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HEAD AND NECK

How uncomplicated total thyroidectomy could aggravate the laryngopharyngeal reflux disease?

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Abstract Swallowing, voice disorders, throat discomfort and subjective neck discomfort are usually reported by patients with a known thyroid nodule and are correlated to nodular thyroid disease itself. Moreover, in endemic goitrous areas, total thyroidectomy (TT) is the most frequently performed surgical procedure. We are used to relate swallowing, voice and throat discomfort to the mechanical effects of nodular goiter or to thyroidectomy itself, but in both these cases the relationship between symptoms and the thyroid mass or its removal is not always clear or easily demonstrated. How can we explain the persistence of local neck symptoms after TT? And how can TT worsen the dysphagic or dysphonic disorders attributed to the goiter's effect over the surrounding structures? During these years, many articles have analyzed the relationship between the thyroid disease and the laryngopharyngeal reflux, finding more and more evidences of their consensuality, leading to important new management considerations and notable medico-legal implications; if the reason of local neck symptoms is not the thyroid disease, we have to study and specially cure the reflux disease, with specific test and drugs. Therefore, the aim of our study, relying on the published literature, was to investigate how, in demonstrated presence of reflux laryngopharyngitis in patients with nodular goiter and local neck symptoms before and after uncomplicated TT, the surgery could influence our anti-reflux mechanism analyzing the anatomical connection as well as the functional coordination; can we play a part in the post-operative persistence of swallowing and voice alterations and throat discomfort?

Keywords Thyroidectomy · Laryngopharyngeal reflux · Nodular goiter · Local neck symptoms

Introduction

Goiter and laryngopharyngeal reflux are two common diseases, with similar prevalence rates and clinical presentation/manifestation. Goiter and/or thyroid nodules are the most prevalent endocrine conditions in the world, affecting over 500 million people with prevalence rates reaching up to 30 % [1, 2]; local neck symptoms range from 13 to 50 % in patients undergoing surgery for benign nodular diseases [3, 4].

On the other hand, laryngopharyngeal reflux (LPR) is a variant of the gastroesophageal reflux disease (GERD) that affects the larynx and pharynx, causing a typical phlogosis and erythema; it had been considered as an "extra-esophageal" manifestation of the GERD which acquired a specific nosological identity only at the beginning of the 90s [5]. The retrograde flow of gastric contents into the laryngopharynx could be present under physiological conditions but in these patients the number of reflux events as well as the "acid exposure times" (AET) of pH $\leq$4 is bigger, resulting in a wide range of laryngeal signs and symptoms [6]. Starting from Koufman's disclosure, according to which "laryngopharyngeal reflux is different from classic gastroesophageal reflux disease" [7], LPR has become an important etiology in otorhinolaryngology, diagnosed in approximately 10 % of patients with otorhinolaryngological symptoms and in at least 50 % of patients

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with voice-related complaints [8, 9]. Gradually, it has been deeply evaluated as the cause of several diseases scarcely studied or cured until now.

Swallowing, voice disorders, throat discomfort and subjective neck discomfort are usually reported by patients with a known thyroid nodule and correlated to nodular thyroid disease itself. Furthermore, in endemic goitrous areas, total thyroidectomy (TT) is the most frequently performed surgical procedure [10].

However, according to our personal experience—which is consistent with the international literature—swallowing and voice disorders may persist after an uncomplicated TT, even after a significant amount of time. Traditionally, they have been related either to a supposed injury to the perivisceral neural plexus innervating the pharyngeal and laryngeal structures or to a normal healing process presumed to result in laryngo-tracheal fixation with impairment of vertical movements [10]. We are used to relate swallowing, voice and throat discomfort to the mechanical effects of nodular goiter or to thyroidectomy, but in both cases it is not always clear, nor it has been efficiently demonstrated, to what extent these symptoms can be related to the thyroid mass or to its removal.

