin, triiodothyronine (T3), and thyroxine (T4) hormones, which are crucial for body growth and several metabolic processes. Its position is just below the larynx on the trachea, and it is made up of 2 lobes connected by an isthmus, which acts as a bridge between them. The thyroid gland consists of lobules surrounded by a two-layered capsule, with septa extending from the inner capsule into the stroma. The lobules contain thyroid follicles, which produce thyroid hormones via their endocrine cells and form the parenchyma of the gland. The parathyroid glands are positioned dorsally and superimposed on the thyroid gland, forming small lens-shaped organs. Their function is strongly linked to the thyroid gland through the production of parathyroid hormone (PTH). (12–14,18) However, it is susceptible to disorders and pathologies

that often result in enlargement and nodules. This increase in size can potentially lead to *globus pharyngeus.* (19)

Epidemiology

The epidemiology of *globus pharyngeus* is highly relevant in clinical research. This symptom can affect individuals of all ages and is thought to be caused by various factors, including anatomical, physiological, and psychological components. (1–3,20)

The prevalence of this phenomenon varies considerably, ranging from 3.5% to 46%, contingent upon the specific population studied and the diagnostic criteria used. (21–23) In a cross-sectional survey of 995 healthy young Iranians, the Rome III diagnostic criteria for functional gastrointestinal disorders were applied. The identified prevalence of *globus pharyngeus* within this context was 3.5%. (22) In a separate research study carried out in the United Kingdom, a thorough survey of 1158 women from the general population provided further insights into the prevalence of globus sensation. The results showed that 6% of the surveyed population experienced globus sensation for more than three months. It is important to note that this study did not apply the Rome III criteria. This highlights the need for standardization in research methodologies to improve our understanding *of globus pharyngeus* across different demographic groups and diagnostic frameworks. (23)

A study conducted in China, encompassing over 3000 participants, robustly unveiled a lifetime prevalence of 21.5% for globus syndrome. The meticulous application of the Rome III criteria played a pivotal role in determining this prevalence, ensuring a standardized and comprehensive diagnostic framework. The noteworthy sample size and adherence to specific criteria not only contribute valuable insights into the prevalence of *globus pharyngeus* within the Chinese population but also underscore the significance of global cooperation in research efforts. (21)

These findings accentuate the importance of consistent adherence to standardized diagnostic criteria, fostering improved comparability and reliability across studies conducted in diverse regions.

Predictive factors

Several factors that can contribute to *globus pharyngeus* are frequently mentioned in the literature but are seldom studied or discussed scientifically. The subsequent subsections will cover various possible factors that may predispose an individual to *globus pharyngeus.*

Age

There may be a higher incidence of *globus pharyngeus* in middle-aged individuals (35-54 years old), (2,20,21) although a more recent study by Tang et al. did not find a correlation with age. (24)

Gender

Batch et al. reported that *globus pharyngeus* is equally common in both genders. (25) Moloy et al. found that women under the age of 50 are three times more likely to be affected compared to men, while the likelihood is equal for both genders over the age of 50. (26) Rasmussen et al. reported that female gender was a predictor of hospitalization, even after symptom resolution. In contrast, the persistence of symptoms was found to be more common in males. (27) It seems that globus is equally prevalent in healthy women and men over the age of 50. (25) However, men are less likely to seek medical help for the symptom than women. (27)

Residence

A study conducted in China found that the occurrence of *globus pharyngeus* was notably higher in urban areas compared to rural ones. Tang et al. suggest that this phenomenon may be explained by the association between the sensation of globus and psychological issues like stress and adverse life events. (21)

Smoking and alcohol

The results of a comprehensive meta-analysis underline the substantial association between alcohol consumption, smoking, and an increased risk of neoplasms of the upper respiratory tract and digestive tract. In particular, alcohol-related risk seems to be more closely associated with the amount consumed than with the duration of consumption. Conversely, both the amount and duration of smoking appear to have an equal effect on the development of cancer in esophagus and larynx. In addition, simultaneous exposure to alcohol and tobacco significantly increases the risk of developing cancers in both esophagus and larynx. Given these risk factors, it is plausible to study their possible correlation with the occurrence of *globus pharyngeus.* (28)

Medication

A cross-sectional study was conducted to examine the hypothesis of a potential association between *globus pharyngeus* and salivary hypofunction, which may be induced by anticholinergic medication. Anticholinergic drugs are known to cause xerostomia and have been linked to an increased risk of *globus pharyngeus*, indicating a relationship between anticholinergic medications and the condition. Additionally, a case report supports the idea that there is a correlation between reduced salivary secretion and the occurrence of *globus pharyngeus*. (2,29)

Allergy

A preliminary report examined the correlation between an atopic factor and the occurrence of *globus pharyngeus.* Thirty-eight patients with *globus pharyngeus* were found to have a higher number of positive allergy skin tests. Among patients experiencing globus sensation and the control group, positive allergy tests were recorded at 77.8% and 28.6% respectively. Patients with *globus pharyngeus* and positive skin tests were administered allergic treatment, with 64.3% exhibiting symptom improvement. Of those, 85.2% reported moderate or excellent improvement. Patients without improvement or negative skin tests exhibited a variety of other medical conditions. The identified conditions were gastroesophageal reflux disease (18.5%), abnormal esophageal manometry (40.7%), and myofascial pain syndrome (3.7%). (30) A conclusive statement regarding the correlation between atopy and *globus pharyngeus* cannot be made due to the limited number of participants in the study. However, further investigation is necessary to establish a definitive link.

Etiopathogenesis

A number of pathologies have been identified as etiological factors that may contribute to *globus pharyngeus.* These will be discussed in the following paragraphs.

Osseous changes

Morbus Forestier

Diffuse idiopathic skeletal hyperostosis is a rather common non-inflammatory entity of the spine and leads to ossified ligaments and sinews. It can manifest in the cervical spine and thus lead to dysphagia.(31)

Stylalgia/ Eagle Syndrome

If the *processus styloideus* is longer than 3 cm or the *ligamentum stylohyoideus* is calcified it can lead to complaints summarized as the Eagle syndrome. Patients suffer from unspecified face pain and dysphagia, often caused by a head-spinning movement. (32) In one case it is described that a patient had globus sensation for years, and over the years the symptoms got severe. The examination was without any pathological laryngopharyngeal findings. The palpation of the oropharyngeal walls revealed a pressured, ossified resistance. It was detected as the punctum maximum of the globus sensation. (33)

Zenker diverticulum

Zenker diverticulum typically occurs at the junction between the hypopharynx and esophagus, located at the level of the 5th to 6th cervical vertebrae. This condition affects the *musculus cricopharyngeus*, which is a part of the *musculus pharyngeus constrictor inferior*. Depending on the location of the diverticulum, it can be classified into the Kilian triangle or the Laimer triangle. The Kilian triangle is located between the *pars obliqua* and *pars fundiformis* of the *musculus cricopharyngeus*. The Laimer triangle lies between the *musculus cricopharyngeus* and the muscular tube of the esophagus.

This condition is called a pseudodiverticulum because not all layers of the wall protrude. The size of the pseudodiverticulum can lead to dysphagia, regurgitation, and a feeling of globus. (34,35)

Autoimmune diseases

In a cross-sectional study at Cambridge University Hospital in Cambridge, UK, the prevalence of globus-like symptoms in patients with a previous diagnosis of autoimmune disease using the GETS was assessed. The test consists of a 10-item questionnaire and assesses throat symptoms. The categories relate to throat symptoms. There are three different subcategories, which refer to dysphagia, globus sensation, and pain/swelling in the throat. The difference is significant when compared to the normal population. Therefore, it can be assumed that autoimmune diseases, for example, rheumatoid arthritis, and systemic vasculitis, influence the development of *globus pharyngeus.* (36)

Anatomical alterations and neck masses

The sensation of a foreign body could be attributed to anatomical changes resulting from space-occupying lesions or anomalies. Possible anatomical alterations and neck masses include for example cartilage changes (37), cysts (38,39), and neck masses of varying dignity.

The presence of an epiglottic cyst has been suggested as a potential contributor to *globus pharyngeus,* as evidenced by a retrospective study where all eligible patients experienced symptom relief after undergoing CO_2 laser therapy. (38) Additionally, cysts or fistula is located in the central area of the neck, between the hyoid bone and the larynx, linked to remnants of embryonic development, the thyroglossal duc*t.* Notably, a diagnostic evaluation of a patient presenting with globus sensation and dysphagia revealed the presence of a median neck cyst as the underlying cause. (39)

Tumors may cause a foreign body sensation due to the expansion of their growth. Possible benign lesions include schwannomas (40), hemangiomas (41–43), and lipomas. Among the various types of malignant growths, squamous cell carcinoma (SCC) is the most prevalent type of head and neck cancer. Head and neck squamous cell carcinoma (HNSCC) develop in the mucous epithelium of the oral cavity, pharynx and larynx. Among all cancers worldwide, HNSCC is the sixth most common. (44) Major causes of cancers in the oral cavity and larynx include tobacco use, alcohol abuse, or both. The main cause of pharyngeal cancers is infection with human papillomaviruses (HPV), in particular HPV-16. Most patients are diagnosed with advanced HNSCC because there are no visible warning signs of early HNSCC or premalignant lesions. Other malignant entities that can lead to a sensation of foreign body presence include lymph node metastasis, lymphomas (45,46), sarcomas (47).

Functional causes

Reflux Disease

In reflux disease, acidic gastric juice rises from the stomach to the level of the esophagus, larynx and pharynx, leading to irritation of the mucous epithelium. It is important to differentiate between gastroesophageal reflux (GER) and

laryngopharyngeal reflux (LPR). GER occurs when acidic gastric juice flows backward into the esophagus, while LPR refers to the same reflux into the larynx and pharynx. In rare cases, reflux can lead to extra esophageal reflux disease (EERD) resulting in complications such as chronic laryngitis, pharyngitis, contact granuloma, and even seromucotympanum due to mucous membrane irritation by gastric acid. (35,48,49) LPR is categorized as a particular manifestation of EERD. The larynx and pharynx are particularly prone to retrograde reflux. (50) Patients primarily experience laryngeal symptoms due to local irritation by gastric acid, including non-specific symptoms such as throat clearing, hoarseness, and coughing, which could potentially be caused by other factors as well. (2,51,52) As can be seen from the previous sentences, the study situation is not yet sufficient to prove or disprove a link between globus and LPR.
Laryngeal findings suggestive of LPR are also non-specific and tend to be under- or overestimated. In asymptomatic subjects, up to 70% of mucosal findings suggestive of reflux have been reported. (2,53,54)

Gastroesophageal reflux disease (GERD) is a very common pathology with a very high prevalence. It was postulated that an additional functional esophageal disorder was a possible cause of globus and not GERD alone. As many globus patients did not respond to Proton Pump Inhibitor (PPI) medication, there was also the question of non-acid GERD as an etiology. However, this was refuted in prospective clinical study using pH manometry. Globus patients without reflux symptoms did not show acid or non-acid GERD. (55)

Upper esophageal sphincter pressure

Previous research investigated the association between globus sensation and increased upper esophageal sphincter pressure (UES).
The UES is a significant anatomical structure situated between the pharynx and the cervical esophagus. Its primary function is to prevent the reflux of food into the respiratory tract and to prevent air from entering the digestive tract. Moreover, the UES consists of various muscles and tissues, wherein the cricopharyngeal muscle (CP) and the thyropharyngeal muscle (TP) serve as the two main components. The CP displays unique characteristics, including tonic activity, high elasticity, and a blend of slow and fast twitch muscle fibers, with slow fibers predominating. These

features enable the muscle to maintain some resting tone while also allowing for stretching when required. The TP spans the upper two-thirds of the UES and functions in tandem with the CP. Together, they safeguard the integrity of the UES and enable the act of swallowing. The functioning of the UES is regulated by numerous reflexes that involve afferent nerve impulses, which control the opening and contraction of the sphincter. Swallowing problems can arise if the UES fails to open properly, and a cricopharyngeal latch can lead to clinical issues if the sphincter opens without the larynx being suitably relaxed. (56) Tokashiki et al. found out that globus sensation is associated with increased UES pressure and GER, suggesting that elevated UES pressure due to reflux, without direct acid exposure to the hypopharynx, may cause the sensation. The increased pressure in the UES seems to be caused by acid perfusion into the distal esophagus, subsequently causing the globus sensation. (57) A retrospective study examined the correlation between globus sensation, UES resting pressure, and GERD. The results indicate a noteworthy link between globus sensation and increased UES resting pressure. Furthermore, globus sensation was observed in patients with normal UES resting pressure, particularly in women. However, the study did not uncover a distinct connection between globus sensation and GERD. In summary, the findings indicate that elevated UES resting pressure is linked to a sensation of pressure in the eyes, whereas GERD is not the primary cause of this sensation. (58) There is conflicting evidence regarding the relationship between increased UES and globus sensation. While some studies have found a statistical correlation, (57–59) others have shown the opposite. (55,58,60) However, more recent data suggests that UES may not have a significant impact on *globus pharyngeus*. (2)

