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Chronic cough in Korean adults: a literature review on common comorbidity

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Chronic cough is a significant medical condition with high prevalence and a strong negative impact on the quality of life. Cough hypersensitivity is thought to underlie chronic cough, with several environmental and host factors interacting to cause neuronal sensitization and chronicity. Comorbid conditions affecting cough reflex pathways, such as upper airway diseases, asthma, and gastroesophageal reflux, play important roles in chronic cough. However, their prevalence may vary in patients living in different geographical regions or with different ethnicities. We conducted a literature review to examine common comorbidities in Korean adult patients with chronic cough, their clinical implications, and the issues that still need to be addressed in the development of clinical evidence of chronic cough in Korean adult patients.

Key words: Asthma; Chronic cough; Epidemiology; Korea; Rhinitis

INTRODUCTION

Cough is a normal defensive mechanism to protect the lower airways [1], but it is also a common troublesome symptom leading to medical consultation [2]. Although criteria to differentiate between 'normal' and 'abnormal' cough are still not clearly defined, clinical observations suggest that cough in patients seeking medical attention is predominantly 'hypersensitive' in nature [3-6]. These patients typically complain that their cough is triggered by trivial or low levels of stimuli, such as perfume, cold air, or talking. 'Cough hypersensitivity syndrome,' as it is now termed, can be demonstrated in tussigen inhalation challenge tests using capsaicin or citric acid [7, 8] and is thought to underlie the phenomenon of abnormal troublesome cough [9-11].

A common example of cough hypersensitivity is upper

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respiratory tract infection (URTI) by rhinovirus [12]. Human neuronal cells infected by rhinovirus can exhibit up-regulated expression of transient receptor potential (TRP) ion channels [13]. Whether cough hypersensitivity in viral infection benefits the virus (facilitating its transmission) or the host (rapid viral clearance) is unknown, but it is mostly self-limiting, disappearing within 2 weeks. In some individuals with URTI, cough hypersensitivity may persist somewhat longer; this postinfectious cough consists of a large proportion of subacute cough (3–8 weeks in duration) patients [14]. However, hypersensitive cough frequently does not remit and may persist for months or years, which is termed as 'chronic cough' (≥8 weeks in duration). Chronic cough is a significant medical condition with a high prevalence and a strong negative impact on the quality of life [15, 16].

Several factors are postulated to underlie the chronicity of cough hypersensitivity. Important among these are comorbidities that affect cough reflex pathways [15]. In the lower airways, type 2 or allergic inflammation, which is frequently found in asthma, can induce a phenotypic switch in sensory neurons and induce cough hypersensitivity [16]. Eosinophilic airway inflammation is associated with chronic cough, even in the absence of asthma [17]. Upper airway inflammation may not directly sensitize vagal pathways but it can modulate cough sensitivity [18, 19]. Additionally, gastroesophageal reflux can cause or trigger cough hypersensitivity, via neuronal sensitization [20]. These are major conditions of high prevalence and clinical relevance in patients with chronic cough, and their identification and management contribute to cough resolution. Accordingly, these comorbidities are regarded as priority targets in the diagnostic pathways specified in international guidelines for chronic cough [21, 22].

However, the prevalence of major comorbid conditions may vary by region. For example, gastroesophageal reflux disease (GERD) is seen in 10%–30% of chronic cough patients in Western populations but in <10% of those in East Asian populations [23]. Cough variant asthma (or asthma-related cough) is commonly prevalent in both groups. Upper airway cough syndrome, also called postnasal drip syndrome or rhinitis/rhinosinusitis-related cough, also has a variable but relatively high prevalence [23]. In our recent review of Asian studies, infectious diseases such as pulmonary tuberculosis and paragonimiasis were identified as important causes of chronic cough in several South and Southeast Asian countries [24]. While the geographic differences reported in the literature may partly result from methodological heterogeneities among studies, they also suggest the necessity to tailor diagnostic pathways to the relevant geographical or ethnic population.

In Korea, chronic cough is reported to have a prevalence of 3%–5% in community-based adult populations [25, 26]. A questionnaire survey found that physicians recognized upper airway diseases and asthma as major conditions associated with chronic cough in Korean patients [27]. Previous individual studies also cited these two common conditions among Korean adult patients [28-30], in contrast to the low prevalence of GERD-related cough (1.7%) (9 of 531). The latter was determined in a study that included 24-hour ambulatory esophageal pH monitoring [30]. Given the population- and time-dependent variations in the prevalence of comorbid conditions, we conducted a literature review to identify the as-yet unaddressed issues that should be taken into account in the clinical assessment of Korean adult patients with chronic cough.