How can we explain the persistence of local neck symptoms after TT? And, more importantly, how can TT worsen the dysphagic or dysphonic disorders attributed to the effect of goiter over the surrounding structures?

In our article titled "local neck symptoms before and after thyroidectomy: a possible correlation with reflux laryngopharyngitis" [10], we claim that the above-mentioned symptoms are not related to the goiter's compression/dislocation/infiltration, but rather to another medical disease characterized by a similar clinical manifestation. In more detail, we assume that the reflux laryngopharyngitis is the primum movens of these symptoms, a different diagnosis with an overlapping clinical presentation.

Recently, on the basis of our hypothesis and other similar accounts, many articles have analyzed the relationship between the thyroid disease and the LPR, finding further evidence of their consensuality, leading to important considerations on how the disease is managed and having significant medical–legal implications. If the reason of local neck symptoms is not the thyroid disease, it is of crucial importance to study and, especially, cure the reflux disease with specific tests and drugs.

The most important evidence of this new approach is offered by the American Thyroid Association Statement on Optimal Surgical Management of Goiter. In a recent article, they assert that "completing a thorough history of the patient's dysphagia symptoms may help discriminate extrinsic compression of the goiter from other causes of dysphagia, such as laryngopharyngeal reflux" [11].

But even if the syncretism between the two diseases is clear and proven, a question remains open: how can the TT worsen and/or simply influence the symptoms reflux-linked? Is it possible to postulate an anatomic liaison which can explain the true role played by the surgery on the anti-reflux defenses?

The recent literature has proven how the local neck symptoms in patients with nodular goiter could arise from a misunderstood LPR disease (LPRD), from an incorrect way to study it and its optimal pharmacological management in the post-operative time. But, none has explained which role the surgeon may play in the development of the laryngeal disease.

Therefore, the aim of our study is to investigate how surgery in patients with a demonstrated presence of laryngopharyngeal reflux and local neck symptoms could influence the anti-reflux mechanism by taking into account anatomical connections and functional coordination. Can surgery play a role in the post-operative persistence of swallowing, voice and throat discomfort?

In other words, if the surgeon's role is recognized, the informed consent has to postulate that possibility and, as a logical consequence, the patients must be informed about the pharmacological therapy he has to apply after surgery.

Discussion

Laryngopharyngeal reflux is a relatively young disease, well investigated in the recent past from several perspectives (anatomical, clinical, pathological and therapeutic ones). Its typical clinical manifestation includes many disorders affecting the phoniatric, respiratory and swallowing systems. This neck discomfort is different from GERD-induced symptoms which are, on the one hand, characterized by the absence of esophagitis and heartburn; on the other hand, they have different patterns and mechanisms of reflux [12].

It has been observed that many patients continue to report throat discomfort after uncomplicated thyroidectomy, a clinical pattern common to many other disorders, especially the LPR disease.

To our knowledge, a clear etiology/relationship between this group of reflux-related symptoms and the thyroid surgery has never been investigated in depth. The main objective of this paper is to explain how the LPR is influenced by the thyroid surgery.

1° hypothesis: the external branch of the superior laryngeal nerve (EBSLN)

As is well known, the thyroid gland is located in an important and equally dangerous area of the cervical

region, near to vital organs (such as the cervical esophagus), critical neural structures (e.g., the recurrent laryngeal nerve and the superior laryngeal nerve), and major blood vessels. A perfect knowledge of the topographic anatomy is a conditio sine qua non for a surgical procedure.