Esophageal motor disorders

Esophageal motility disorders can disrupt the normal muscle contractions responsible for propelling food through the esophagus. They are categorized into primary disorders originating in the esophagus and secondary disorders. Primary disorders include achalasia, distal esophageal spasm, hypercontractile esophagus, and absent peristalsis, affecting intrinsic esophageal muscle function. Secondary disorders result from systemic diseases. Diagnosis involves various tests, such as esophagography, manometry, endoscopy, and biopsies. Treatment varies depending on the disorder and may involve medications, endoscopic procedures, or surgery. Precise diagnosis requires distinguishing between types of dysphagia and considering the patient's medical history. Prognosis varies, necessitating comprehensive patient education. An interdisciplinary healthcare team aids in accurate diagnosis and optimal care. (61) Only a few studies have examined the connection between esophageal motor disorders and globus sensation. In patients with *globus pharyngeus*, most diagnosed esophageal motor disorders were non-specific and diagnosed using conventional manometry. Future patients with globus sensation should benefit from high-resolution manometry (HRM), which should yield more information regarding esophageal motor dysfunction. (2)

A systematic review aimed to investigate the causes of globus sensation and esophageal motility disorders. The research found that abnormalities were detected in 57% of patients during endoscopic examination. These were mainly antral gastritis and hiatal hernia. Esophageal manometry revealed issues in 67% of patients, primarily non-specific motility disorders. While 76% of patients had normal pH levels, 62% showed a positive succinic acid perfusion test. Psychiatric assessments found that a quarter of patients had additional psychiatric diagnosis. The investigation determined that globus sensation can be linked to esophageal abnormalities, alongside other factors. The study suggested that esophageal manometry and pH monitoring are valuable diagnostic tools. Treating the underlying cause is important as the frequency of psychiatric disorders in globus patients is not considerably higher than in the general population. (62)

Hyperplasia of base of tongue

Hyperplasia of the base of the tongue is a rare but potentially dangerous change in the upper respiratory tract. The pathogenesis of this condition remains largely

unknown. (63) Two studies investigated factors linked with hyperplasia of the base of the tongue. (63,64) One of them was a retrospective study from 2022, which investigated the relationship between tongue base hyperplasia, tonsillectomy, and BMI. Results indicated a low incidence of 4.7% for tongue-based hyperplasia. (63)There was no association between post-tonsillectomy condition and compensatory tongue base hyperplasia (63), however in both studies there was a statistically significant association found between tongue base hyperplasia and BMI. (63,64)

Struma

A struma is any enlargement of the thyroid gland, regardless of its etiology or metabolic status. The most common cause of Struma is iodine deficiency. In certain cases, endemic thyrocyte hyperplasia occurs in iodine-deficient regions. Diagnosis of Struma is primarily by physical examination, with other diagnostic techniques used for specific suspected diagnoses. While euthyroid Struma without autonomy responds well to iodide therapy, possibly in combination with levothyroxine, the Struma may even regress. For large struma and/or thyroid autonomy, radioiodine therapy is used. Surgical procedures are warranted if the enlargement causes compression of significant neck structures or if malignancy is suspected. (16,35,65) Penović et al. conducted a study to examine the correlation between globus sensation and LPR and thyroid volume. (66) In conclusion, it was found that the severity or frequency of LPR did not have an impact on globus sensation. Nevertheless, patients with consistent thyroid volumes were more prone to experience globus sensation. The research was limited by a low percentage of male participants. (66) Another study by Nam I. et al. investigated the correlation between thyroid nodules and the globus sensation. (19) It was found that nodules larger than 3 cm located in front of the trachea were more likely to trigger globus symptoms. In addition, nodules with all parts directly in front of the trachea were more likely to cause globus symptoms than nodules with only some parts in front of the trachea. Therefore, the study indicates that certain dimensions and positions of thyroid nodules may result in globus symptoms. For thyroid nodules associated with globus sensation, the research recommends conservative or surgical treatment. (19)

Psychological Factors

In the scientific literature, there are various studies both supporting and refuting the psychological component in *globus pharyngeus* symptoms. (21,23,67) Generally, psychological symptoms like anxiety, depression, and stress are related to somatic globus symptoms. It is important to note that anxiety, depression, and stress can as well aggravate chronic globus sensation. The underlying causes of this symptom are identified and categorized under Code F45.8, indicating a somatoform disorder, in the 10th edition of the International Classification of Diseases (ICD-10). Randomized controlled trials have shown benefits of cognitive behavioral therapy for medically unexplained physical symptoms as a possible treatment pathway. (68) Lee et al. found that 96% of patients with globus symptoms report a worsening of their symptoms when subjected to high emotional stress. (20) Oishi et al. conducted a study to investigate the effect of excluding serious pathology in the head, neck and esophagus on symptom reduction and concluded that reducing anxiety levels had the most significant effect on improving globus symptoms. (67) As of January 2022, the 11th edition of the ICD has been amended to include a fresh classification of Code DD90 for functional disorders of the esophagus or gastroduodenal area, as well as DD90.0 for *globus pharyngeus*. (2,69) Regarding *globus pharyngeus* with major depression disorder (MDD), in two cases, patients with MDD and weight loss due to swallowing problems and *globus pharyngeus* responded positively to electrical convulsive therapy (ECT). Therefore, ECT is discussed as a potential first-line therapy for *globus pharyngeus* with MDD.(70)

Neurogenic/ Visceral Hypersensitivity

Local hypersensitivity can occur in pharyngitis with postnasal drip or other forms of irritation or inflammation in the pharynx or larynx, as well as irritation from reflux. All of these factors could potentially contribute to a neurogenic cause, resulting in a foreign body sensation caused by local hypersensitivity. (2,71)

In summary, the development of *globus pharyngeus* may arise from a single factor or a combination of various factors. As highlighted in the preceding section, there are numerous entities associated with *globus pharyngeus*, each with its own distinct etiology. However, it is important to note that these entities are not always isolated occurrences; rather, they often have interconnected relationships and can mutually

influence one another. For instance, GERD may cause muscular tension in the throat, worsening the sensation in the throat. Likewise, psychological factors, such as stress and anxiety, can worsen the perception of *globus pharyngeus* symptoms. These interconnections among the contributing factors add complexity to the understanding of globus syndrome. Consequently, pinpointing a specific cause for it can be challenging due to the intricate web of interactions between these factors. (2,3,20)

Diagnostics

Flexible transnasal endoscopy, Narrow Band Imaging

The entire pharynx and larynx can be examined using the flexible endoscope inserted through the nasal passage. Different diametrical sizes are utilized for examining children and adults. It is made more comfortable by utilizing decongestants or surface I of the mucosa. (16) The endoscopic examination is part of the basic examination in any Ear, Nose and Throat (ENT) and phoniatrics clinic nowadays. The transnasal endoscopy represents an in-office procedure without sedation, with minimal risk of perforation and significant cost and time savings. (72) There is no data on the diagnostic accuracy of globe sensation per se, but diagnosis aims to find or rule out benign or malignant changes. However, the primary aim of this examination is to assess the superficial anatomical structures and the mucosa. Changes that can be detected by flexible endoscopy and are accompanied by a globus sensation are, for example, inflammatory and tumorous events. (73)

Ahmadzada et al. conducted a study investigating the diagnostic accuracy of narrow band imaging (NBI) for the identification of laryngeal cancer, reporting a sensitivity of 95% and a specificity of 83.3%. (74) In addition, Zhou et al. investigated the overall diagnostic accuracy of NBI through a meta-analysis for differentiating between benign and malignant head and neck lesions. They found that NBI had a diagnostic accuracy of 88.5% and a specificity of 95.6%. (75) Furthermore, in a meta-analysis focusing on the detection of primary nasopharyngeal carcinoma using NBI, a sensitivity of 90% (0.73-0.97) and a specificity of 95% (0.81-0.99) were observed. However, there was no significant difference compared with white light endoscopy. (76) Additionally, it is an inexpensive and easily accessible examination. (77)

The potential to optimize flexible transnasal endoscopy with NBI is now possible. This cost-effective and easy method has already been implemented in numerous hospitals as part of their endoscopy program. NBI is an optical technique that has various applications across different specialties. Its ability to accentuate even the tiniest alterations in mucosal and vascular features is aided by the use of different light wavelengths. These wavelengths are readily absorbed by hemoglobin, allowing for optimal distinction between blood vessels and mucosa. This technology offers a simple and inexpensive method for early detection and characterization of neoplasia with little diagnostic effort. The likelihood of missing a lesion is greater when using white light endoscopy. Conversely, NBI highlights capillaries, thus reducing the chances of neoplasms being overlooked. (78)

Neck ultrasound

Ultrasound is also a cost-effective diagnostic tool that does not pose any risks to the patient. Older studies have shown that patients with *globus pharyngeus* without clinical findings do not benefit from the examination.(2,79,80) In 2022, Fukuhara evaluated the role of ultrasound in the routine examination of the *globus pharyngeus* in a retrospective cohort study of 74 patients. In 45 patients (60.8%), abnormal ultrasound findings were found. 42 showed thyroid changes (56.8%), 2 salivary gland changes (3%) and 1 showed a lipoma (1%). The neck ultrasound primarily revealed these findings, and there were no pathological findings in the otolaryngological examinations. Based on the research conducted by Fukuhara, it is recommended that ENT clinics use cervical ultrasound as a standard examination for patients experiencing globus sensation. This would ensure objectivity and a clear, logical structure in the diagnosis process. (80) Ultrasound examination has been established as a reliable technique for assessing thyroid neoplasms and determining post-diagnosis treatment. The study conducted by Ibrahim Abobaker Al-Ghanimi et al. found a high accuracy rate in diagnosing the risk of malignant differentiation in thyroid nodules, with a sensitivity of 88.9% and specificity of 91.8%. (81) Thyroid imaging reporting and data system (TIRADS), a standardized algorithm for the detection and evaluation of thyroid nodules by ultrasound, is designed to identify high-risk individuals who require fine-needle aspiration to rule out thyroid cancer. (82) This approach improves the efficiency of thyroid nodule diagnosis and significantly minimizes the need for unnecessary fine-needle aspirations. (83,84)

X-Ray

Imaging methods provide precise anatomical images of the cervical spine. The choice of method depends on the clinical scenario and the treatment options available. (85) Traditional radiography continues to play an important role in evaluating bone alterations and alignment in the cervical spine. A diverse range of alterations in the cervical spine may be identified via an X-ray. For example, the consistency of osteophytes might indicate cervical spondylosis. In addition, other conditions such as tumors, neoplasms, infections, or fractures can also be identified. It serves as a rapid and cost-effective tool for identifying mainly osseous sources and degenerative conditions with reduced radiation exposure. (86,87) Nonetheless, literature reports bone-associated changes that induce dysphagia and globus sensation symptoms. (88–90) Various options exist to classify an X-ray for cervical spondylosis for example. (91) The Kellgren classification provides a reliable method for diagnosing degenerative changes in the cervical spine through X-ray. This entails assessing the lateral radiograph of the cervical spine. This classification can additionally be used to evaluate Magnetic Resonance Imaging (MRI) images. (92) The diagnostic accuracy in radiographic imaging is reportedly 68.3%. Yu X et al. employed a quantitative X-ray diagnostic model utilizing maximum likelihood in the study, which led to an 80% increase in diagnostic rate. However, there was no significant statistical difference in the diagnostic rates. (91) In another study of cervical spine fractures, the sensitivity and specificity of cervical spine radiography in diagnosing cervical spine fractures due to blunt trauma were 89.7% and 87.8%, respectively. Therefore, the conclusion is that cervical spine radiography serves as an inexpensive, easily accessible, and low-radiation option for promptly assessing the cervical spine. (93)

CT/MRT of the neck

Several benign and malignant conditions can affect the pharynx and larynx. Clinical and endoscopic examinations can detect several of these conditions. Detailed imaging provides more precise and complementary data and may identify lesions that would otherwise go unnoticed. It is crucial to identify benign findings and avoid redundant testing while quickly detecting malignant disease. Due to the proximity of

many different structures, neighboring structures in the pharynx and larynx can also cause discomfort.

