Laryngopharyngeal Reflux as Causative Factor of Vocal Fold Nodules

Dear Editor,

We reviewed the article entitled: "*Does Pepsin Play a Role in Etiology of Laryngeal Nodules?*" by Tasli et al.[1] The authors assessed the presence of pepsin in formalin-fixed, paraffin-embedded specimens of vocal fold nodules of 28 patients who were considered as laryngopharyngeal reflux (LPR) patients on the basis of a Reflux Finding Score (RFS) >7. Authors put into question the relationship between LPR and the development of vocal fold nodules because they did not detect pepsin in the histological tissue samples of nodules. The involvement of LPR in the development of vocal fold benign lesions is an interesting research topic given the high incidence of LPR disease in patients visiting voice centers.[2,3] However, we wish to draw attention to many points.

First, in this study, it is still difficult to know if the included patients really suffered from LPR at the time of the surgery. Indeed, with regard to the current controversy about LPR diagnosis, particular attention should be paid to the LPR diagnostic method. In the present study, the diagnosis was only based on RFS >7 without evaluation of LPR symptoms or additional examination (ie, pH impedance metry). To date, two main approaches can be used for the diagnosis: the detection of LPR episodes with pH impedance metry or the identification of both LPR signs and symptoms with validated clinical instruments whilst excluding confounding factors.[4] Although these two clinical tools are not perfect (poor interjudge reliability, lack of consideration of some symptoms, or extra-laryngeal findings), the concomitant use of reflux symptom index >13 and RFS >7 remains the best clinical way to make the diagnosis.[4] Naturally, this approach imperatively requires the strict exclusion of many common conditions that can lead to the development of laryngeal inflammation including allergy,[5] chronic consumption of alcohol or very hot drinks,[6] the postnasal drip encountered in chronic rhinosinusitis, and the occurrence of upper aerodigestive tract infection(s) within the last month before the evaluation.[7] The lack of exclusion of these common conditions as well as the lack of evaluation of LPR symptoms are two elements that could bias the inclusion of LPR patients.

Second, detection of pepsin is undoubtedly a promising method for the LPR diagnosis but the detection should be particularly done on epithelial tissue such as vocal fold epithelium or pharyngeal mucosa.[8] As developed in a previous review, pepsin acts primarily on epithelial cells of upper aerodigestive tract tissue, supporting the interest to focus the research of this protein in epithelium. It has been demonstrated in many studies that pepsin alters both the defense mechanisms of the vocal folds (ie, secretion of mucus and bicarbonate, mucus dehydration, etc) and the mucosal healing that can weaken the tissue. Therefore, vocal folds are more subject to the development of microtraumas caused by excessive mechanical stress that remains the central cause of vocal fold nodule formation.[8–10] The lack of identification of pepsin in nodule tissue, which is fibrotic tissue due to mechanical stress and aberrant would healing, cannot exclude the diagnosis or the involvement of LPR. In addition, phonotraumatic lesions of the vocal folds can also be related to phonotraumatic activity such as throat clearing and coughing that are often associated with LPR. Thus, the lack of pepsin in vocal fold tissue but the occurrence of these LPR symptoms did not exclude the diagnosis.

Third, the difficulty to identify a potential relationship between LPR and the formation of nodules is strengthened by the natural history of the LPR disease. Indeed, 25–50% of patients with LPR have chronic course of the disease with periods of relapse and remission.[11] This specific profile of patients with chronic LPR disease suggests that the lack of LPR at the moment of the phonosurgery did not exclude the possibility that the patient had chronic irritation of vocal folds by pepsin during the months/years before the development of nodules. The paper of Tasli et al is an interesting step in the study of the involvement of LPR in the development of benign lesions. Further studies that aim to study the relationship between LPR and nodules should imperatively identify the presence of LPR with objective examination (pH impedance metry or pepsin detection in epithelial cells) during the period before the development of nodules that still remains very difficult.

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SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at doi:10.1016/j.jvoice.2018.06.006.