In the course of TT, the EBSLN could be subjected to injury during the ligature of the superior thyroid vessels due to its adjacency to the superior pole. The relationship between the EBSLN and the superior thyroid pedicle has different anatomical manifestations depending on the crossing level of the thyroid vessels. Cernea et al. [13] propose a three-way distinction which consists of type I (nerve crossing the vessels 1 cm above a horizontal plane along the border of the superior gland pole), IIA (crossing the vessels less than 1 cm over plane) and IIB (below the above-mentioned plane).The most critical type is the third one, considerably at risk of lesion. Injury to EBSLN, which occurs in approximately 20 % of cases, causes lower airway protection mechanisms and changes as well as palsy of the cricothyroid muscle. This muscle maintains the vocal folds under tension during phonation and it also helps them to produce high-frequency sounds. Unilateral injury to the nerve causes changes in vocal timbre and markedly reduces the capacity to project any loudness, while bilateral injury can result in a hoarse, monotonous and faint voice [14]. Thus, EBSLN palsy may alter the ability to produce acute sounds but could lead to dysphagia, especially with liquids. Why does this occur?

The hypothesis we advance starts from an anatomical consideration: as showed by Lennquist and colleagues, approximately 20 % of external superior laryngeal nerves run through the fibers of the pharyngeal inferior constrictor muscle, an essential component of the upper esophageal sphincter (UES) [15]. Friedman et al. propose a classification based on three different anatomic patterns of the main trunk of the EBSLN before its terminal branching and the inferior constrictor muscle. In type 1, it runs superficially or laterally to the inferior constrictor muscle, descending until the superior thyroid vessels. In type 2 variation, the EBSLN penetrates the inferior constrictor muscle in the lower portion of the muscle, in this condition the nerve is only partially covered by the inferior constrictor. And finally, type 3 nerve dives under the superior most fibers of the inferior constrictor, remaining protected by this muscle throughout its course to the cricothyroid muscle [16].

The anatomical proximity between EBSLN and the inferior constrictor muscle could explain the compromised swallowing coordination caused by an unrecognized damage of the EBSLN. But can anatomy be explanatory enough to demonstrate a function? Lang et al. have done more; in a recent article, they take into account "the role of the superior laryngeal nerve in esophageal reflexes "and highlight how, despite many anatomical and neurophysiological studies provide evidence of the ESLN's innervation of the esophagus and UES, it is not still clear the role played by this nerve in the swallowing function [17].

Through testing different esophageal responses (e.g., UES contractile reflex, low esophageal sphincter (LES) relaxation reflex, secondary peristalsis, pharyngeal swallowing and belching) after nerve transaction, Lang et al., interestingly enough, observe that the transection of EBSLN blocks the activation or reduces the sensitivity of the UES contractile reflex generated by the cervical esophagus (but not by the thoracic esophagus), and of the LES reflex, stopping the pharyngeal swallowing elicited by the cervical and thoracic esophageal distension; but it has not any role in the secondary peristalsis [17].

Starting from these assumptions, we are ready to conjecture a new hypothesis. Many local neck symptoms arising after uncomplicated thyroidectomy are caused by the LPR disease, and we know that the thyroidectomy could lead to unrecognized injury to the EBSLN, but we cannot demonstrate how the operation could make the LPR worse; but if the EBSLN plays a crucial role on the esophageal reflex and we prejudice it, it could be possible that the LPR symptoms or lesions become more intense.

Based on the course of the EBSLN, really closed to pharynx and UES, and the functional testing positive for an EBSLN influence on the coordination mediating afferent fibers, we believe that surgery may be one of the causes behind worsened LPR disease.

2° hypothesis: the upper esophageal sphincter

As previously pointed out in the literature, thyroid surgery could condition the UES reflex, through the action of the two laryngeal nerves, the internal branch of the superior one and the recurrent nerve. How can we explain this phenomenon when it occurs after an uncomplicated thyroidectomy? As postulated above, EBSLN could partially stimulate the UES contraction via the little peripheral branches and we know that a great deal of EBSLN's injury runs hidden. We have demonstrated that the persistent local neck symptoms after thyroid surgery could be linked to the LPR; so, if we worsen the UES functionality, the LPR and consequently the clinical manifestations of dysphagia, dyspnea, throat discomfort, dysphonia and so on will undergo an aggravation.