Computed tomography (CT) scanning provides rapid and meaningful results and is a painless examination that can usually be performed quickly, depending on the nature of the medical problem. Nevertheless, it might entail a minimal amount of radiation exposure, which is considered to be very low. (94)

In 2014, in a study of isolated *globus pharyngeus*, Alhilali et al. found a positive finding in one of 148 neck CT scans. A cyst of the thyroglossal duct, which in this case led to a change in clinical management. (95) Diagnosis of patients presenting with uncomplicated *globus pharyngeus*, without a history of an upper aerodigestive or esophageal malignancy (both primary and secondary), lymphoma, neck, esophageal or gastric surgery, or abnormalities noted on clinical examination, presents no significant clinical findings and is unlikely to require further clinical management. Alhilali et al. report an overall diagnostic efficacy of 3.4% for CT scans. The therapeutic effectiveness of 0.7% is measured by the number of instances where clinical treatment was altered divided by the total number of studies conducted. These data demonstrate how CT serves as a marker for the impact on the clinical treatment of patients.(95) Routine CT of the neck is not recommended for the assessment of *globus pharyngeus*. (95,96)

MRI is a non-invasive diagnostic technique that uses radio waves and a strong magnetic field to generate detailed images of the body's internal structures. It is particularly effective in visualizing soft tissue structures with high resolution and accuracy. (97,98) Benefits include the absence of radiation exposure, which allows for detailed viewing of soft tissue structures, especially in the head and neck area. As a result, this examination is ideal for detecting many differential diagnoses. However, one drawback is that the examination is often long and can be very tiring for the patient. (97) Various MRI modalities can distinguish between different tumor types, as revealed by prior research. Sumi and colleagues investigated identifying various types of head and neck tumors - such as SCC, lymphoma, malignant salivary gland tumor, Warthin tumor, pleomorphic adenoma, and schwannoma - using different signal curves and their combination. By combining various metrics through a multiparametric approach, benign and malignant tumors could be differentiated with a precision rate of 97%, while different types of tumors could be diagnosed with an 89% accuracy. (99,100)

Barium swallow and video fluoroscopic swallow

The barium swallow examination performed to examine the *globus pharyngeus* rarely provides findings that change the clinical management of patients. (96) In addition, barium swallow studies have low sensitivity for detecting small malignancies. Therefore, a normal examination may be falsely reassuring. Barium swallow radiography should not be used as the primary test for suspicion of malignancy. (96)

In a series of 194 barium swallows, cervical osteophytes were the cause of globus in 63.9% of cases, accounting for half of the abnormalities. Other benign causes included retroverted epiglottis and enlarged lingual tonsils, but these should be ruled out by clinical nasopharyngolaryngoscopy if present. (96,101) Although positive findings do not usually have a direct impact on the clinical management of the patient, the examination itself may help to reassure the patient and improve understanding of this symptom. (96) In cases where oropharyngeal dysphagia is present, consideration should always be given to the possibility of a Zenker diverticulum. The barium swallow has become the preferred examination method. It is crucial to rotate the patient during the procedure to identify small diverticula. To verify the diagnosis, a meticulous endoscopy should also be carried out.(102)

The videofluoroscopic swallowing study (VFSS) is more sensitive than barium swallow in detecting abnormalities associated with *globus pharyngeus*. It is another radiographic procedure that provides a direct, dynamic view of oral, pharyngeal, and upper esophageal function. (103) In this examination, a video-recorded contrast swallow with barium, which is used with food and drink of varying consistency and thickness. (96,103) The VFSS is a valuable tool for objectively evaluating and quantifying different aspects of swallowing function, including the oral, pharyngeal, and esophageal phases of swallowing. Subjective scoring of VFSS parameters is inconsistently accurate when compared to objective assessment, with the accuracy ranging from 45.3% to 71.6% for specific parameters such as hyoid elevation, pharyngeal area, pharyngeal constriction ratio and pharyngoesophageal segment opening. (104) A review assessed the specificity of VFSS against FEES as the reference standard. The findings demonstrated that VFSS had a specificity of 0.58 to 0.79 while FEES had a specificity of 0.97 to 1.00. Accordingly, VFSS showed sensitivity for aspiration at 77%, penetration at 83%, laryngopharyngeal residue at

80%, and pharyngeal premature spillage at 80%. The specificity of both tests was comparable at 93%-98%. (105) Therefore, it is a good tool, especially for patients with globus sensation and dysphagia, and it is under discussion if these patients have difficulties in the pharyngeal phase. According to Liu J's research, there was no notable contrast in the swallowing parameters of the pharyngeal phase between patients with *globus pharyngeus* and those without it. (106) Hence, it can be inferred that the swallowing function of the pharynx has a less significant role in patients experiencing *globus pharyngeus*. Therefore, the present study does not recommend VFSS for patients with globus sensation. Nonetheless, any associated symptoms, including difficulties in swallowing, VFSS should be considered. (96,106)

Manometry and pH Monitoring

Esophageal manometry and 24-hour pH tests are often conducted simultaneously. The pH measurement using two probes is regarded as the ideal methodology for assessing reflux. High-resolution esophageal manometry is deemed standard for determining esophageal motility disorders. (96) In 2020 Van Daele et al. revealed in a study that these examinations exhibit a higher proportion of anomalies in globus patients than endoscopy or fluoroscopy. It was found that 62.8% of manometry examinations yielded abnormal results. (103) The dual-probe pH Monitoring results revealed that 19.8% of the tests showed an elevation in acidity levels within the proximal esophagus. (96,103) The sensitivity and specificity of high-resolution manometry (HRM) for GERD are low, at approximately 53.6% and 72.5%, respectively. However, in one trial, a straight leg raise maneuver was employed to increase intraesophageal pressure in GERD patients, increasing intraesophageal pressure. As a result, this maneuver increased the sensitivity to 79% and the specificity to 85% when identifying GERD patients. (107)

In a study conducted by Yadlapati et al., two additional methods were evaluated: the Restech Dx-pH method developed by Respiratory Technology Corp in San Diego, USA, and the Peptech test. (96,108) The Restech Dx-pH method involves measuring the acidity in the posterior pharynx using a nasopharyngeal catheter, while Peptech is a rapid test designed to detect oropharyngeal pepsin. In 2016, Yadlapati's study confirmed that neither testing method could differentiate between

healthy participants and those experiencing symptoms of laryngeal irritation and reflux symptoms. (108) Therefore it is not suitable for a diagnostic statement.

Rigid Esophagoscopy/ Panendoscopy

Rigid endoscopy is considered the gold standard in otolaryngology, in terms of endoscopic examinations. Although, rigid endoscopy has not proven useful in the diagnosis of *globus pharyngeus*. (2) However, a survey by Webb J. et al. found that 61% of ENT specialists have used rigid endoscopy for the diagnosis of *globus pharyngeus*. (109) In a study by Takwoingi et al. on rigid esophagoscopes, 220 examinations were conducted, revealing no abnormalities in 86.8% of cases. Pathologies identified included cricopharyngeal spasm, reflux, pharyngitis, esophageal tissue, and retention cysts. (110) Notably, none of the participants were diagnosed with malignant diseases.

This procedure requires general anesthesia and has a higher incidence of complications such as esophageal perforation, in comparison to flexible esophagoscopy. (111) Hence, rigid endoscopy is not advised for *globus pharyngeus*. If unusual upper aerodigestive tract symptoms are evident, potential diagnostics should be appraised on an individual basis. (96,110) Cervical heterotopic gastric mucosa has been identified as a cause of globus in multiple studies. However, no recent data regarding this has been found. Effective management of this condition necessitates an endoscopic assessment of the upper esophagus and a prescription of PPI medication. (112–114)

Flexible Esophagogastroduodenoscopy

Flexible esophagogastroduodenoscopy (EGD) can be carried out without requiring general anesthesia, making it a useful tool for many patients with minimal invasiveness. EGD is a widely used procedure for diagnosing upper gastrointestinal tract issues. The procedure involves examining the entire oropharynx, esophagus, stomach, and proximal duodenum with a gastroscope and associated accessories. The procedure can help in diagnosing and treating disorders. The equipment must be chosen and assembled based on the intervention’s aim. It is crucial in diagnosing and treating upper gastrointestinal tract diseases such as dysphagia, gastrointestinal bleeding, peptic ulcer disease, drug-resistant gastro-esophageal reflux, esophageal strictures, celiac disease, and unexplained diarrhea. (115) A

comparison was made between endoscopic and histological diagnosis of esophageal SCC. NBI was employed in the endoscopic diagnosis and it was determined that the accuracy of endoscopic diagnosis was comparable to that of biopsy. The endoscopic diagnosis had a diagnostic accuracy of 91%, while biopsy had an accuracy of 85.6%. This finding could be beneficial in facilitating optical diagnosis through endoscopy. (116) One study evaluated capsule endoscopy as a diagnostic modality. The study found that esophageal capsule endoscopy has moderate sensitivity and specificity in diagnosing Barrett's esophagus in patients with GERD. The study continues to recommend EGD as the method of choice for the evaluation of suspicion of Barrett's esophagus. (117) The impact of esophagoscopy on the clinical management of globus has been investigated by Liang S. et al. The study resulted in a minority of patients having the diagnostic and therapeutic pathways changed. Interestingly, the change in treatment did not correlate with the presence of typical gastroesophageal reflux symptoms. (118)

Micro-laryngoscopy

Micro-laryngoscopy (MLS) enables the removal of tissue samples from the larynx, pharynx, or areas of concern in a controlled way. Both diagnostic and therapeutic uses can be made of this technique. Patients receive general anesthesia. Depending on the entity, micro-pharyngoscopy (MPS) or MLS may be required. Possible causes for an MPS or MLS include cysts, polyps, vocal fold edema, medialization of a vocal fold through injections, arytenoidectomy, epiglottoplasty, removal of a benign mass, or a malignant tumor through laser ablation. Gräfe L. et al. conducted a study on direct MLS and found it to be effective with low postoperative complications. (119)

Allergy testing

If an allergenic disease is suspected, a thorough history and examination should be a priority for clarification. In allergic rhinitis, topical glucocorticoids may be considered empirically. If patients respond positively to treatment with nasal glucocorticoids, the suspected diagnosis can be supported. A formal diagnosis can be made by either serum testing for allergen-specific IgE or allergy skin testing. (120) One particular study examined the correlation between an atopic factor and the occurrence of *globus pharyngeus*. Patients with *globus pharyngeus* were found

to have a higher number of positive allergy skin tests. Consequently, this symptom should be considered as part of an atypical allergic manifestation. Among patients experiencing globus sensation and the control group, positive allergy tests were recorded at 77.8% and 28.6% respectively. Patients with *globus pharyngeus* and positive skin tests were administered allergic treatment, with 64.3% exhibiting symptom improvement. Of those, 85.2% reported moderate or excellent improvement. Patients without improvement or negative skin tests exhibited a variety of other medical conditions. The identified conditions were gastroesophageal reflux disease (18.5%), abnormal esophageal manometry (40.7%), and myofascial pain syndrome (3.7%). (30)

Methods and Materials

A retrospective cross-sectional study was conducted to evaluate the research question and its results. The study cohort consisted of patients who consulted the Department of Phoniatrics, University Hospital Graz, Austria, between 2014 and 2019. Epidemiological data were collected using the electronic medical information database openMEDOCS (SAP, Walldorf, Germany). Patients were included from January 2014 to December 2019. Patients were selected based on their ICD-10 coding as well as their free-text diagnosis in the medical reports, which were provided by the Institute for Medical Informatics, Statistics, and Documentation at the Medical University of Graz.

Ethical consideration

Prior to data collection, approval was obtained from the local ethics committee.

Exclusion

The only exclusion criterion was an age below 18 years.

Statistical analysis

Statistical analyses were performed using Microsoft Excel version 16.61.1 (via the collaborative platform 'Citrix'). Patients were identified by a free text search or the ICD-10 code, F45.8 other somatoform disorders: dysphagia, including "globus hystericus". A chart containing all the case numbers and treatment information was generated using Microsoft Excel version 16.61.1. Using the case numbers, all patients identified by the system could be retrieved via "openMEDOCS". The next step was to transfer all the collected data into an Excel file. The raw data was then further analyzed primarily via Excel and put into a processable format (all categories were coded with 0 or 1). During the data analysis, the patient data was reevaluated to ensure that it was entered correctly. These numbers were then presented in tables and graphs using Microsoft Excel and Microsoft PowerPoint (version 16.63.1).

In addition to epidemiological data, diagnostic and treatment pathways before and after the first visit were recorded. Evaluation follow-up appointments and monitoring of symptom relief were also part of the research methodology.

Descriptive statistics were used to analyze the data. Patient data were anonymized. Five categories were created to stratify the data.

These are in detail:

Amnestic data	• Patients ID • Age • Sex • Active smoker • Allergy status • Via ENT
Symptoms	• Primary • Acute/ Chronic • Secondary
Previous history	• Previous medical evaluation • Previous therapy
Phoniatric outpatient clinic	• ENT status • Initiated diagnostics • Abnormal findings • Initiated therapy • Lost to follow up • Relief of symptoms
Progressive history	• Follow up necessary

Figure 1: Excel matrix structure comprising all parameters

Anamnestic data

The patient's age at presentation was calculated using their date of birth. Sex was recorded as either female or male. The smoking status of all patients who were active smokers at the time of presentation was included. Allergy was noted as present if an entry was found in the medical record or existing doctor's letter. Patients with a written referral from their treating external otolaryngologist in private practice were recorded as 'via ENT'. The patient's referral by a specialist was further differentiated during data collection. This included "walk-in" patients, those introduced by ENT specialists or specialists from other disciplines, patients referred from both internal and external departments, as well as those already admitted to the ENT hospital.

