

Current Review



Impact and disease burden of chronic cough

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ABSTRACT

Cough is an important physiological mechanism to protect the lower airways, but it is also one of the most common symptoms that lead patients to seek medical consultations. Chronic cough, usually defined by cough duration longer than 8 weeks in adults, is prevalent in the community and impairs quality of life in individual patients. There are several characteristics that may differentiate pathologic coughs from protective cough responses, including cough duration, frequency, hypersensitivity, impaired cough suppressibility, or treatment refractoriness. However, the impact of cough, or its perceived severity, is a sum of the patient's experience of coughing and is a factor that may finally define cough as a disease. Social isolation is a major impact of chronic cough, which is now worse due to the coronavirus disease 2019 pandemic and a widespread fear of cough as a source of contagion. Emotional impact and economic impact (medical cost, reduced work productivity, and job loss) are also important complications of chronic cough, and they interact in a vicious cycle, aggravated by social isolation and treatment failures. This paper is a narrative review that aims to address the impact and disease burden of chronic cough in adult patients. We review the literature, but also introduce the findings from recent qualitative interviews and the patients' experiences of the impact and burden of chronic cough and discuss unmet needs in these patients.

Keywords: Cough; Quality of life; Cost of illness

INTRODUCTION

When cough becomes a disease? Cough is a crucial physiological reflex to protect airways against aspiration, but also it is one of the most frequent symptoms that lead patients to seek medical services [1]. Therefore, implications of coughing, either protective or harmful, should vary with clinical context.

Traditionally, cough duration is commonly used to define a pathologic cough condition, as chronic cough (usually defined by cough duration longer than 8 weeks in adults) is less likely to be self-limiting in nature and warrants active interventions [2-4]. However, the cutoff duration of 8 weeks is arbitrary [3], and it alone may not well differentiate pathologic coughs from protective cough responses to environmental irritant exposure [5].

Recently, the concept of cough hypersensitivity syndrome (CHS) was proposed by the European Respiratory Society Taskforce in 2014 [6], and hypersensitivity in the cough reflex has been suggested to be the key mechanism underlying chronic cough [7]. In clinical observations, patients with chronic cough frequently report that their coughs are triggered by trivial environmental or mechanical stimuli, such as cold air, dust, perfume, talking, or eating, and are accompanied by throat hypersensations like itching, tingling, or urge-to-cough [8, 9]. The number of cough triggers significantly correlated with the degree of cough-related quality-of-life (QoL) impairment and also was associated with treatment refractoriness or cough persistence [10-12]. In addition, studies using sophisticated cough challenges [13, 14] or functional brain imaging [15] suggested that impaired cough control or suppression is associated with chronic refractory cough. The validity of the CHS concept was supported by clinical trials with novel antitussives targeting cough hypersensitivity pathways (such as P2X3 antagonists [16]) or speech pathology language therapy (involving cough trigger identification and voluntary cough control education) in patients with chronic refractory cough [17, 18].

Frequency is another important disease-defining parameter in cough. In a previous study comparing objective cough counts across different health conditions, the median (interquartile range) of cough frequency per 24 hours was 18.6 (0.5) in healthy controls, 33 (0.6) in smokers, 107 (0.3) in asthmatics, and 477 (0.3) in patients with unexplained chronic cough [19]. However, objective cough frequency is still not readily measurable in clinics, and as in cases with cough syncope, the impact of cough can be severe even with a relatively small number of coughing. In this regard, the impact of cough, or its perceived severity is a key factor that may finally define cough as a disease, as it is a sum of the patient's experience of coughing, including cough duration, frequency, hypersensitivity, impaired cough suppressibility, or treatment refractoriness.

The present paper is a narrative review to address the question: what is the impact and disease burden of chronic cough in adults? We review the literature, but also introduce recent qualitative interviews on the patients' experiences of the impact and burden of chronic cough and discuss unmet needs.

IMPACT OF CHRONIC COUGH

In the literature, the study by French et al. [20] was the first to prospectively address the impact of chronic cough on patients' QoL. They consecutively recruited 39 unselected patients with chronic cough (32 women and 7 men) and administered the Adverse Cough Outcome Survey (ACOS) and Sickness Impact Profile (SIP) questionnaires. The ACOS included 29 binary items on complications of coughing, and the SIP was a scaled measure of general health status based on the patient's perception of the effects of sickness on usual daily activities [20]. As expected, chronic cough was significantly associated with the overall SIP scores. Of note, a few specific cough-related complications more contributed to the SIP score variability, such as (1) exhaustion, (2) the need for reassurance that nothing is serious, (3) the inability to go to the movies, and (4) spouses not being able to tolerate the cough (most of them were psychological complications) [20]. The relevance of chronic cough to psychosocial impact was further supported by comparison of pre- and posttreatment data in the ACOS responses. Also, the number of cough-related complications decreased from 8.6 ± 4.8 to 1.9 ± 3.2 ($p < 0.001$) after successful treatment of cough, confirming the causal

relationships between cough and QoL impairment [20]. On the basis of the ACOS items, a 28-item cough-specific quality-of-life questionnaire (CQLQ) was later developed [21].