While foniatric and respiratory changes have been consistently investigated in the literature, very few studies on swallowing disorder after thyroidectomy have been carried out. Scerrino et al. examined the swallowing changes after uncomplicated total bilateral extracapsular thyroidectomy, evaluating LES and UES pressures, esophageal motility and coordination by esophageal

manometry carried out preoperatively and at 30–45 days after surgery. In the post-operative follow-up, all patients showed a significant decrease in UES pressure, no difference for the LES values, unchanged body motility. As far as swallowing disorders are concerned, clinical symptoms were strictly connected to the UES changes while the voice discomforts were linked to the proximal acid reflux [18].

Starting from Moosman and DeWeese, who show that the external branch usually lies adjacent to the inferior constrictor muscle outside the surgical capsule of the thyroid gland [19], we assume that the close anatomy and the surgical alteration of the fibro-connective atmosphere may influence the cricothyroid muscle contractility and consequently lead to the UES deficit. Indeed, the striated muscles of UES are the most important barriers against pharyngeal reflux of acid contents; the cricopharyngeal muscle is one of the principal components of the UES, placed in front of the cervical vertebrae and behind the cricoid cartilage, very close to the thyroid capsule [20].

These implications are fundamental to explain the persistence of local neck symptoms after thyroidectomy. Symptoms depend on the LPR, the surgery may worsen the anti-reflux defenses, ipso facto the surgery might aggravate the LPR.

3° hypothesis: the hyoid–laryngeal elevation and laryngopharyngeal reflux

It is a well-known fact that normal swallowing needs a precise neuromotor coordination of the upper aero-digestive tract which changes from a respiratory conformation to a digestive one. During the pharyngeal phase of swallowing, there is a delicate crossroad characterized by:

- Velo-pharyngeal closure to isolate the nasal cavity;
- Peristaltic contraction of the pharyngeal constrictor muscles;
- Airway closure, with two types of movement—laryngeal and hyoid elevation—the flipping over (retroversion) of the epiglottis to cover the glottis, the adduction of the true and false vocal folds;
- UES opening to allow passage of bolus into esophagus [21].

All these movements last approximately 1 s.

Valleculae and pyriform sinuses are two important areas not frequently analyzed in the swallowing disorder's literature. The first one is a borderline area between the pharynx and the larynx—though covered by the epiglottis—where lingual tonsils and the hyoepiglottic ligament, which links the epiglottis to the hyoid bone, are located [22].

The pyriform sinuses are two closed spaces, made up of the attachment of the inferior constrictor muscle to the laryngeal cartilage; therefore, UES is closely located to the pharyngeal recesses [21].

We have taken into exam swallowing disorders through a videofluoroscopic swallowing methodology—in which barium bolus marks all the phases of the swallowing sequence—that allowed us to calculate transit time, contrast medium residue and demonstrate contractile incoordination (i.e., UES opening and epiglottic closure) as well as the efficacy of oral–pharyngeal–esophageal clearing [23]. Also, it allowed us to study the elevation/anteriorization of the laryngeal–hyoid complex and the consequent respiratory exclusion, significant aspects of the deglutition. A classical find in case of reflux laryngopharyngitis is the persistence of barium in the valleculae and pyriform sinuses. This specific type of laryngopharyngitis shows a severe edema, hyperemia and phlogosis of posterior laryngeal wall and these signs, common but not exclusive of the LPR, are easily verifiable through a fiberoptic videolaryngoscopy (VLS) [24]. Symptoms such as vocal fatigue, hoarseness and globus pharyngeus, in a not yet well-defined percentages, if associated with edema and hyperemia of the arytenoid cartilage and interarytenoid area, salivary stagnation in the piriform sinus, vocal nodules, vocal fold edema determine the simple LPRD; if associated with granulomatous lesions of the posterior glottis, subglottic stenosis, precancerous lesions and carcinoma of the larynx, they determine the complicated LPRD [25].