Symptoms

Patients' symptoms were categorized into different groups, with the primary self-reported symptom documented as the main complaint. In addition, the classification of symptoms into acute or chronic categories was facilitated by a cut-off of 4 weeks. Patients presented with various symptoms such as globus/remote sensation, sore throat/reflux sensation, subjective dysphagia, throat clearing/coughing/swallowing, subjective dysphonia, mucus/postnasal drip, dryness, tension/pressure in the throat, carcinophobia/anxiety, hoarseness, subjective dyspnea, and snoring.

Previous history

All relevant examinations conducted before the visit, as well as completed and ongoing therapies, were extracted from the medical records and included in the study.

ENT and Phoniatric outpatient clinic

During the examination, any previously identified findings, as well as those detected through laryngoscopy (such as flexible or rigid laryngoscopy) conducted by an ENT specialist, were documented. Recorded abnormal findings resulting from diagnostic procedures previously performed or newly indicated. Patients without any abnormal findings were assigned a value of 0 in the matrix. Others received a specific code based on the diagnosis, which included: reflux symptoms, tumors (malignant and benign), anatomical esophageal changes, functional esophageal changes, degenerative and muscular cervical spine conditions, thyroid disease, mental illness (including anxiety and depression), advanced age, tongue base hyperplasia, chronic and acute laryngitis, and craniomandibular dysfunction. Glottic insufficiency, cysts, anatomical changes in the pharynx, recurrent paralysis, contact granulomas, Zenker diverticula, pathologies in the larynx (vocal fold pathologies, including polyps and nodules), pharyngitis, symptoms of neurogenic dysphagia, tongue base edema, obstructive sleep apnea syndrome, foreign objects. Any additional diagnostic tests ordered through the phoniatric outpatient clinic were documented in the initiated diagnostic record. Diagnostic procedures patients have undergone range from x-rays or MRI/CT scans of the neck, pH manometry, gastroscopy, oesophagoscopy, barium swallow, thyroid and neck ultrasound, psychiatric evaluation, orthopedic referral, allergy testing, neurological referral, throat biopsy, laboratory testing,

angiography and panendoscopy/MLS. The ENT specialist in the phoniatrics outpatient clinic prescribed the newly initiated therapies based on the previous information. The treatments included PPI, physiotherapy, psychological therapy, local therapy, antibiotics, non-steroidal anti-inflammatory drugs (NSAID), antihistamines, muscle relaxants, and foreign body removal techniques.

Progressive history

Patients who were advised to undergo further interventions and had scheduled follow-up appointments but did not attend, were classified as 'lost to follow-up'. Patients who had a pre-arranged follow-up appointment at a specific date and time were checked for attendance and then, if appropriate, included in the 'follow-up group'. The symptoms relief' group included patients who had fully recovered and were symptom-free at their clinic follow-up visits.

Results

Demographics

211 patients fulfilled the inclusion criteria. The oldest patient was 87 years old, and the youngest was 18 years old. The mean age of the patients was 53.5 years.

Regarding the sex distribution, there were 86 (40.8%) male and 125 (59.2%) female patients. There were 26 (12.3%) active smokers and 72 (34.1%) nonsmokers. Smoking status was not documented in 113 (53.6%) patients. Furthermore, the allergy status of the patients was determined by reviewing their medical records. Of the patients, 55 (26.1%) had a known allergy, while 51 (24.2%) reported no allergy. In most patients, 105 (49.8%) had undocumented allergy status.

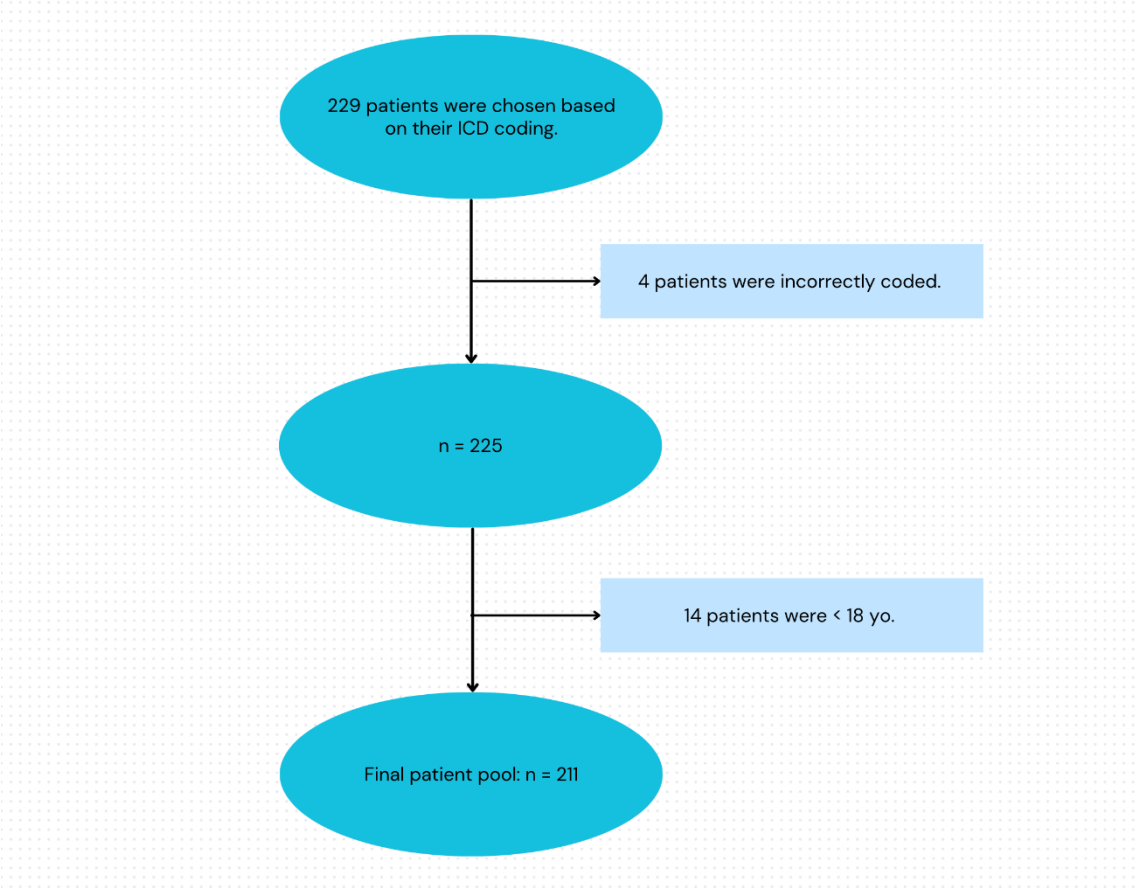

Figure 2: Patient selection flowchart: A schematic overview of the selection process.

Symptoms and History

Primary complaints

The patients included in the study were further selected according to their most important self-reported symptoms that were relevant to the presentation. By far the most common symptom reported by 136 (64.5%) patients was the sensation of a foreign body in the throat, in the classic sense of a globus sensation. This symptom was followed by a subjective feeling of dysphagia, one of the most frequently reported main complaints, in 22 (10.4%) patients. Sore throat or reflux were also reported by 13 (6.2%) patients, as was a subjective feeling of hoarseness by 12 (5.7%) patients. Smaller numbers of patients reported discomfort due to mucus or post-nasal drip (eight patients; 3.8%) and phlegm, cough, and choking or dysphonia (seven patients each; 3.3%). Approximately 0.5% (one patient each) reported pressure and tension in the cervical spine and dryness and snoring as their main complaints.

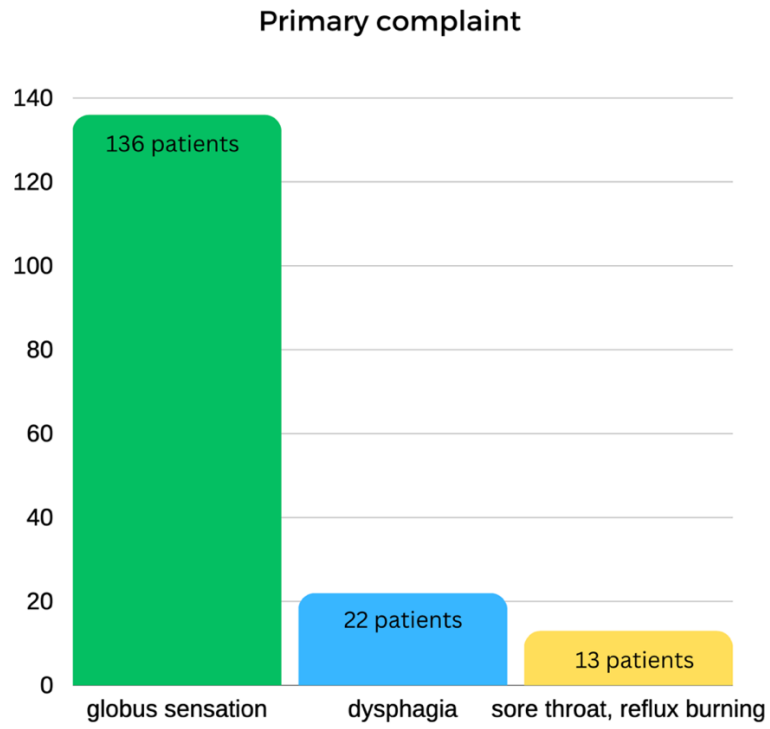

Figure 3: Column chart of primary complaints – A visual representation of the main complaints reported by all 211 patients.

Secondary complaints

Furthermore, all secondary complaints that were reported were evaluated. The data shows that the two most common secondary complaints were reflux, reported by 43 patients (20.4%), and dysphagia, reported by 39 patients (18.5%). Classic globus and foreign body sensations were reported in 36 (17.1%) patients. These were followed by throat clearing, coughing, and choking (in 26 patients; 12.3%) and dyspnoea (in 15 patients; 7.1%). Mucus with or without nasal drip and a feeling of tightness and pressure in the throat were reported in 13 patients (6.2%) and 14 patients (6.6%), respectively. Subjective dysphonia was reported as a troublesome side effect by 24 patients (11.4%). Concern about carcinophobia or anxiety was reported by seven patients (3.3%). Dryness and snoring were reported in five patients. (2.4% each). Only three patients mentioned stress as a secondary factor (1.4%).

Duration of symptoms

168 (79.6%) patients reported chronic (>4 weeks) and 40 (19%) patients reported acute (<4 weeks) symptoms. In three (1.4%) patients the time course of the symptoms was not documented.

Previous Diagnostics

To examine the diagnostic pathways of patients prior to their presentation at the outpatient clinic, an analysis of patient referrals was conducted. These were classified as: Referral from a general practitioner (GP), referral from a specialist in private practice or from another department within the hospital, and finally those, referred to here as "walk-in" patients, who had no referral at all. It is also important to mention that there are two departments within the ENT Clinic, namely the General ENT Department and the Phoniatrics Department. Since only the general otolaryngology department has an emergency department, walk-in patients are referred from there to the phoniatrics department in cases where globus was diagnosed.

Of the 211 patients included in the study, 139 (65.9%) were considered 'walk-in'. They were later referred to the specialized phoniatric outpatient clinic for further evaluation.

The second largest group comprised patients referred to our clinic by an ENT specialist, with a total of 37 (17.5%) patients. Additionally, two patients were directly referred to the phoniatrics clinic by their ENT specialist (0.9%).

There were 12 patients (5.7%) who were referred internally, which means that they were initially admitted as in-patients to other departments of the University Clinic Graz. Subsequently, they were directed from their primary departments to the ENT department for consultation due to experiencing globus sensation. Of these patients, 5 (41.6%) came from Internal Medicine, three (25%) were from Surgery, two (16.7%)

were from Neurology, and one patient each (8.3%) came from Dermatology and Psychiatry.

Medical specialists referred 13 patients (6.2%), while specialists in internal medicine referred two (0.9%), and general surgeons referred one (0.5%). The department of origin was unspecified for ten patients (4.7%).

Five patients (2.4%) were referred by a GP, while four patients (1.9%) were referred from a hospital external to Graz Regional Hospital, which encompasses all external hospitals. During an inpatient admission to the ENT ward, one patient (0.5%) underwent an examination at the phoniatric outpatient clinic. This patient was admitted for another medical issue but also complained of globus sensation, which prompted referral to the phoniatric outpatient clinic.

