



Original article

Gastroesophageal dysmotility is associated with the impairment of cough-specific quality of life in patients with cough variant asthma



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Abbreviations:

AHR, Airway hyperresponsiveness;

CVA, Cough variant asthma;

FeNO₅₀, Fractional exhaled nitric oxide at 50 mL/s; FEV₁, Forced expiratory volume in 1 s; FSSG, Frequency scale for the symptoms of gastroesophageal reflux; FVC, Forced vital capacity; GERD, Gastroesophageal reflux disease; IgE, Immunoglobulin E;

LCQ, Leicester Cough Questionnaire;

QoL, Quality of life; Rrs, Respiratory resistance; VAS, Visual analog scales

ABSTRACT

Background: Gastroesophageal reflux disease (GERD) is known as a common comorbidity of asthma and chronic cough. The impact of GERD symptoms on cough-specific quality of life (QoL) in patients with asthmatic cough is poorly understood. The aim of this study is to determine the association of GERD symptoms with cough-specific quality of life in patients with cough variant asthma (CVA) using the Leicester Cough Questionnaire (LCQ).

Methods: A total of 172 consecutive patients (121 females) with mean cough duration of 45.1 months (range 2–480 months) completed the Japanese version of the LCQ. The Frequency Scale for the Symptoms of Gastroesophageal reflux was administered to assess symptoms of acid-reflux and dysmotility. A range of clinical variables that may determine cough-specific QoL (LCQ) were estimated.

Results: The mean LCQ scores was 12.9 (SD 3.5), consistent with severe impairment in QoL. Female gender, symptoms of gastroesophageal dysmotility, sensitization to allergens (house dust and Japanese cedar pollen) and the number of sensitized allergens were associated with lower LCQ scores (i.e. impaired cough-specific QoL) in univariate regression analysis. Acid-reflux symptoms, airway hyperresponsiveness, fractional exhaled nitric oxide, and sensitization to molds were unrelated to the LCQ score. After adjustment for gender, symptoms of gastroesophageal dysmotility was the only significant determinant of impaired cough-specific QoL accounting for 23% of the variance.

Conclusions: Cough-specific QoL is severely impaired in patients with CVA. Symptoms of gastroesophageal dysmotility are an independent predictor of cough-specific QoL of patients with CVA.

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Introduction

Cough is a very common complaint for which patients seek medical attention. Although most cases are acute and self-limiting, some patients develop chronic cough that persists for 8 weeks or longer and are referred to specialists because chronic

cough is associated with impairment of health-related quality of life (QoL).¹ Cough variant asthma (CVA) is considered one of the most common causes of chronic cough worldwide.^{2–6} The factors that contribute to the impairment of cough-specific QoL in patients with CVA or asthmatic cough are only partly understood. In studies of patients with asthma, cough-specific QoL assessed with the Leicester Cough Questionnaire (LCQ) was associated with objective cough counts,⁷ but not with pathophysiological parameters such as airway hyperresponsiveness (AHR), airway inflammation and pulmonary function.⁸ The impact of other potentially relevant factors on cough-specific QoL such as gastroesophageal reflux disease (GERD) and atopy have not been studied. The

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identification of important comorbidities may lead to a more targeted therapeutic approach.

GERD is another common cause of chronic cough.⁹ GERD coexists frequently in difficult-to-treat patients with asthma and CVA.^{10,11} In a survey of a general population, symptoms of regurgitation and irritable bowel syndrome, but not heart burn, were significantly associated with the presence of chronic cough, suggesting that gastroesophageal dysmotility may be more importantly associated with chronic cough than acid reflux.¹²

The Frequency Scale for the Symptoms of GERD (FSSG) is a questionnaire which has been developed for not only diagnosis but also evaluation of the treatment response of GERD.¹³ It covers the 12 most common symptoms of GERD consisting of 2 domains: acid-reflux symptoms and dysmotility symptoms. Previous study has demonstrated association of endoscopic¹³ and manometric¹⁴ findings with FSSG scores. Thus, the FSSG could be a simple and useful tool to assess symptoms of GERD in clinical and research fields of respiratory medicine.^{15–18}

The aim of this study was to determine the impact of GERD symptoms on cough-specific QoL in patients with CVA. This involved the development and validation of a Japanese version of the LCQ.