In our study [10], we evaluated the swallowing activity pre- and post-thyroidectomy to investigate how the surgical procedure could modify it. Once defined the possible reflux-linked origin of the local neck symptoms, could the swallowing study explain the extent to which surgery worsen the normal swallowing sequence to induce the reflux injury?

The striated muscles, the sternohyoid and the sternothyroid muscle can be damaged in the thyroid surgery during the operation time or by contracture surrounding laryngeal structures [26]. Hong et al. [27] have demonstrated that the contraction of the sternohyoid and sternothyroid muscles causes the laryngo-tracheal downward pull, causing high-volume air in the subglottic air space. In our opinion, similar mechanisms could explain the compromised elevation/anteriorization of the hyoid–laryngeal complex, keeping the sub-epiglottic space open and worsening the LPR. Additionally, this downward pull determines the shortening of the cricothyroid distance, the lengthening of the vocal folds, and the increasing of frequency [27], causing the persistence and exacerbation of the local neck symptoms.

All these factors may work synergistically, even if it is difficult to determine how each of them acts. The pharyngeal phase of swallowing is an important muscular step

that can be surgically influenced, explaining both the swallowing disorders post-TT and the hampered anti-reflux defenses; so we can worsen the LPR.

Discussion

The correlation between laryngopharyngeal reflux and goiter has been a new investigative field in these last years. It has led to new important approaches to local neck symptoms' persistence or aggravation after uncomplicated total thyroidectomy, a common event, difficult to control. The first striking result is the distinct therapeutic management we have to perform. A reflux-linked disease needs a Proton Pump Inhibitors (PPIs) therapy. This is unavoidable in the GERD and in local neck symptoms' management after thyroidectomy. In a recent publication, Zawawi et al. have highlighted how "patients treated with PPIs had less pain and swallowing disability in the first week following thyroid surgery, when compared to patients not treated with PPIs" [28].

The pathophysiologic mechanisms of supra-esophageal manifestations of reflux disease or LPR are still today poorly understood [20], but there is another unsolved question: can surgery worsen LPR? The aim of this article is just speculative; starting from other important investigations in the literature and from our personal experiences, we have developed three main hypotheses.

Sørensen et al. [29] have recently published a readable review (the first one on this topic) trying to find the impact of goiter and its therapy on adjacent organs, such as trachea, esophagus and so on. In the paragraph, "effect of thyroidectomy on the trachea and respiratory and oesophageal function" they appeal to the same articles mentioned in this paper, Scerrino et al.'s one and our own article [10, 18]. In the former, effects are seen as a decrease pressure of the UES; we have, instead, registered a normal hyoid bone elevation, even if we established a different relationship between surgery and LPR. We claim that this paper is the first attempt to study, strictly speaking, the effects of the surgery on LPR, which could explain the clinical spectrum.

All our considerations are hypotheses, based on up-to-date articles. Additional insights and empirical data are necessary, but we strongly believe that the present investigation establishes an interesting basis for a better understanding of the process aimed at effective pre- and post-operative management.

Conclusion

LPR is a recent etiological diagnosis in which the acid reflux involves posterior pharynx and hypopharynx, leading to clinical manifestations similar to those due to the thyroid disease (including hoarseness, cough, vocal fatigue, globus, excessive throat clearing, dysphonia, and mild dysphagia) [30]. The presence of local neck symptoms before thyroid surgery and/or the persistence after it could be motivated by the incorrect association with the thyroid disease in place of the LPR as primum movens [10]. The American Thyroid Association Statement on Optimal Surgical Management of Goiter underlines the need to investigate other causes possibly responsible for the local neck symptoms, in addition to the thyroid gland itself [11]. To our knowledge, this is the first article explaining how surgery may worsen the reflux disease, if it is true that the clinical manifestations depend on the LPR. Data collected are not homogeneous, but may provide an insightful basis for future investigations aimed at significant improvements in the management of similar diseases.

Conflict of interest None.

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