Subsequent studies using the CQLO provided additional meaningful observations. First, a sex difference in the impact of cough. Women with chronic cough reported poorer cough-specific QoL than men, which was particularly related to “wetting pants” and psychosocial issues (such as “family can't tolerate it,” “embarrassed,” and “upset by the response of others”) [22]. The sex difference is in line with general population-based findings that health-related QoL is particularly worse among elderly women with chronic cough than men or younger subjects with chronic cough [23]. Higher impact of cough in older women may be one of the reasons why they are predominant among chronic cough patients visiting specialist cough clinics [24]. Cough-induced stress urinary incontinence is perhaps one of the factors impairing QoL in older women. In a recent study by Peter Dicipinigitis, cough-induced stress incontinence was present in about 60% of women visiting the cough clinic (median age, 61 years) [25]. Meanwhile, peripheral and central nervous responses to tussigen inhalations are significantly enhanced in women than in men [24], suggesting that sex-related differences in cough processing pathways are also relevant to the sex difference in cough impact.

Second, a potential relationship between cough duration and impact. The CQLQ score was significantly higher (a higher score indicates a poorer cough-specific QoL status) among women with chronic cough than women with acute cough [26]. However, the score was not significantly different between acute cough and chronic cough among men. The original study using the ACOS similarly found that cough duration correlated with total and psychological domain score of the SIP questionnaire [20]. The findings suggested that women are more susceptible to the impact of cough when cough lasts longer. Longer disease duration implies that the patients experienced more diverse impact of disease, and as discussed earlier, the impact is more pronounced in women. However, the correlations between duration and impact of cough may not be linear or consistent [23], suggesting that there are more factors constituting patient experiences.

Third, the importance of measuring cough severity or impact in capturing clinically relevant cases. The study compared the impact of cough between chronic cough patients and control smokers. The CQLQ of control smoker group (smokers who were observed to be coughing but were not complaining of cough) was much lower than that of chronic cough patients [22]. In general population studies, simply asking “the presence of chronic coughing” (which is the most common definition used in general population studies for the prevalence [27]) did not differentiate clinically relevant cough patients from smokers with mild coughing; unlike the patient profile observed at specialist cough clinics (mostly women without a smoking history), the prevalence of chronic cough correlates with that of smoking at population levels ($r = 0.378$, $p = 0.009$), and there is no clear female predominance among subjects with chronic cough [24, 27].

The Leicester Cough Questionnaire (LCQ) is another well-validated tool widely used to measure cough-specific QoL in patients with chronic cough [28]. It consists of 19 items allocated in 3 domains (physical, psychological, and social). The items in the LCQ were chosen through several steps including literature review, multidisciplinary meeting, patient interviews, and item reduction and validation phases. A notable difference in the LCQ, compared to the CQLQ, is that the former did not include an item on stress urinary incontinence, as only a minority of the study participants reported the problem [28].

However, the sex difference in the impact of cough is well captured by the LCQ, through the items related to psychosocial impact. The LCQ has been validated in multiple Asian languages, including Chinese [29], Japanese [30], Korean [31], and Thai [32].

Cough-specific QoL is now considered as a critically important outcome in decision making for patients with chronic cough, and is also a major endpoint in clinical trials with antitussives [3]. The use of validated tools such as CQLQ or LCQ may help to quantify the impact of coughing in clinics (as the score range indicates a certain degree of cough impact or severity). The score changes are also useful in interpreting whether the improvements are clinically meaningful (e.g., minimal importance difference). However, cough-related issues may vary between individuals, and the cough-specific QoL questionnaires may not fully capture the impact in some patients, as they were designed for use in a wider population and to have the minimum number of items (through item reduction process). Therefore, detailed history taking is a key to understanding an individual patient's disease experience in clinics.

PATIENT EXPERIENCE: FINDINGS FROM QUALITATIVE INTERVIEWS

Qualitative study is a research methodology that helps to understand patients' disease experiences in detail and to identify unmet needs and treatment targets in the management. In the study by Hulme et al. [33] to examine the disease experience among patients with chronic refractory cough, they recruited 14 patients with chronic refractory cough in the UK (12 women and 2 men), and identified 8 key themes related to the impact of chronic refractory cough [33]. Expectedly but notably, the social impact of cough most frequently emerged as it was captured in theme key words such as “more than just a cough,” “cough in the social sphere,” and “cough as identity.” Uncontrollable coughing led the patients to get unwanted attention from others (‘embarrassment of having to explain that I have not got you to know like the plague’) [33]. Also, the fear of contagion was another major concern (‘obviously, they do not know I have a problem with a cough so they must just think I'm a big walking germ’) [33].