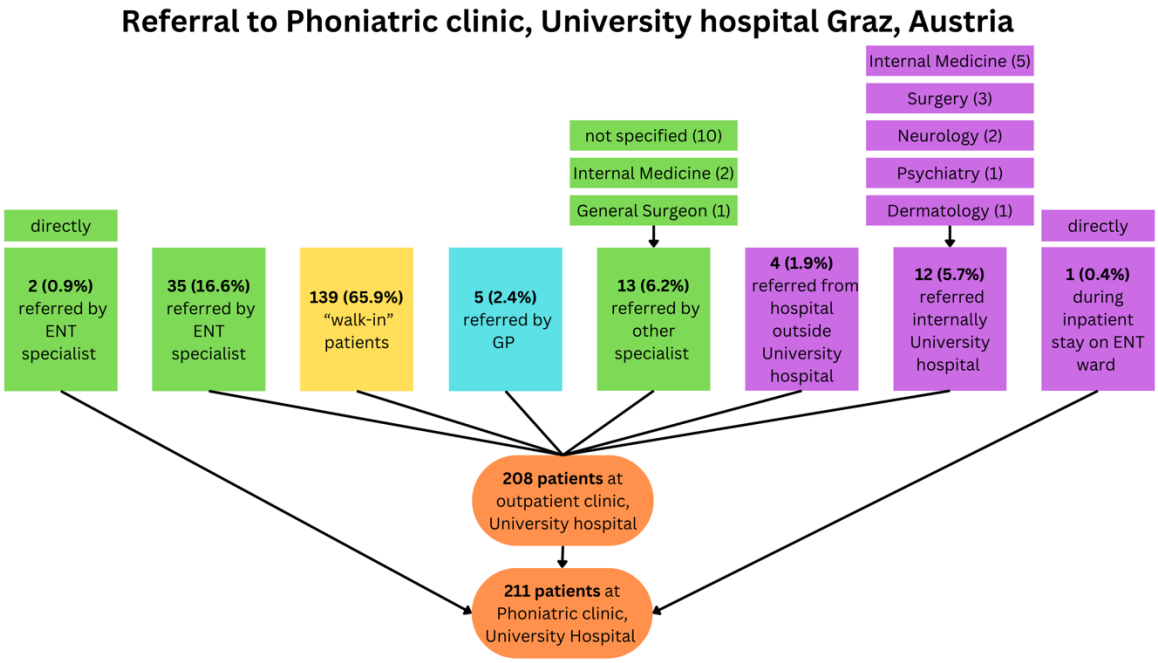

Figure 4: Flowchart: Referral Process to the Phoniatric Clinic – A visual representation outlining the steps involved in referring individuals to the phoniatric clinic.

Despite the absence of documentation from the specialist who conducted these examinations, many patients had already undergone prearranged diagnostic procedures and therapy. Before presenting at our outpatient clinic, GPs and other medical specialists frequently requested neck imaging with X-ray, CT, or MRI (53 of the patients; 25.1%) and barium swallow radiography and VFSS in 50 patients

(23.7%). These were followed by an ultrasound of the thyroid and neck in 30 patients (14.2%) and flexible laryngoscopy (29 patients; 13.7%). A smaller number of patients also have undergone EGD (21 patients; 10%). Further investigations were MLS and psychiatric examinations in three patients each (1.4%), lung function in two patients; 0.9%), and only one patient (0.5%) each had allergy testing or pH-manometry in advance.

Previous Therapy

Anti-acid treatment with PPIs was given to 62 patients (29.4%). There were 17 patients (8.1%) who had received physiotherapy. There were 15 people (7.1%) who had used topical therapies such as local intranasal steroids, topical anti-inflammatory treatment and inhalation of saline solution. Other treatment attempts included NSAIDs in six patients (2.8%) and antibiotics in four patients (1.9%). Only one person (0.5%) was taking antihistamines.

Phoniatric status

The following diagnoses were identified as the cause of the globus sensation on presentation to the specialist outpatient phoniatrics clinic, during subsequent flexible or rigid endoscopy examinations and on the basis of the diagnostic tests already carried out: muscular or degenerative changes in the spine (17 patients; 8.1% of the sample), reflux disease (11 patients; 5.2%) and tongue base hyperplasia (nine patients; 4.3%), anatomical changes in the esophagus (eight patients; 3.8%). Vocal fold nodules and polyps were detected in six patients (2.8%).

Functional dysphonia, cysts in the area of the larynx, contact granuloma, OSAS, and foreign bodies, were also rare (three patients; 1.4%). Two patients (0.9%) were diagnosed with thyroid disease, malignant or benign neoplasms, or anatomical changes of the pharynx or larynx.

Functional diseases of the esophagus, gastritis, psychological factors such as anxiety or depression, acute and chronic laryngitis, recurrent nerve palsy, pharyngitis, or tongue base edema were among the abnormalities diagnosed during the process and were only found in one patient each (0.5%).

Diagnostics/Therapy – initiated

Following this, patients were often recommended further diagnostic examinations or therapies were prescribed. The most frequently recommended further examination was an X-ray or CT/MRI of the neck (98 patients; 46.4%), followed by EGD (49 patients; 23.2%) and thyroid gland and neck ultrasound (47 patients; 22.3%). Barium swallow radiography was performed on 45 patients (21.3%). In 16 patients (7.6%) a psychological/psychiatric consultation was required. On a smaller scale, a specific orthopedic examination in 12 cases (5.7%), pH manometry, and MLS in nine patients each (4.3%) were requested. Allergy tests were performed on four patients (1.9%).

Neurological referral and lung function testing were performed in five individuals each (2.4%). Biopsies and non-specific blood tests (i.e. complete blood count with differential blood count) were performed on two patients each (0.9%). One patient (0.5%) was registered for angiography.

Finally, the medication prescribed by the phoniatrician was analyzed. Similar trends were observed as in the previous therapy data. PPIs were strongly represented in 86 of the patients (40.8%).

The prescription for manual therapy, such as physiotherapy or logopedics could be recorded in 85 of the patients (40.3%). In 20 cases (9.5%), the persons were also prescribed topical therapies such as local intranasal steroids, and topical anti-inflammatory treatment, and saline inhalations. A further psychological assessment was specified in ten medical records (4.7%). An indication for surgical intervention, such as pre-treatment biopsies, was required in seven (3.3%) of the 211 cases. Drug therapy using antibiotics or antihistamines was prescribed in eight patients each (3.8%). Foreign body removal, such as fish bones and food scraps, or the use of NSAIDs were indicated in five patients (2.4%) each. Muscle relaxants were given in two patient cases; 0.9%.

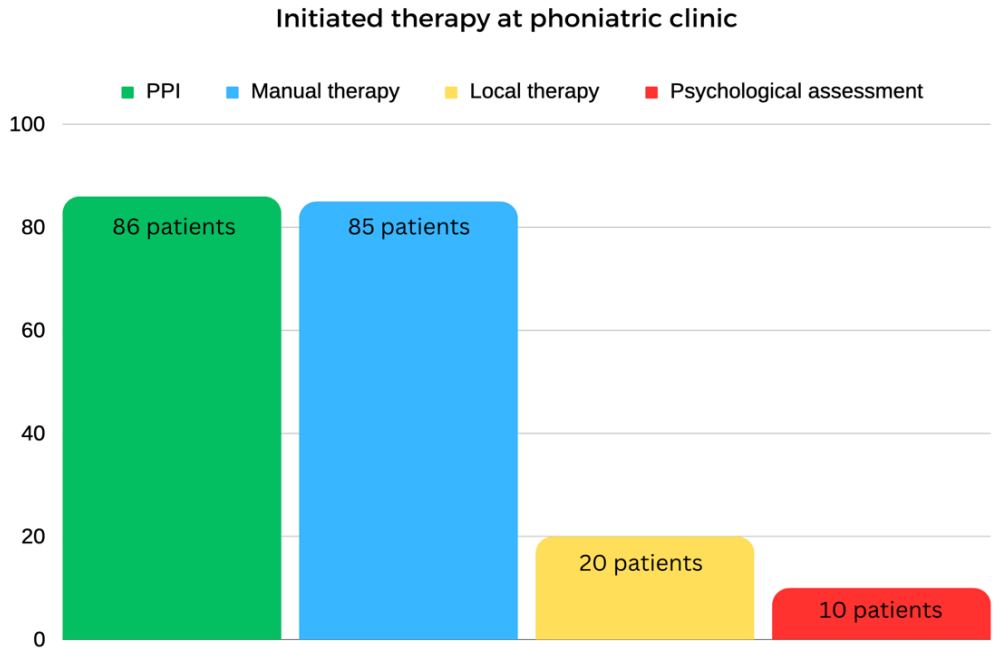

Figure 5: Column Chart: Initiated Therapy – A graphical representation illustrating the types and frequency of therapies initiated by phoniatric specialists.

Follow up

Key elements of the data analysis focused on patient compliance with follow-up recommendations. Of the 211 participants enrolled in the study, a significant proportion of 168 patients (79.6%) had no follow-up information. Within this group, two distinct subgroups emerged: firstly, those who were not instructed to return (66 patients; 31.3%); and secondly, those who were given diagnostic instructions and a follow-up appointment but did not return (102 patients; 48.3%). Concerning readmission and symptom improvement, 43 patients (20.4%) were readmitted to the outpatient clinic. Within this group, 28 patients (13.3%) experienced an improvement in symptoms, while the remaining 15 patients (7.1%) did not show any progress.

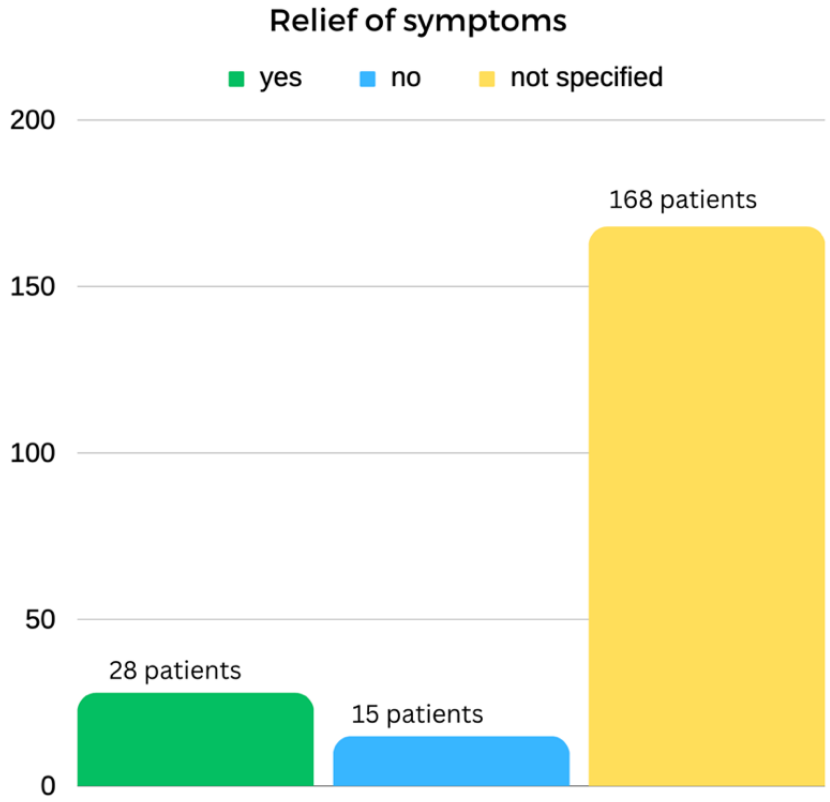

Figure 6: Column Chart: Relief of Symptoms: A visual representation depicting the extent of symptom relief observed across the 211-patient cohort.

Discussion

Globus sensation can either be an isolated symptom or part of a symptom complex. Researchers have been investigating the primary cause of globus, but none of the investigated hypotheses regarding its origin seem to apply universally to all patients. (2,3,20) Despite a large number of publications, a standardized definition, which is necessary to ensure the validity of studies, is frequently absent. This lack of uniformity leads to inconsistencies in the diagnostic process, resulting in multiple examinations, prolonged waiting times, increased costs, and strain on healthcare system capacity. (1–3,20,79)

The aim of this retrospective study was to develop a diagnostic algorithm by synthesizing findings from a literature review and patient data acquired at our institution. To this end, all patients diagnosed with *globus pharyngeus* and categorized with the corresponding ICD code or free text diagnosis by phoniatricians at the Department of Otolaryngology, Medical University of Graz, between 2014 and

2019 were evaluated. Patient information such as demographic details, symptom information, duration of illness, diagnosis, treatment before and after the initial outpatient presentation, initial phoniatric status, and subsequent follow-up examinations were collected and analyzed using descriptive statistics. Finally, a diagnostic algorithm was created based on these results. Such an approach holds the promise of providing a uniform level of clinical consistency and standardization in the diagnosis of *globus pharyngeus.*

Limitations

Retrospective studies pose several challenges, including compromised data quality, biases, limited variable control, and temporal restrictions. Additionally, capturing precise information can be difficult, and causal inference can be hindered. (121) Therefore, the retrospective nature and data collection method significantly constrained also this study. The lack of standardized documentation presented a significant challenge. This was primarily due to the widespread use of free text entries in patient files. This is partly because of the absence of standardized methods for assessing the symptoms of *globus pharyngeus,* making it difficult to collect parameters and draw conclusions from a research perspective.