LITERATURE SEARCH

The PubMed and KoreaMed databases were searched to identify studies on the clinical epidemiology of chronic cough in Korean adult patients. Publications were selected if they reported the prevalence of major comorbid conditions (asthma, upper airway diseases, or GERD) or infectious diseases within the chronic cough population, either as a primary or secondary outcome. A manual search was conducted using Google. The search was updated until September 2016, and the publication language was not restricted.

COMMON COMORBIDITIES IN ADULT PATIENTS WITH CHRONIC COUGH IN KOREA

The 18 studies published between 1995 and 2014 (Table 1) [5, 28-44] were conducted at referral clinics at the level of single university hospitals. As these studies varied with respect to study period and purposes, they differed widely in both their definition of chronic cough and their inclusion criteria. Three different cutoff criterion were used to define chronic cough: ≥3 weeks (n = 11), ≥8 weeks (n = 5), and ≥4 weeks (n = 2). Common inclusion criteria were normal chest X-rays, no history or underlying lung diseases, and no evidence of drug-induced cough.

Nonetheless, because there were considerable differences in

Table 1. Prevalence of major comorbid conditions among adult chronic cough patients in Korea

Source	Setting	No. of participants	Definition (wk)	Inclusion criteria	Female (%)	Comorbid conditions (%)			
Yoo 1995 [31]	Referral clinic*	69	≥8	A, B, C, D, E, F, G	62.3	Asthma (42)	Others (58)	-	-
Kim 1997 [33]	Referral clinic*	46	≥3	A, G	24.0	Upper airway diseases (35)	Unexplained (25.9)	Bronchitis (21.7)	Asthma (17.4)
Cho 1997 [32]	Referral clinic*	92	≥3	A, B, C	65.2	Asthma (47.8)	Unexplained (29.3)	Upper airway diseases (10.9)	Upper airway diseases with asthma (8.7)
Oh 1997 [34]	Referral clinic*	44	≥3	A, E	71.7	Asthma (45.5)	Others (44.5)	-	-
Jee 1998 [28]	Referral clinic*	105	≥3	A, E	NA	Upper airway diseases (39.7)	Asthma (32.2)	GERD (14.1)	Unexplained (5) Bronchitis (5)
Cho 1999 [35]	Referral clinic*	93	≥3	A, E	61.0	Upper airway diseases (52)	Bronchitis (16)	Asthma (11)	Upper airway diseases with asthma (8)
Cho 2002 [36]	Referral clinic*	77	≥3	A, B, C, D, F	63.6	Upper airway diseases (42.9)	Unexplained (38.9)	Asthma (18.2)	-
Joo 2002 [29]	Referral clinic*	92	≥3	-	NA	Upper airway diseases (33)	Asthma (16)	Chronic bronchitis (15)	EB (12)
Lee 2004 [38]	Referral clinic*	382	≥3	A, B, E, F, G	63.9	Upper airway diseases (37.4)	Post-infectious (29.1)	Asthma (17.3)	EB (8.4)
Jeon 2004 [37]	Referral clinic*	60	≥8	A, B, E, F	60.0	Unexplained (45)	Upper airway diseases (23.3)	Asthma (21.6)	EB (6.7)
Kwon 2005† [30]	Referral clinic*	531	≥3	A, C, D, F	NA	Upper airway diseases or post-infectious (37.5)	Asthma (28.8)	Unexplained (11.1)	EB (6.8)
Lee 2006 [39]	Referral clinic*	69	≥8	A, B, E, F, G	58.3	Unexplained (53.6)	Upper airway diseases (23.2)	EB (18.8)	Asthma (13.0)
Lee 2007 [40]	Referral clinic*	378	≥4	A, F	51.0	Upper airway diseases (67.5)	Asthma (38.1)	GERD (7.8)	-
Shin 2009 [41]	Referral clinic*	1518	≥8	-	55.9	Asthma (33.6)	Upper airway diseases (27.3)	Chronic bronchitis (14.2)	COPD (2.6)
Chun 2010 [42]	Referral clinic*	68	≥3	A, B	72.0	Unexplained (33.8)	Upper airway diseases (26.5)	EB (20.6)	Asthma (16.2)
Kim 2010 [43]	Referral clinic*	37	≥4	D, E	67.6	Asthma (48.6)	Others (51.4)	-	-
Kim 2012 [44]	Referral clinic*	811	≥3	A, E	69.9	Unexplained (29.8)	Upper airway diseases (23.8)	EB (14.4)	EB with Upper airway diseases (13.4)
Song 2014‡ [5]	Referral clinic*	272	≥8	A, E	69.1	Unexplained (29)	EB with upper airway diseases (25)	Upper airway diseases (24)	EB (15)

