

# Atypical Symptoms Are Related to Typical Symptoms Rather Than Histologic and Endoscopic Esophagitis

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**Article:** Atypical symptoms in patients with gastroesophageal reflux disease

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Gastroesophageal reflux disease (GERD) is a chronic and frequently occurring disease. Its prevalence has been found to be much higher in the Western world, where 20% of the adult population has the typical symptoms such as heartburn or acid regurgitation once or more per week.<sup>1</sup> In the Eastern world, its prevalence has gradually increased. The prevalence of symptom-based GERD was found to be 5.2%-8.5% from 2005 to 2010 in Eastern Asia. In Southeast and Western Asia, it was 6.3%-18.3% after 2005. The prevalence of endoscopic reflux esophagitis in Eastern Asia was 4.3%-15.7% after 2005. The prevalence of extraesophageal syndromes in Asia was higher in GERD group than in controls.<sup>2</sup> GERD causes troublesome symptoms including typical and extraesophageal symptoms.<sup>3</sup> Besides, it has impacts on the quality of life in terms of one's physical state, emotional state, social function and productivity.<sup>4</sup> The quality of life associated with GERD may be more related to psychological factors (anxiety and depression) than to symptom severity.<sup>5</sup> A variety of pulmonary and ENT symptoms and disorders may actually be

manifestations of GERD. Symptoms of extraesophageal reflux could include cough, asthma, chronic laryngitis, hoarseness and sinusitis. Chronic cough is associated with GERD in 21%-41% of the cases on the basis of epidemiological data.<sup>6</sup> Hoarseness caused by GERD occurs in an estimated 10% of all cases seen by ENT physicians. Persistent sore throat and chronic laryngitis are associated with GERD in as many as 60% of the patients while globus related to GERD is in up to 50% of them.<sup>7</sup> Additionally, laryngeal cancer may be associated with GERD.<sup>8</sup> Recent studies suggested that gastroesophageal reflux could play a role in chronic cough, but the role of reflux in chronic laryngitis and asthma was uncertain.<sup>9,10</sup> Laryngopharyngeal reflux (LPR) may be different from classic GERD in that LPR patients have head and neck symptoms, but heartburn is uncommon and most do not have esophagitis.<sup>11</sup>

There is no gold standard for establishing the association between GERD and extraesophageal manifestation of GERD because many of the extraesophageal manifestations may have a va-

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riety of etiologies. Although patients with the typical reflux syndrome or endoscopically reflux esophagitis are easy to recognize, not all patients have reflux complaints, and considerably less than 50% have reflux esophagitis.<sup>12</sup> Many patients with suspected extraesophageal manifestations of GERD have no typical signs; especially the diagnostic yield of endoscopy seems to be low. Concomitant typical GERD symptoms of heartburn and regurgitation were present in nearly half the subjects. Esophageal mucosal injury was present in only 18% of subjects.<sup>13</sup> Data is scarce regarding its prevalence and clinical characteristics in patients with extraesophageal symptoms in Asia. In this issue of *Journal of Neurogastroenterology and Motility*, Yi et al<sup>14</sup> described that atypical symptoms appeared to be associated with the presence of typical reflux symptoms irrespective of endoscopic and histological reflux esophagitis. In this study, they investigated the association between typical symptoms and atypical symptoms among GERD patients which was divided into 2 groups, erosive reflux disease (ERD) and non-erosive reflux disease (NERD). They showed that atypical symptoms including non-cardiac chest pain, dysphagia, globus, cough, hiccup and belching were common in patients with ERD as well as NERD. This result was similar to another study which demonstrated 74% of GERD patients had atypical symptoms and their distribution was approximately equal in those with ERD and with NERD.<sup>15</sup> A peculiar observation is that the authors did the endoscopy with biopsy in order to find out the association of histological esophagitis and clinical manifestations in GERD patients. The presence of basal cell hyperplasia and papillary elongation is considered as a hallmark of reflux esophagitis and histology is an accurate and reliable tool for detecting microscopic inflammatory and regenerative lesions in patients with GERD.<sup>16,17</sup> The results showed that histological esophagitis was found in half of the patients in proximal and distal esophagus, and occurred equally in patients with ERD and NERD. Neither histological nor endoscopic esophagitis was related to the presence of atypical symptoms.

Treatment benefit for extraesophageal manifestations of GERD is not satisfactory, since these conditions are multifactorial in etiology. Meta-analysis showed that proton pump inhibitors for cough associated GERD probably have some effect in some adults, though the effect is not universal.<sup>18</sup> The predictors of pharyngeal acid reflux such as typical reflux symptoms, hiatal hernia and overweight were suggested in Taiwanese patients with suspected reflux laryngitis.<sup>19</sup> Vaezi et al<sup>20</sup> concluded that the twice-daily esomeprazole 40 mg therapy was of no therapeutic benefit on signs and symptoms associated with LPR compared

with placebo for 16 weeks. However, this study excluded the subjects with typical symptoms in their study. Another study showed opposite results. In a double blind, placebo controlled trials of suspected reflux laryngitis with typical symptoms, twice-daily esomeprazole 20 mg therapy was effective for symptoms and signs associated with LPR compared to placebo.<sup>21</sup> Atypical GERD symptoms improved significantly as typical symptoms after laparoscopic antireflux surgery.<sup>22</sup> The potential benefit of anti-reflux surgery should be weighed against its potential morbidity.