Risk Factors

Risk factors identified in the literature review and research include medications and allergies, as well as nicotine and alcohol abuse. (30,122) A meta-analysis highlights alcohol consumption and smoking as significant risk factors for cancers of the upper respiratory and digestive tracts. (28) Alcohol-related risk seems to be more influenced by the amount consumed than by the duration of consumption. In contrast, the amount and duration of smoking have an equal effect on cancer development at these sites. In addition, concurrent exposure to alcohol and tobacco further increases the risk of these specific cancer types. (28) In a study by Rasmussen et al, risk factors for persistent globus sensation included male gender, self-perceived dyspnoea, and smoking. (27)

In the present study population, 12.3% were current smokers, and 34.1% were nonsmokers. However, the smoking status of 53.6% of the remaining patients was not recorded, making it difficult to accurately analyze smoking-related risk factors.

Similarly, patients' alcohol consumption could not be determined from their medical records. Drawing conclusions regarding these factors remains challenging. Although the malignant tumors mentioned in this paragraph may also be associated with globus sensation (9), they were diagnosed relatively rarely in the present study population (0.5%). This is probably mainly due to the fact that globus sensation in such patients is not usually mentioned in the diagnostic text.

One study found an association between *globus pharyngeus* and positive allergy skin tests, suggesting an unusual allergic manifestation. (30) Patients with positive skin tests experienced relief of the globus sensation with allergy treatment. Conversely, patients with no improvement or negative skin tests were diagnosed with alternative conditions, including GER disease (18.5%), abnormal esophageal manometry (40.7%), and myofascial pain syndrome (3.7%). (30) Allergy documentation was missing for 49.8% of patients, making it impossible to conclusively determine the presence of allergies. Of the remaining patients, 24.2% had no allergies, and 26.1% had documented allergies.

Allergy testing was recommended in only 1.9% of patients. The available literature suggests that an allergic component should be considered in cases of *globus pharyngeus* without a clear etiology. However, this evidence comes from a single publication and lacks extensive supporting data. (30) Despite this limitation, it is important to consider and discuss this potential factor with patients. Therefore, allergy diagnosis is included in the diagnostic algorithm. Notably, other existing algorithms, such as that proposed by Järvenpää et al, do not include this factor in their evaluation. (2,30) The low number of documented allergies, as well as the infrequent recommendation of allergy testing, highlights the lack of attention to the allergic component that could trigger the sensation of a lump in the throat.

Another overlooked factor highlighted by research is patients' medications. Few studies have examined medications and their side effects and potential influence on *globus pharyngeus.* For example, xerostomia, which can be caused by certain medications (e.g., diuretics, anti-anxiety medications, antidepressants, anticholinergics, antihistamines, decongestants, pain medications, antihypertensives, and medications for Parkinson's disease), can cause difficulty swallowing and potentially trigger *globus pharyngeus.* (122,123) Another study

found an association between decreased salivary secretion, a side effect of anticholinergic medications, and the occurrence of *globus pharyngeus.* (29) Polypharmacy, the regular use of five or more medications, may be considered a risk factor that increases with patient age and may lead to *globus pharyngeus* through interactions or side effects. (124) In this data, any long-term medications leading to *globus pharyngeus* were not studied in detail. In the future, as outlined in the algorithm, medications with risk profiles specifically for xerostomia, as mentioned above. Therefore, in addition to smoking and alcohol status, allergies and medications are relevant in the proposed algorithm.

Demographics

The average age of the study participants was 53.5 years, with 59.2% being female and 40.8% male. Based on the data and other studies, *globus pharyngeus* rarely occurs in patients under the age of 20. (125) The incidence of *globus pharyngeus* may be more common in middle-aged people (35–54 years), although studies have not found a correlation with age. (2,20,21,126) The incidence of *globus pharyngeus* in this study is within the range of the findings reported in the literature. (20)

Studies have reported that women are more likely to be affected than men (3), while others have found no significant difference in incidence between the sexes. (21,125) Thus, the literature is conflicting.

The predominance of women may be due to the fact that they are more likely to seek medical advice. (2,3,125) The higher prevalence in women in the present population is therefore consistent with the results of several studies.(2,3,125)

A study conducted in China showed that the incidence of *globus pharyngeus* was significantly higher in urban than in rural areas, which may be attributed to the association between globus sensation and psychological problems, such as stress and adverse life events. (21) Although the study provides interesting epidemiologic data, this information was obtained from populations in China; (21,24) therefore, the conclusions may not be generalizable to the populations in Europe and Austria.

The current study did not collect information on the patient's place of residence or a code number to determine location. However, nine patients (4.3%) were referred to

the university hospital from hospitals or doctors in private practices outside the district, suggesting that the district is more rural than urban. Because the study was limited to a single institutional survey, it is not possible to make a definitive statement about locality and therefore on the distribution of *globus pharyngeus* between urban areas and rural areas in Austria.

Referral

Data on patient referral were collected by tracking patients' previous consultations. The results revealed that most patients (139 patients; 65.9%) were walk-in patients. This means that they came to the hospital without being admitted. The considerable number of patients who came without prior referral and who had undergone multiple previous examinations made it difficult to accurately document their clinical pathways. However, patients who were referred directly from a hospital or specialist could be monitored more closely in terms of their previous diagnostic tests.

A comprehensive analysis was conducted to examine patient flows within the hospital and between external healthcare facilities, with a focus on the influx of patients into the Otorhinolaryngology (ENT) clinic. The study revealed that 12 patients accessing the clinic were referred from other departments within the university hospital. Referrals originated from the Department of Internal Medicine, Surgery, Neurology, Dermatology and Psychiatry. Additionally, a total of 13 patients were referred to the ENT department by specialists from various medical fields. Furthermore, five patients were referred by general practitioners and four by hospitals outside Graz University Hospital, encompassing all external hospitals within the county of Styria.

With the substantial number of “walk-in” patients, suggests a potential lack of clarity in patient complaints and an unstructured flow of patients to the university hospital. This ambiguity could be addressed by improving patient flow. (127) Therefore the implementation of a standardized diagnostic guideline across different care levels could offer a solution to this challenge.

Patients should consult with their GP to begin their Globus evaluation. A GPs ability to examine the throat and larynx is limited. However, through a comprehensive

assessment of potential differential diagnoses, careful history-taking, and assessment of associated risk factors, GPs can identify patients who may require a more specialized evaluation. This identification may lead to a referral to a specialist in private practice who can perform targeted investigations to rule out structural changes and provide the necessary reassurance to the patient.

Diagnostics

Different diagnostic investigations were conducted prior to and following the presentation at our clinic. Subsequently, these examinations will be scrutinized concerning the existing literature and our data.

Flexible laryngoscopy/ rigid endoscopy

Flexible laryngoscopy or rigid endoscopy is routinely performed in ENT clinics for patients with globus sensation, aiding in the detection of upper aerodigestive tract abnormalities like mucosal changes or space-occupying lesions.

In a retrospective study by Harar et al., 451 patients (64.5% of the study population) presented with typical globus sensation, without warning symptoms (i.e. without dysphagia for fluids or solids, weight loss, pain, aspiration, choking, regurgitation, or halitosis). (9) The outpatient examination and flexible laryngoscopy were able to detect all pathologies except for two cases (an insignificant pharyngeal pouch and a distal esophageal stricture, which did not require any intervention). In patients with atypical symptoms, a combination of flexible laryngoscopy and barium swallow detected all pathologies except one distal peptic stricture and five aerodigestive tract malignancies. (9) In our research, 31.3% of flexible endoscopies revealed noteworthy findings.

Building upon these investigations and results, the algorithm delineates patient flow by discerning red flags, as outlined in the classification chapter on page three. For patients with red flags, prompt referral to an ENT specialist (secondary care) or an ENT clinic (tertiary care) is necessary.

The most frequently documented change observed during the first presentation at the general ENT outpatient clinic through flexible endoscopic examination was

hyperplasia of the base of the tongue, accounting for 12.8% of cases. Although this condition does not represent a specific disease and relies on the examiner's subjective judgment, it may play a role in a foreign body sensation.

In a 2022 study, researchers delved into the link between tongue base enlargement, tonsil removal, and BMI. The study looked at the relationship between tonsillectomy and tongue base enlargement in 300 patients. The results show a low incidence of tongue base enlargement of 4.7%. No association was detected between tonsil removal and the subsequent tongue base enlargement. Nonetheless, the study identified a statistically significant relationship between tongue base enlargement and BMI. (63) Further studies are needed to confirm the correlation between an elevated BMI and the base of tongue hyperplasia, potentially establishing a connection between BMI and the globus sensation. However, there is insufficient data for evidence that BMI correlates with *globus pharyngeus.*

Narrow band imaging

In terms of cost-effective and readily available diagnostic examinations, the usage of NBI can be suggested. Research has shown that NBI is effective in distinguishing between benign and malignant lesions in head and neck cancers, with high levels of sensitivity and specificity. (74–76) However, despite its potential, there is currently insufficient trial evidence to make an evidence-based recommendation regarding *globus pharyngeus*. Further research is needed to establish standardized diagnostic criteria and compare the efficacy of NBI with MRI. This could potentially position NBI as a preliminary diagnostic tool and reduce the need for MRI in some cases. In our study, tumors (both benign and malignant) were documented in 1.4% of cases. In such scenarios, NBI is helpful in determining the subsequent diagnostic procedure.

Barium swallow and videofluoroscopic swallow study

The barium swallow and VFSS are two radiographic examinations that are commonly used to assess *globus pharyngeus.* While the VFSS focuses on real-time imaging of the oral and pharyngeal phases of swallowing, the barium swallow provides static X-ray images of the entire swallowing process, including the esophagus. It is important to note that both examinations have their own utility and efficacy in managing *globus pharyngeus.* (96)

The barium swallow, typically used to investigate swallowing issues, offers static images of the upper digestive tract post-ingestion of barium contrast. However, its usefulness in assessing *globus pharyngeus* is minimal, as studies suggest its findings rarely alter clinical management. (96,101)

VFSS, as a radiographic modality, surpasses barium swallow in sensitivity for identifying abnormalities associated with *globus pharyngeus*, offering dynamic visualization of oral, pharyngeal, and upper esophageal function. (103) While Järvenpää et al. concluded that barium swallow did not confer any diagnostic advantage for globus sensation (79), VFSS retains significant clinical utility, particularly among patients presenting with concurrent symptoms like dysphagia, notwithstanding ongoing debates surrounding its efficacy in isolated cases of globus, attributed to subtle variations in pharyngeal function. (106)

This study did not distinguish between patients who underwent barium swallow and those who had VFSS. Prior to their visit to our clinic, 50 patients (23.7%) had already undergone either barium swallow or VFSS. Additionally, barium swallow/VFSS were initiated at our clinic for 21.3% of patients.

As can be seen, these examinations were prescribed in large numbers both before and after presentation to our clinic. Whether all of these patients had red flags and thus justified these examinations is questionable. However, subjective dysphagia, reported as the primary complaint by 10.4% of patients, was the second most frequently mentioned issue and the only red flag noted by patients.

Our findings suggest that a barium swallow examination or a VFSS may not be necessary for patients with globus sensation in general. Instead, we recommend considering diagnostic tests in cases with the aforementioned red flags. The choice between a barium swallow and VFSS depends on the clinical context, as they provide complementary insights into the pathology of *globus pharyngeus*. A barium swallow examination is necessary when structural issues in the esophagus are suspected. Similarly, a VFSS is required for patients exhibiting symptoms of

functional impairment, such as swallowing difficulties or suspected aspiration. (128,129)

MRI/ CT/X-ray of the head and neck

The primary use of CT and MRI scans was to eliminate the possibility of malignancies, particularly those situated at the base of the tongue, which are difficult to evaluate clinically. In terms of neck X-rays aiming to evaluate spinal changes, the data did not differentiate between patients who underwent CT/MRI scans versus X-rays, preventing an accurate count of MRI/CT and X-ray instances.

Regarding the aim to eliminate the possibility of malignancies. The studies by Järvenpää et al. (79) and Cashman et al. (126) both concluded that none of their subjects developed malignancies during their respective follow-up periods - three years in the former and an average of five years and three months in the latter. Although malignant tumors may also be associated with globus sensation, as mentioned previously, they were diagnosed relatively rarely in the literature and present study population (0.5%). (79,126) In our clinic neck X-rays or CT/MRI scans were the most frequently initiated diagnostic tool, representing 46.4% of cases.