A, normal radiological findings; B, normal pulmonary lung function; C, nonsmoker; D, noninfectious condition; E, no underlying lung disease; F, no history of drug-induced cough; G, no abnormal lung auscultation (wheezing or rale); PNDS, postnasal drip syndrome; UACS, upper airway cough syndrome; CVA, cough variant asthma; EB, eosinophilic bronchitis; GERD, gastroesophageal reflux disease; ACEI, angiotensin converting enzyme inhibitor; NA, not available.

*Referral clinic at a university hospital. †Incidence rates were calculated based on the result of article. ‡Incidence rates were calculated based on the result of raw data.

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the diagnostic criteria, particularly for upper airway disease (Table 2), we arbitrarily categorized postnasal drip syndrome, upper airway cough syndrome, and rhinitis- or rhinosinusitis-associated cough as 'upper airway diseases.' Cases in which there were no identifiable comorbid conditions (originally termed as 'idiopathic cough' or 'nondiagnostic case') were categorized as 'unexplained cough'. Overall, upper airway diseases and asthma (including eosinophilic bronchitis [EB]) were the most two common conditions, occurring in 40%–90% of the study populations (Table 1, Fig. 1).

Upper airway diseases

In Korean studies, upper airway diseases had a prevalence of 23.3%–67.5% and were thus more common than other conditions. However, because the definition of these diseases is largely based on subjective findings or empirical treatment responses, the exact proportion of upper-airway-disease-associated cough is difficult to establish. Moreover, this category includes several upper airway disease conditions [45], and each of which may have a distinct pattern of cough association. Direct causal relationships between upper airway diseases and cough have been questioned [46, 47]; however, experimental studies suggest that upper airway conditions can up- or down-regulate cough hypersensitivity [18] and general population studies support a positive associations across age groups in various countries including Korea [26, 48-50].

Asthma and EB

Asthma occurs in 6.3%–56.5% of chronic cough patients in Korea, and three studies that focused on 'asthma only' reported prevalence rates as high as 42%–48.5% [31, 34, 43]. A comparison of two series of analysis performed at the same cough clinic at a single tertiary institution (2007–2011 and 2012–203) revealed a decrease in the prevalence of asthma from 18.5% (2007–2011) to 6.3% (2012–2013) [5, 44]. Whether this decreasing trend at the tertiary clinic was due to an increase in asthma screening activity at primary or secondary clinics is unclear.

EB is a clinical condition characterized by eosinophilic

Table 2. Diagnostic criteria for major comorbid conditions with chronic cough among previous Korean adult studies

Source	No.	Upper airway diseases	Asthma	GERD	Diagnostic test for GERD
Yoo 1995 [31]	69	A, C	E		
Kim 1997 [33]	46	A, B	E		
Cho 1997 [32]	92	A, B, C	E	A, D	
Oh 1997 [34]	44		E		
Jee 1998 [28]	105	A, B, C	E	A	
Cho 1999 [35]	93	A, B, C	A, E	A, F	24-Hour esophageal pH monitoring
Cho 2002 [36]	77	A, C, D	E	A, D	
Joo 2002 [29]	92	A, B, D	E	A, D	
Lee 2004 [38]	382	A, B, D		F	24-Hour esophageal pH monitoring
Jeon 2004 [37]	60		A, E, G		
Kwon 2005† [30]	531	A, B, D	A, D, E	A, F	24-Hour esophageal pH monitoring
Lee 2006 [39]	69	C	A, E, G		
Lee 2007 [40]	378	B, D	D, E	D	
Shin 2009 [41]	1518	C, D	D, E	F	Esophagogastroduodenoscopy
Chun 2010 [42]	68	A, B	D, E		
Kim 2010 [43]	37		A, E, G		
Kim 2012 [44]	811	A, B, C	E		
Song 2014 [5]	272	A, B, C	E		

A, constellation of symptoms; B, positive physical examination; C, radiographic findings; D, clinical response to treatment; E, positive objective test; F, positive test of reflux; G, previous diagnosis by physician; GERD, gastroesophageal reflux disease.