In summary, as the incidence of GERD is increasing, atypical symptoms are considered to be increasing as well. This study can be used as an important data for understanding the clinical characteristics of atypical symptoms in GERD patients. Much more studies are needed regarding this field in Asia.

## References

1. Locke GR 3rd, Talley NJ, Fett SL, Zinsmeister AR, Melton LJ 3rd. Prevalence and clinical spectrum of gastroesophageal reflux: a population-based study in Olmsted County, Minnesota. *Gastroenterology* 1997;112:1448-1456.
2. Jung HK. Epidemiology of gastroesophageal reflux disease in Asia: a systematic review. *J Neurogastroenterol Motil* 2011;17:14-27.
3. Vakil N, van Zanten SV, Kahrilas P, Dent J, Jones R; Global Consensus Group. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. *Am J Gastroenterol* 2006;101:1900-1920.
4. Quigley EM, Hungin AP. Review article: quality-of-life issues in gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 2005; 22(suppl 1):41-47.
5. Oh JH, Kim TS, Choi MG, et al. Relationship between psychological factors and quality of life in subtypes of gastroesophageal reflux disease. *Gut Liver* 2009;3:259-265.
6. Morice AH. Epidemiology of cough. *Pulm Pharmacol Ther* 2002; 15:253-259.
7. Vaezi MF. Sensitivity and specificity of reflux-attributed laryngeal lesions: experimental and clinical evidence. *Am J Med* 2003;115 (suppl 3A):97S-104S.
8. Vaezi MF, Qadeer MA, Lopez R, Colabianchi N. Laryngeal cancer and gastroesophageal reflux disease: a case-control study. *Am J Med* 2006;119:768-776.
9. Moore JM, Vaezi MF. Extraesophageal manifestations of gastroesophageal reflux disease: real or imagined? *Curr Opin Gastroenterol* 2010;26:389-394.
10. Kotby MN, Hassan O, El-Makhzangy AM, Farahat M, Milad P. Gastroesophageal reflux/laryngopharyngeal reflux disease: a critical analysis of the literature. *Eur Arch Otorhinolaryngol* 2010;267:171-179.
11. Koufman JA. Laryngopharyngeal reflux is different from classic gastroesophageal reflux disease. *Ear Nose Throat J* 2002;81(9 suppl 2): 7-9.
12. Labenz J. Facts and fantasies in extra-oesophageal symptoms in

- GORD. *Best Pract Res Clin Gastroenterol* 2010;24:893-904.
13. Fletcher KC, Goutte M, Slaughter JC, Garrett CG, Vaezi MF. Significance and degree of reflux in patients with primary extra-esophageal symptoms. *Laryngoscope* 2011;121:2561-2565.
  14. Yi CH, Liu TT, Chen CL. Atypical symptoms in patients with gastroesophageal reflux disease. *J Neurogastroenterol Motil* 2012;18:278-283.
  15. Dore MP, Pedroni A, Pes GM, et al. Effect of antisecretory therapy on atypical symptoms in gastroesophageal reflux disease. *Dig Dis Sci* 2007;52:463-468.
  16. Ismail-Beigi F, Horton PF, Pope CE 2nd. Histological consequences of gastroesophageal reflux in man. *Gastroenterology* 1970;58:163-174.
  17. Zentilin P, Savarino V, Mastracci L, et al. Reassessment of the diagnostic value of histology in patients with GERD, using multiple biopsy sites and an appropriate control group. *Am J Gastroenterol* 2005;100:2299-2306.
  18. Chang AB, Lasserson TJ, Kiljander TO, Connor FL, Gaffney JT, Garske LA. Systematic review and meta-analysis of randomised controlled trials of gastro-oesophageal reflux interventions for chronic cough associated with gastro-oesophageal reflux. *BMJ* 2006;332:11-17.
  19. Lien HC, Wang CC, Hsu JY, et al. Classical reflux symptoms, hiatus hernia and overweight independently predict pharyngeal acid exposure in patients with suspected reflux laryngitis. *Aliment Pharmacol Ther* 2011;33:89-98.
  20. Vaezi MF, Richter JE, Stasney CR, et al. Treatment of chronic posterior laryngitis with esomeprazole. *Laryngoscope* 2006;116:254-260.
  21. Reichel O, Dressel H, Wiederänders K, Issing WJ. Double-blind, placebo-controlled trial with esomeprazole for symptoms and signs associated with laryngopharyngeal reflux. *Otolaryngol Head Neck Surg* 2008;139:414-420.
  22. Brown SR, Gyawali CP, Melman L, et al. Clinical outcomes of atypical extra-esophageal reflux symptoms following laparoscopic antireflux surgery. *Surg Endosc* 2011;25:3852-3858.