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First direct correlation of proton pump (H/K-ATPase) expression in human laryngeal epithelium with pharyngeal pH monitoring in patients with suspected laryngopharyngeal reflux

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Background

The prevalence of laryngopharyngeal reflux (LPR) has experienced a dramatic growth in the last years but pathophysiology is still unclear. LPR might be caused by pharyngeal acid exposure and it is thought to be associated with gastroesophageal reflux disease (GERD). However, correlation between GERD, LPR symptoms and response to proton pump inhibitors is poor. Therefore, alternative pathophysiological mechanisms are discussed. Recently, proton pumps (H+K+-ATPase) expressed in the human larynx were identified by immunohistochemistry (IH). Laryngeal acid production might be responsible for LPR symptoms.

Aim of this study was to correlate H+K+-ATPase expression in human laryngeal epithelium with pharyngeal pH monitoring and combined pH/ impedance measurement (pH/MII) in patients with LPR.

Methods

In all patients, upper endoscopy was performed to exclude neoplasia or erosive reflux disease. Biopsies (2 for IH, 2 for RT-PCR) were taken from the post cricoid area. IH staining of paraffin embedded tissue sections was performed with monoclonal mouse antibodies against the alpha and beta subunit of the human H+K+-ATPase. Furthermore, quantitative real-time RT-PCR for each of the both H+K+-ATPase subunits as well as Cyclophilin as housekeeping gene for normalization was performed.

PH values were assessed in the aerosolized environment of the oropharynx (DxpH Catheter, Restech, San Diego, USA). Additional, combined pH/MII was used to detect potential gastroesophageal reflux episodes. DxpH was pathological if the Ryan Score was <9.4 in an upright position (pH<5.5) or <6.8 in a supine position (pH<5.0). pH/MII was regarded as pathological if pH dropped below 4 in more than >4% of the recorded time and/or >73 mixed reflux episodes occurred.

Patients and Results

In total 15 patients suspected for LPR were analyzed. 12 of 15 patients had pathological results in DxpH; 5 of 15 patients had pathological results in pH/MII. Four patients had pathological results in both functional tests. In one patient, laryngeal H+K+-ATPase expression was verified by immunohistochemical staining. Both, DxpH and pH/MII showed pathological results. In another patient, real-time RT-PCR for each of the two H+K+-ATPase subunits were positive, whereas immunohistochemistry was negative. Pathological results were assessed by DxpH, regular results in pH/MII.

Conclusion

Our preliminary clinical data support these new pathophysiological mechanisms in patients with LPR for the first time. We detected relevant acid pH levels in patients with laryngeal H+K+-ATPase expression and excluded gastroesophageal reflux. We assume evidence of laryngeal H+K+-ATPase expression in a higher number of patients, which might be missed due to sampling error. Pharyngeal pH measurement has the potential to detect these patients.