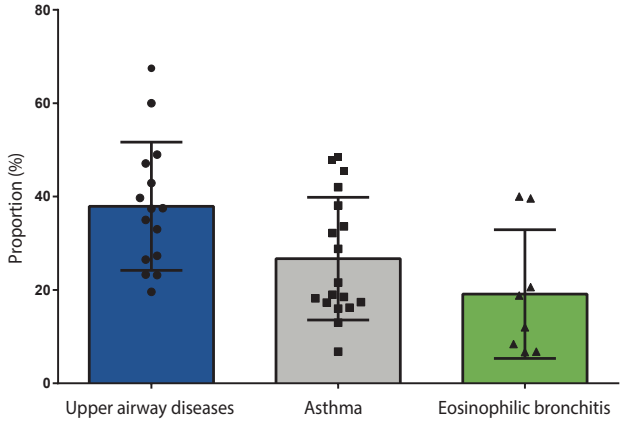

Fig. 1. Common comorbid conditions in Korean adult patients with chronic cough.

inflammation in nonasthmatic lower airways [17]. Its identification is highly relevant, as these patients respond very rapidly to corticosteroid therapy (within 1 or 2 weeks of treatment initiation) [17, 51]. In eight Korean studies of EB, the prevalence of the disease ranged from 5.4%–40.8%, which is similar to rates in other countries, either Asian or Western. The prevalence of nonasthmatic EB in Western population, such as United Kingdom, Australia, or Turkey, was 7%–33% [52-57]. A recent multicenter study in China (n = 704) reported that the prevalence of nonasthmatic EB among chronic cough patients was 17.2% [58]. EB frequently overlaps with upper airway diseases, as demonstrated in a single-center study in Korea, where the comorbid rate of upper airway diseases among non-asthmatic EB patients was 59.3% [59].

The summed prevalence of asthma and EB was 25.7%–47%. As both diagnoses are based on the findings of objective tests, their high prevalence rates support early objective investigation or empirical treatment for both conditions in Korean patients. However, conventional diagnostic tests such as methacholine challenge and induced sputum tests are not feasible in most clinical settings. Instead, simple diagnostic tests, such as fractional exhaled nitric oxide (FeNO) measurement [60] or blood eosinophil determination, could aid in identifying asthmatic or eosinophilic cough patients who are likely to respond to corticosteroid therapy [61-63].

Gastroesophageal reflux disease

Several studies reported the prevalence of GERD in Korean cough patients, but this was mostly determined using subjective criteria. One study carried out 24-hour esophageal pH monitoring and found that only 1.7% of patients had acid-reflux-associated cough [30]. East Asian studies have reported a low prevalence of GERD-related cough (2% in a Japanese study and 10% in a Chinese study) [58, 64], but in Western population studies the prevalence is as high as 36% [23]. This regional or ethnic difference has been attributed to different degrees of obesity or to different diets. In a Korean elderly community population survey, the prevalence rates of clinically diagnosed GERD and obesity (defined as body mass index ≥ 30 kg/m^2) were only 1.1% and 3.8%, respectively, and neither condition was significantly related to chronic cough [26, 65]. However, in the UK adult population, the prevalence rates of regurgitation and obesity were 15% and 20%, respectively; moreover, reflux was significantly associated with chronic cough [66]. As the prevalence of reflux disease has been increasing in the Korean population [67], the epidemiology of reflux-related cough will probably change in the coming years.