The studies suggest that the indication for specific radiological investigations using CT and MRI should be more narrowly defined. As previously described, clinical examination with flexible laryngoscopy can adequately assess patients. Any further diagnostics without clinical weighting represent a waste of resources.

Regarding X-rays and the aim to evaluate spinal changes, there have been isolated case reports suggesting an association of globus with bone-associated changes, such as osteophytes. (9,88,90) However, due to the high incidence, it is difficult to determine whether these osteophytes are truly responsible for the globus. It may also depend on their extension.(9)

Based on the data from this study, it is evident that only 5.7% of patients underwent specific orthopedic examinations, even though neck radiographs or CT/MRI were the primary investigation. This discrepancy in orthopedic assessment indicates potential missed opportunities for a comprehensive investigation. Moreover,

patients presenting with cervical and musculoskeletal changes should be initially referred to a GP or orthopedic specialist.

Manometry and pH monitoring

According to Van Daele et al., esophageal manometry and 24-hour pH tests, often conducted together, reveal a higher rate of anomalies in globus patients compared to EGD or VFSS, with 62.8% of manometry tests showing abnormalities. They also noted that if globus sensation persists despite PPI therapy, esophageal motility disorders should be considered highly likely. Esophageal manometry, which employs a probe to measure pressure in the esophagus, is a valuable tool for detecting such motility disorders, providing crucial insights into the underlying pathology of persistent globus symptoms. (103) According to the literature, esophageal manometry may be more reliable in cases of a persistent sensation of a lump in the throat. (3,4,103)

In the present study, pH manometry was conducted in 4.3% of the patients, with reflux and heartburn reported as the third most common main complaint at 6.2%. Based on the above-mentioned literature, we advocate for the utilization of pH monitoring, particularly in patients with a reflux component. Nevertheless, we emphasize the necessity to implement such monitoring only after a thorough course of PPI therapy to ensure a comprehensive assessment and management of the symptoms.

Cervical sonography

Cervical ultrasound can detect abnormalities such as thyroid and salivary gland issues, cervical masses, or esophageal cancer that may be missed by routine ENT exams. (80) As mentioned earlier, studies by Järvenpää et al. found no head and neck malignancies in globus patients over a three-year follow-up period, despite persistent symptoms in half of them, suggesting that ultrasound examination is not always warranted. (79)

Nonetheless, an ultrasound examination of the thyroid gland and neck was conducted in 22.3% of cases. This examination is cost-effective and provides rapid clarification of morphological changes, particularly in the neck. Therefore, this algorithm recommends sonography for patients with relevant changes and

symptoms such as thyroid struma/mass and lymph node adenopathy. However, it should be noted that a clinical examination and detailed history should precede sonography to identify patients who may benefit from and derive diagnostic value from this examination.

Esophagogastroduodenoscopy

EGD, a non-invasive diagnostic procedure, is essential for identifying and treating various upper gastrointestinal tract disorders like dysphagia, bleeding, and ulcers by examining the oropharynx, esophagus, stomach, and duodenum. (115) Lee et al. investigated the impact of esophagoscopy on managing globus sensation, finding that only a few patients had changes in diagnostic and therapeutic approaches, notably independent of typical gastroesophageal reflux symptoms.(118)

EGD is used to investigate reflux-related symptoms. While GERD is widely recognized, its association with globus sensation is complex. Functional esophageal disorders may contribute to globus, particularly in PPI-unresponsive patients. (55)

EGD was recommended by our specialists in 23.2% of patients. Given that approximately 30% of patients were prescribed PPIs as part of previous therapies, it suggests that antacid therapy was ineffective after 4 to 8 weeks despite suspicions of GERD. From our data, it's not possible to determine the exact number of patients taking PPIs and who underwent an EGD.

Psychological assessment

The role of psychological well-being in *globus pharyngeus* remains uncertain, with some studies suggesting an association between psychological disorders and this condition, while others did not. (21,23,25,130) Van Daele et al. found no significant psychiatric disorders in patients. (103) However, Tang et al. found higher rates of anxiety, depression, and sleep disturbance in those with *globus pharyngeus* compared to those without. (21,24)

In the present study, there was no standardized assessment of psychological factors conducted in the investigations. A small percentage (3.3%) of patients reported anxiety or carcinophobia as reasons for seeking medical advice, while stress was

reported by 1.4%. Based on the data, further psychological/psychiatric consultation was sought in 7.6% of patients, and psychological tests were recommended for 4.7% of patients. These findings raise concerns about the underreporting of mental health problems.

The algorithm includes a diagnostic pathway focusing on psychological factors, such as depression, carcinophobia, and anxiety disorders, distinct from sleep disorders. Although empirical evidence in this area is still limited, these psychological aspects must be considered, particularly in cases where a definitive cause is not apparent.

Sleep disorder

Another possible factor, which may be associated with psychological causes, is related to the sleep health of patients. Tang et al. found a higher frequency of sleep disturbances among patients with *globus pharyngeus.* (21,24)

In our data, 2.8% of patients reported snoring as a bothersome complaint with *globus pharyngeus*. OSAS was diagnosed in 1.4% of patients during the study period. Further investigation into sleep hygiene should be pursued in the future and is therefore considered in the algorithm.

Therapy

Various therapeutic interventions were administered both before and after patients presented to our clinic. Subsequently, these treatments will undergo evaluation in the context of existing literature and the clinical data we have gathered.

Systemic therapies

Antidepressants

As previously described, studies have shown that treatment for anxiety led to symptom improvement (67) and low-dose amitriptyline reduced symptoms and improved sleep quality. (131) In this study, none of the patients were treated with tricyclic antidepressants., highlighting a therapeutic gap.

Proton pump inhibitors

Globus pharyngeus may be caused by both GER and LPR. While PPI therapy is the preferred approach, persistent symptoms warrant further investigation. Based on the data, the efficacy of high-dose PPIs remains inconclusive. (71)

Kirch et al. emphasized that several factors contribute to partial or no response to PPI therapy, including inadequate dosage, treatment duration, poor adherence, misdiagnosis, and other underlying causes. (71) Thorough investigations are essential in cases of unsatisfactory patient progress, and if no improvement with PPIs is observed, reassessment is recommended. (132) Ensuring patient adherence through comprehensive education is critical. (133) If the patient's symptoms persist despite adherence to therapy, further evaluation, including esophageal manometry and pH monitoring may be necessary to determine the underlying cause. (1)

In this study, 29.4% of the patients had previously received PPI therapy. In 6.2% of the patients reflux or sore throat was reported as the main symptom. Temporary PPI therapy *ex iuvantibus* is recommended in cases of suspected reflux disease. Ultimately, reflux disease was diagnosed in 5.2% (11 patients) of cases. In contrast, PPI therapy was prescribed in 40.8% of cases. These data suggest a potential overuse of PPI therapy in nearly 30% of the patients.

Nonsteroidal anti-inflammatory drugs and antibiotics

Additionally, NSAIDs and antibiotics were employed, suggesting a focus on addressing inflammation and pain. This situation raises the question of whether neurogenic hypersensitivity plays a role in this scenario. Kirch et al. suggested that the observed response to gabapentin, suggesting a possible neurogenic origin of the *globus pharyngeus*, similar to sensations experienced after application of topical anesthetic spray or laryngeal anesthesia, is an interesting hypothesis worthy of further investigation. (71) However, this hypothesis cannot be substantiated due to a lack of literature and extensive supporting data.

Within this research, NSAIDs were used by 2.8%, while antibiotics were prescribed to 1.9% of patients, indicating an approach geared towards managing inflammation and pain.

Anticonvulsants

Gabapentin, an anticonvulsant approved in Austria, is indicated for partial-onset seizures in adults and children aged six and older, both as adjunctive and monotherapy. Additionally, it is used to treat peripheral neuropathic pain such as diabetic neuropathy and post-herpetic neuralgia. (134,135) Despite its efficacy, gabapentin may cause xerostomia, necessitating thorough discussions with patients regarding its off-label use and potential side effects. (135)

According to the study by Kirch et al, treatment of reflux or neuralgia may benefit most patients with globus pharyngeus. If reflux treatment proves ineffective and no other cause seems to explain the symptoms, gabapentin should be considered. (71)

In this study, Gabapentin was not prescribed; however, it seems to present a significant option. Therefore, we recommend “off-label” therapy with Gabapentin for patients exhibiting a potential chronic inflammatory component under the “suspected neurogenic hypersensitivity” algorithm pathway.

Topical therapies

In this study, various topical therapies were utilized, such as local intranasal steroids, topical anti-inflammatory treatments, and saline inhalation. Based on the hypothesis (71) outlined in the previous paragraph, it is plausible that patients with infection-related conditions, prescribed topical anti-inflammatory medications, might perceive a throat lump sensation, prompting them to seek medical attention at the hospital.

Based on the results presented, topical therapies, including local intranasal steroids, topical anti-inflammatory treatment, and saline inhalation, were administered to 7.1% of the patients.

Manual therapy

Literature suggests that managing osseous changes in the cervical spine may contribute to dysphagia, globus sensation, and laryngeal structure changes related to *globus pharyngeus*, underscoring the need for discussion on this potential cause. (88) Studies of speech therapy employing relaxation techniques have shown success in treating globus. (136) Wareing et al. reported symptom improvement in

92% of treated patients. (137) Another study found that 3 months of speech therapy in 98 patients resulted in a significant reduction in symptoms, which was more effective than reassurance alone. (138) However, further research is needed to confirm these findings and assess their long-term efficacy.

During assessments, experts directly identified various changes, with the most common abnormality being muscular or degenerative spine changes in 8.1% of patients. The recommendation of manual therapies such as physiotherapy, speech therapy, or swallowing consultations in 40.3% of cases suggests a recognition of the importance of addressing musculoskeletal and functional aspects in patients with *globus pharyngeus.* Notably, the study did not distinguish between the different types of therapies. However, the low rate of specific orthopedic investigations, carried out in only 5.7% of patients, raises questions about the appropriateness of these patients presenting to an ENT clinic.

These cases, particularly those requiring orthopedic evaluation for cervical and musculoskeletal problems, would arguably be better managed by a GP or orthopedic specialist. Referral of such patients to the appropriate healthcare provider could optimize the use of resources and ensure that patients receive the most appropriate and comprehensive care for their condition.

Follow-up

A crucial aspect under investigation is the follow-up care of patients. In the study by Järvenpää et al., 27 out of 30 patients (139) returned for follow-up appointments, and in the study by Cagney et al., 73 out of 80 patients (140) returned for a follow-up. Despite the smaller study populations, both studies show a significantly lower rate of loss to follow-up than the present study. Variations in tracking methods, patient engagement, quality of communication or study design factors may explain the significantly lower loss to follow-up rate in both the Järvenpää et al. (139) and Cagney et al. (140) studies compared to the present study. One hypothesis for the high proportion of patients' loss to follow-up is that they may have felt reassured after the clinic examination that there was no foreign body in their throat or evidence of malignancy, contrary to their subjective perception. (2,139,140)

Based on these findings by Cagney et al, it is reasonable to assume that a proportion of the absent patients may have experienced symptom relief. (140)
The proportion of patients who did not attend follow-up appointments in external healthcare facilities (e.g. GP), cannot be determined from the available study data. A more detailed investigation of these connections could provide further insights.

Regarding readmissions and symptom improvement, in the study by Cagney et al., 50% of patients became asymptomatic or experienced symptom relief within 27 months. (140) In the present study, patients had a minimum of 28 months between the first and last visit. Of these 43 patients who underwent follow-up, 28 reported symptom improvement and the remaining 15 did not. It is important to note that the number of perceived follow-up visits in this study was significantly lower than in Cagney et al. (140), and thus the number of patients experiencing symptom relief may not be representative for comparison.

Economic factors

According to the Austrian Federal Ministry of Social Affairs, Health, Care and Consumer Protection, public health expenditure in 2020 will exceed the expenditure ceiling by EUR 765 million, which corresponds to an overrun of 2.6% based on the financial target management report. (141) Healthcare costs in Austria exceeded EUR 50 billion for the first time in 2022, marking an increase of 3.4% from EUR 32.3 billion in 2010. This increase highlights the growing financial burden on the healthcare system. (142)

The development of a diagnostic algorithm for the management of *globus pharyngeus* is significant to healthcare. It has the potential to reduce patient distress by shortening the time between the initial symptom onset and diagnosis. In addition, such an algorithm may prevent unnecessary diagnostic and treatment. Ideally, diagnosis and subsequent treatment should primarily occur in outpatient settings, with tertiary care facilities reserved for exceptional cases. This approach ensures efficient care and reduces the economic burden on the healthcare system. (127)

Risk profile

There is a predominance of females, accounting for 59.2% in the present study. In terms of lifestyle factors, 12.3% of individuals reported a history of smoking, while

26.1% reported an allergic status. The calculated mean age of the cohort is 53.3 years, with 79.6% experiencing symptoms for more than four weeks.