Methods

Patients

Among patients who visited the Asthma and Chronic Cough Clinic of Kyoto University Hospital between July 2009 and December 2012, 260 patients were newly diagnosed as having CVA. This was according to the Japanese Respiratory Society guidelines for management of cough on the basis of isolated cough persisting for 8 weeks or longer without dyspnea or wheezing, no remarkable findings on chest X-ray and auscultation on the lung, presence of AHR to inhaled methacholine and improvement of coughing in response to inhaled short-acting β_2 agonists (SABA).³ Double-blind controlled study conducted by Irwin *et al.* clearly demonstrated that improvement of cough with bronchodilators such as SABA was the essential diagnostic feature of CVA.¹⁹ The patients had no history of typical asthma with wheezing, or upper respiratory infection within the previous 8 weeks. A total of 88 patients were excluded from the study because they were current smokers or ex-smokers who had smoked within 6 months or had a smoking history of more than 10 pack-years, failed to complete the LCQ or the FSSG or had been taking inhaled corticosteroids within 4 weeks prior to the first visit. As a result, the study involved 172 patients (121 females) in a cross-sectional design. This study was approved by the ethics committee of Kyoto University (Approval number E715), and was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of the Japanese government (23591117). Written informed consent was obtained from all participants.

Measurements of clinical indices

Patients underwent spirometry and measurement of AHR, fractional exhaled nitric oxide (FeNO), blood eosinophil counts and serum levels of total/specific IgE. They also filled in the LCQ and the FSSG questionnaires. Spirometry was performed using a Chest-Graph HI-701 spirometer (Chest MI Corp, Tokyo, Japan) according to the current guidelines.²⁰ AHR was examined by a continuous methacholine inhalation with simultaneous measurement of respiratory resistance (Rrs) (cmH₂O/L/s) (Astograph; Chest, Tokyo, Japan) as described previously.²¹ FeNO levels were measured at an expiratory flow rate of 50 mL/s with a chemiluminescence analyzer

(NOA 280; Sievers, Boulder, CO, USA) according to current guidelines.²² Specific IgE titers were measured against nine allergens: house dust, *Dermatophagoides pteronyssinus*, Japanese cedar pollen, mixed gramineae pollens (orchard grass, sweet vernal grass, bermuda grass, timothy, reeds), mixed weed pollens (ragweed, mugwort, goldenrod, dandelion, oxeye daisy), mixed moulds (*Penicillium*, *Cladosporium*, *Aspergillus*, *Candida*, *Alternaria*), cat dander, dog dander, and *Trichophyton rubrum*) (ImmunoCAP®; Phadia K.K., Tokyo, Japan). Specific IgE levels ≥ 0.35 UA/mL were considered positive. If patients had one or more sensitized allergens, they were considered as having atopic predisposition.

Measurement of cough-specific QoL and cough severity

Cough-specific QoL was evaluated using the LCQ, which was translated into Japanese. The Leicester Cough Questionnaire (LCQ) is a validated questionnaire that evaluates the degree of chronic cough and reflects cough-specific QoL.²³ It consists of 19 questions covering 3 subdomains (physical, social, and psychological); the total scores range from 3 to 21, with the higher scores indicating better QoL.²³ We performed forward and backward translation according to The International Quality of Life Assessment protocol.²⁴ Briefly, two Japanese specialists of cough, both of who are familiar with English, produced the Japanese version of the LCQ (first forward translation). Followed by first backward translation conducted by a professional English editor who belongs to Forte corporation (Tokyo, Japan), the original developer (SSB) checked it and pointed out problems. Based on the original developer's comments, some parts of the original questionnaire were retranslated into Japanese (second version of the forward translation). After this version was re-translated into English again, original developer rechecked it and confirmed that intended questions did not change.^{23,24} The Japanese translators including one of the present authors (AN) were authorized to do the translation of the LCQ and to have the copyright for the Japanese version of LCQ by the original author.²³ Previous studies demonstrated significant correlations between the LCQ and objective cough monitoring.^{7,25}

The use of LCQ questionnaire was permitted by the original developer (SSB)

In addition to the LCQ, cough visual analog scales (VAS) and numeric cough scores,²⁶ both of which have been used to measure the severity and frequency of cough, have been also determined since January 2012. Cough VAS is a 100 mm-line scale where its length represents the severity of cough^{7,25} (i.e. 0 mm = no cough, 100 mm = worst cough imaginable). Numeric cough scores were developed by Hsu *et al.*²⁶ ranging from 0 to 5 reflect the cough frequency and severity in the daytime and nighttime.^{7,25,26} Lower score indicates less severe or less frequent coughing.

The GERD questionnaire

GERD symptoms were evaluated using the original version of self-reporting FSSG questionnaire originally developed in Japan,¹³ which was validated on the basis of endoscopic findings. It consists of the most prevalent 12 symptoms chosen from 50 symptoms of GERD. Each symptom was scored according to its frequency as follows: 0 = never, 1 = occasionally, 2 = sometimes, 3 = often, and 4 = always.¹³ The maximum scores of the acid-reflux symptoms domain (comprised of 7 items), dysmotility symptoms domain (comprised of 5 items), and the total of both were 28, 20, and 48 points, respectively.¹³ A previous study demonstrated that esophageal peristaltic pressures during dry swallow which were measured using a manometry catheter via a transnasal endoscope

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