Infection-related cough

Several studies have examined the prevalence of pertussis among adult patients with cough, but not specifically for chronic cough. In earlier clinical study conducted at an outpatient clinic of a large university hospital in 2002–2003, only 2.9% of 102 adult patients with persistent cough (1- to 12-week duration) had positive polymerase chain reaction (PCR) for Bordetella pertussis [68]. In a multicenter study of 607 adult patients with bothersome cough (≥2 weeks) who were recruited from nonoutbreak, ordinary outpatient settings in 2009–2011, the positivity rate for pertussis on PCR was 0.7% [69]. In another study of 310 adolescent and adult patients with cough of 1- to 8-week duration (in Seoul and Incheon, 2009–2011), the pertussis positivity rate in culture, PCR, and serology tests was 1.0%, 3.2%, and 24.5%, respectively [70]. A case-control study found a positive association between acute Chlamydia pneumoniae infection and chronic cough [71]. However, in another study, only 1 of 68 patients with cough ≥3 weeks had a positive PCR for Chlamydia [42]. Prevalence of pulmonary tuberculosis or paragonimiasis infection among Korean adult patients with chronic cough is not reported. Among Korean patients (n = 36) with pulmonary paragonimiasis, 47% had cough [72]. As these studies did not specifically focus on chronic cough, their findings warrant further investigation of infection-related cough in the chronic cough population.

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Smoking, medication, and lung parenchymal diseases

Cigarette smoke is an irritant and can activate TRPA1 channels [73]; it is thus considered a risk factor for cough. In experimental studies, guinea pigs exposed to cigarette smoke had heightened cough responses to capsaicin inhalation [74]. In general population studies, the prevalence of chronic cough was correlated significantly with the current smoking rate at the population level [75]. Conversely, in a 1-year Danish population-based intervention study, the cessation of smoking significantly reduced the rate of self-reported chronic cough [76]. According to the Korean National Health and Nutrition Examination Survey (KNHANES) 2010–2012, the current smoking rate in Korea is ~25% in the general population but twofold higher among individuals with current cough, indicating a significant relationship between cigarette smoking and current cough [77].

Angiotensin converting enzyme (ACE) inhibitor can up-regulate cough sensitivity [7]. The prevalence of ACE-induced cough was reported as 1.9% in an earlier study of Korean patients (1995–1996) [28]. However, as later studies commonly excluded those receiving ACE inhibitors as the selection criteria [5, 30, 37-39, 42], its recent prevalence is unclear.

Chest X-rays are recommended at the initial stage of the diagnostic work-up for cough [21, 22], but the prevalence of lung parenchymal diseases among patients seeking medical consultation for chronic cough was difficult to obtain in the present review. However, the KNHANES 2010–2012 analysis reported that the rate of any chest X-ray abnormality was 9.2% among adults without current cough vs. 18.7% among those with current chronic cough [77].

Unexplained cough

The reported prevalence of unexplained cough varies widely, from 5%–53%. However, given the considerable heterogeneity in diagnostic procedures and in the definitions of unexplained cough (idiopathic cough or nondiagnostic case) between studies, its prevalence cannot be reliably estimated. Rather, these findings point out the need for a consensus definition of unexplained cough and for prospective investigations to accurately determine the proportion of affected patients in Korea.

CLINICAL IMPLICATIONS AND ISSUES STILL TO BE ADDRESSED

In this brief review, we examine the proportion of common comorbid conditions in Korean adult patients with chronic cough and identified the clinical implications as well as the issues to be addressed in further studies. These can be stated as follows:

- Upper airway diseases, asthma, and EB are by far the most frequent conditions accounting for 40%–90% of the study populations in Korea. These 3 conditions should thus be considered priority targets in developing clinical evidence and diagnostic pathways for Korean adult patients with chronic cough.
- A diagnostic approach for asthma and EB would be helpful in the early stage of investigation, as the two conditions were reported by 25.7%–47% of the patients and can be objectively diagnosed. However, conventional diagnostic methods, such as methacholine challenge and induced sputum tests, are not available in most clinical settings. Alternative diagnostic algorithms utilizing convenient tests, such as FeNO or blood eosinophil counts, need to be developed.
- GERD- and infection-related cough had low prevalence rates (<5% overall) but their epidemiology may change with time or outbreak and continuous updates are necessary. Meanwhile, the burden of infection-related cough needs to be examined specifically in the chronic cough population.
- All previous Korean studies were conducted at referral clinics. Further studies at primary care level would help to develop clinical pathways for primary physicians.
- Development of a consensus definition for 'unexplained cough' will improve our understanding of the intrinsic mechanisms of cough hypersensitivity.
- Standardization of diagnostic protocols and definition will facilitate the development of clinical evidence in Korean patients with chronic cough.

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