However, it is important to emphasize the limitations of incomplete documentation, particularly regarding smoking and allergy status, as well as the lack of documentation of other relevant risk factors such as medication and alcohol. These data gaps prevent accurate risk assessment. Further investigation and data collection is therefore essential to refine our understanding of the risk factors associated with *globus pharyngeus* in this population.

The Algorithm

The following algorithm for the evaluation and management of *globus pharyngeus* was developed based on the results presented and a review of the literature. Critical elements of the diagnostic pathways were taken from algorithms (143) proposed by Järvenpää et al. (2), Van Daele et al. (103), Selleslagh et al. (3), and Kumar et al. (4,144). However, specific items were added, modified, and adapted. A separate algorithm was developed for each level of service to provide a specific and clear guideline for each healthcare setting (primary, secondary, and tertiary).

Algorithm for Primary Care

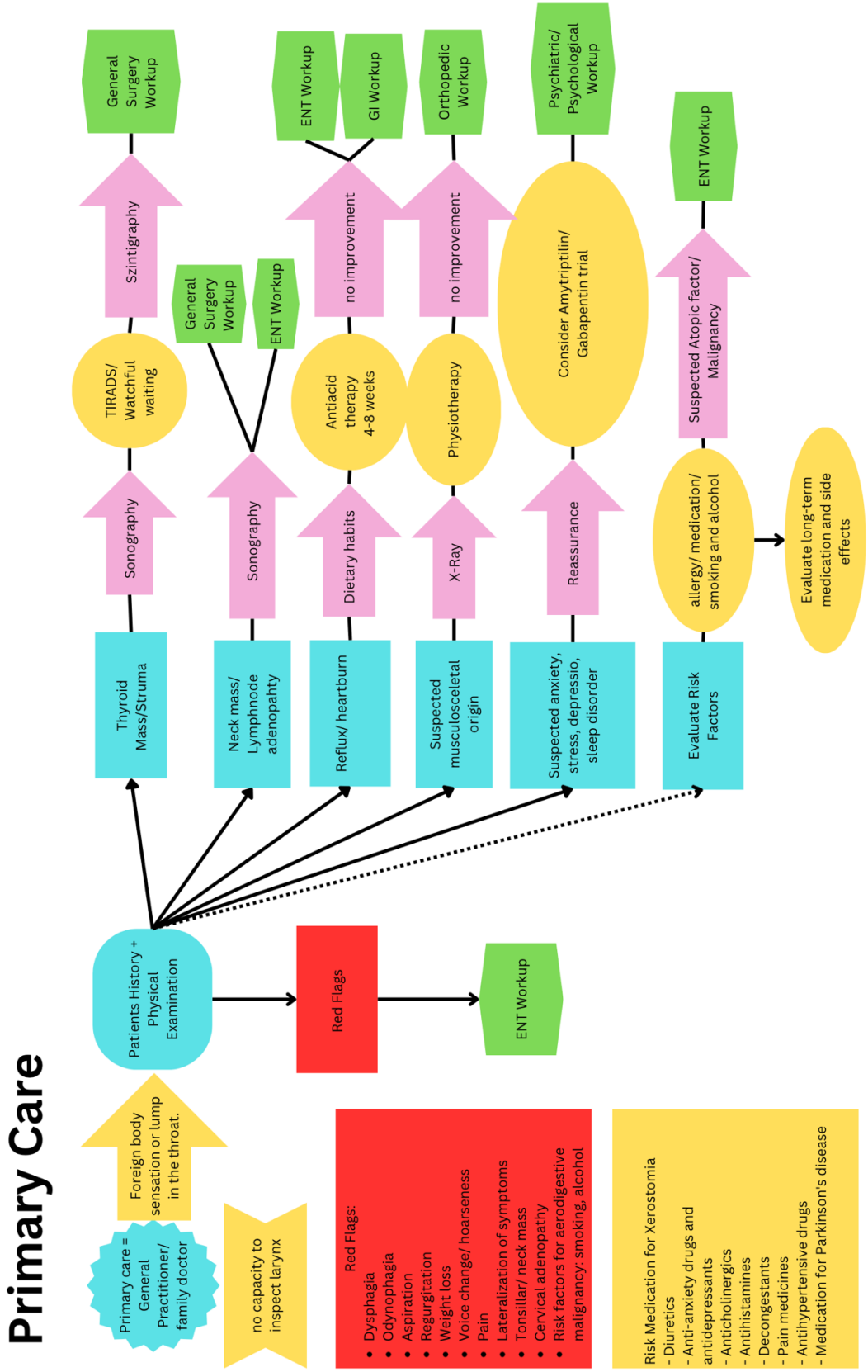

Figure 7: Self-developed Algorithm for Primary Care: A specific guide for the initial medical management of globus pharyngeus based on original research, own data, and adjustments.

Algorithm for Secondary Care

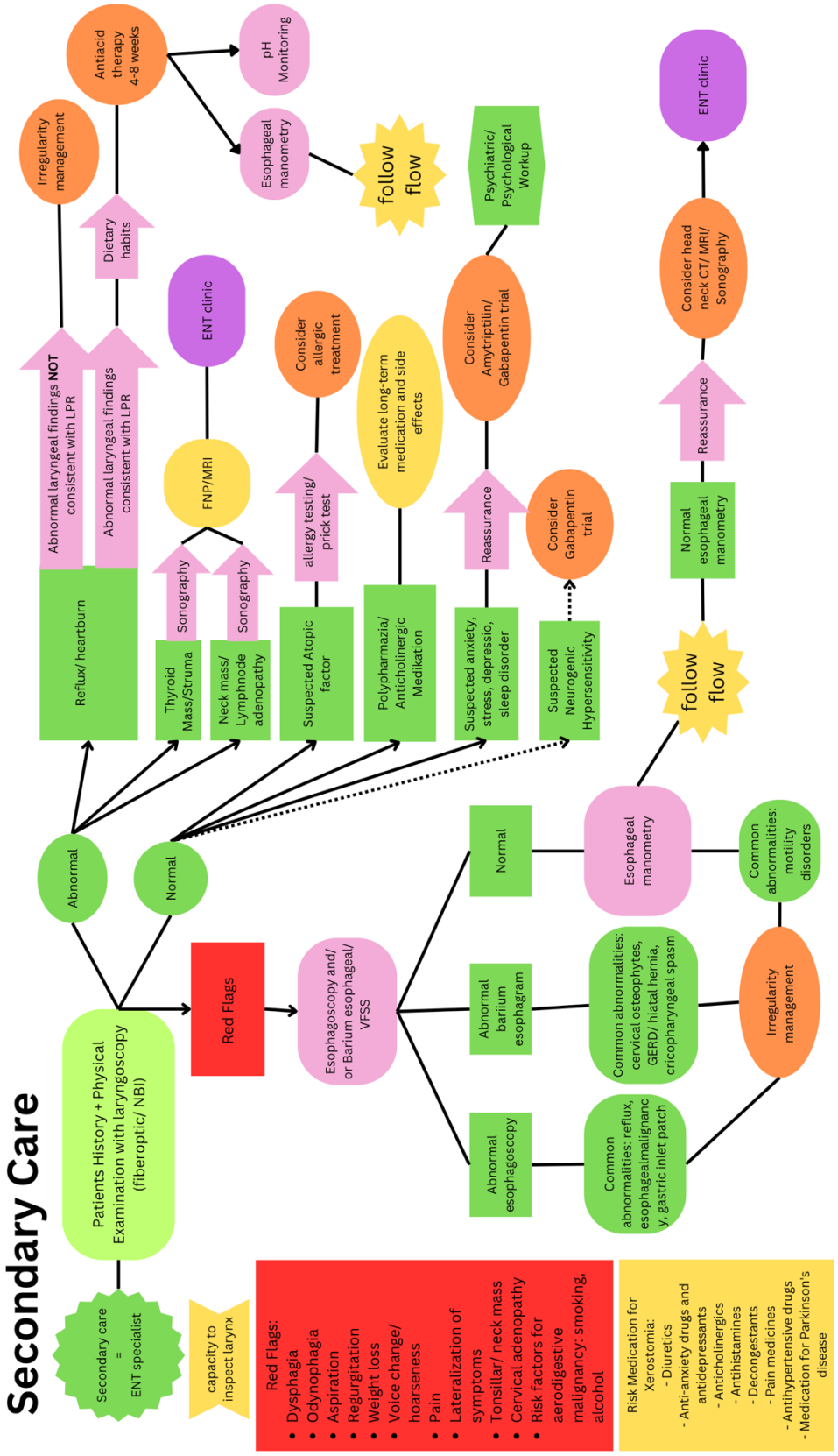

Figure 8: Self-developed Algorithm for Secondary Care: A specific guide for the initial medical management of globus pharyngeus based on original research, own data, and adjustments.

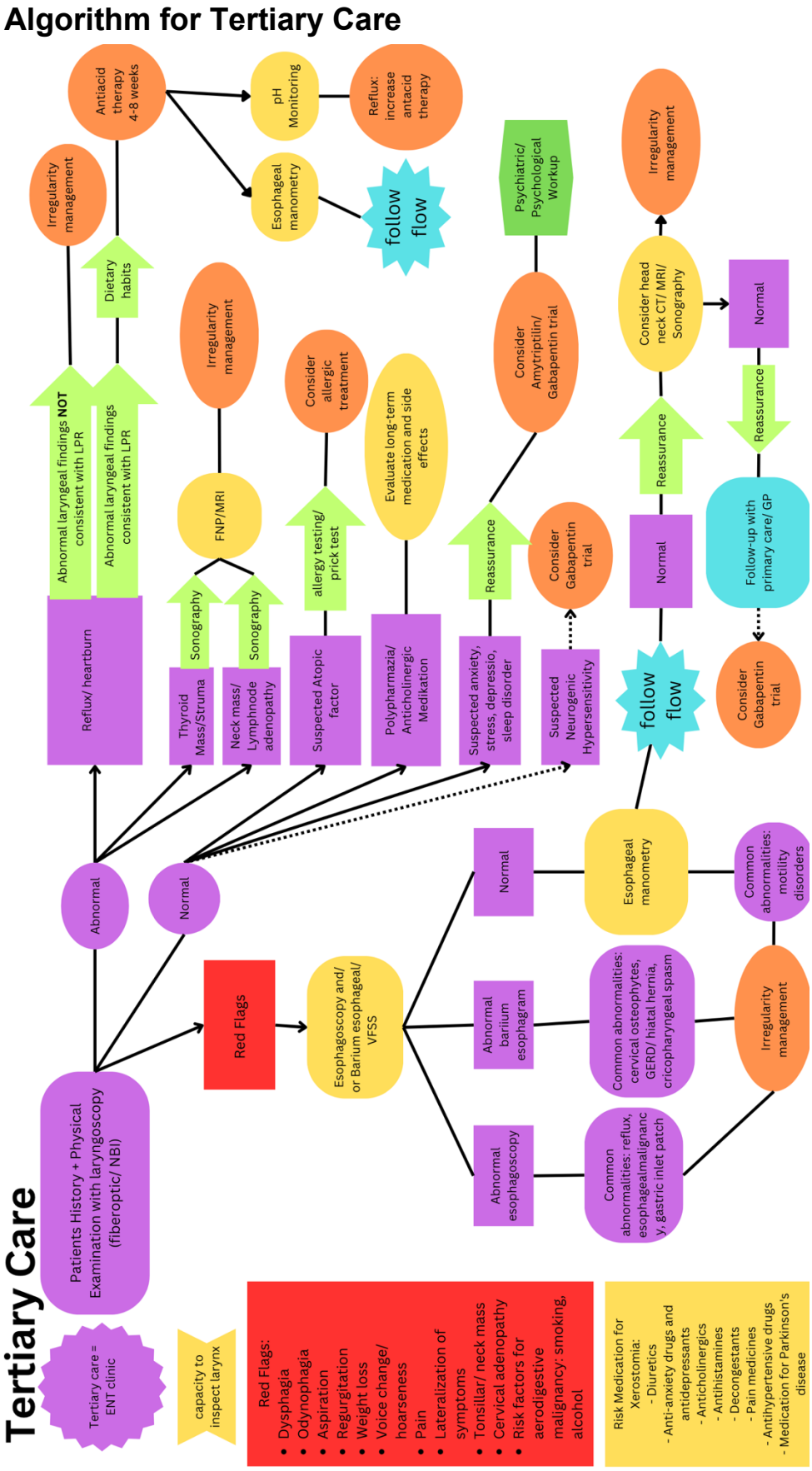

Figure 9: Self-developed Algorithm for Tertiary Care: A specific guide for the initial medical management of globus pharyngeus based on original research, own data, and adjustments.

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