We recently conducted a qualitative study to explore the disease experience in Korean patients with chronic refractory cough, and briefly introduce some common findings from 5 patients in this paper (unpublished data). Three interrelated themes emerged in relation to the disease impact and burden, including social isolation, emotional impact, and economic impact (Fig. 1).

Theme 1. Social isolation

Social isolation (from family, friends, or work colleagues) was the most common outstanding issue in our study participants. First, loneliness and isolation in the family relationships. Long-standing cough not only caused health concerns to the family, but also disturbed their usual activity and sleeping. Some stated that they should sit at a distance, eat alone, or sleep alone due to coughing.

“Even with my family, I should live, eat, and sleep almost separately. I'm worried if it's an infectious disease.”

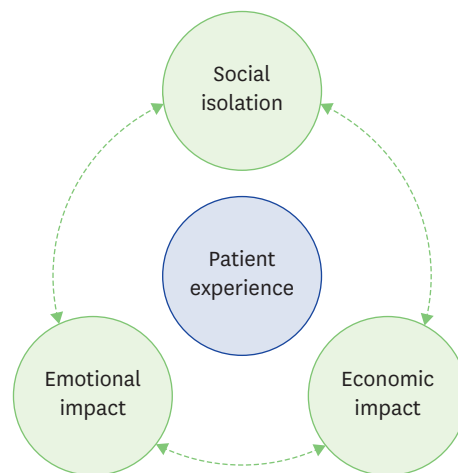


Fig. 1. Conceptual diagram of interrelated themes regarding the impact of chronic cough in patients with chronic refractory cough.

They were living with guilty feelings, but they found difficulties in sharing the physical and emotional distress with the family members, even with a spouse. Second, uncontrollable coughing limited their relationships with friends. They could not get together with friends in public places, as they could not predict when coughing would be triggered. Not only environmental exposure (dust, cold air, or perfume), but also talking and eating were frequent triggers for their coughs.

“Since it is difficult for me to control my cough, I should avoid public places... it's comfortable just to stay at home alone.”

“It's alright if I don't talk when I meet my friends, but if I have to talk, I just start coughing. It shrinks me.”

Third, work life was also affected. They were worried about what their colleagues might think about coughing, and were also concerned that they might be getting avoided due to a concern of contagion. The patients were criticizing themselves with guilty feelings, worrying that they might be suspected as a disease-transmitting entity. Overall, fear for contagion was a major reason for the social isolation from friends and colleagues.

“I'm very cautious that I might spread it to other people.”

Theme 2. Emotional impact

The patients were suffering from several emotional issues including depression, anxiety, fear, helplessness, or embarrassment due to coughing. The main was social isolation and treatment failures. First, the shrinkage in relationships with friends and family and the limitations of their work life led them to feel depressed. Repeated and uncontrollable coughing also lowered self-esteem and caused anxiety, aggravating their social isolation.

“Because of the cough, I refrain from going outside, my work was reduced, and now I have no reason to go out. Since I have a lot of time alone... when the cough gets worse, I wonder what I'm doing when I see myself taking medicine.”

Second, uncontrolled cough led them to have health anxiety and sometimes fear of death. The patients tried various drugs under different diagnoses, which were not successful; and some feared that they may have a rare, undetected, and incurable disease which finally might lead to death. Third, they felt helpless, embarrassed, or sometimes angry in their healthcare journey, due to the experiences of different diagnoses or repeated treatment failures.

“I’ve tried almost all the medicines, but cough persists.” and “When I realized I can’t control it (coughing), I wanted to die...I suffered too much and long from coughing.”

Theme 3. Economic impact

Economic impact varied between individuals, and the issue was expressed in different ways, such as medical expenses, reduced work productivity, or job loss. The patients coughed for several years (mean duration: 3.8 years among the participants), and visited different clinics, taking several diagnostic tests and drug treatments. Thus, the bills for outpatient clinics and drugs were incurred

“I did not think it’s really something first time, but it’s a burden to pay 300,000 to 500,000 Korean won (about 450 United States dollar [USD]) each time (when I visit the hospital).”

Also, some should have reduced their work or quitted jobs due to cough, which led to their income loss. The impact on work productivity or job loss was more remarkable in patients who taught children or interacted with people.

“Because of the cough, my work was reduced a lot, so I am losing about 1,000,000 Korean won (about 900 USD) in monthly salary.”

“I have to talk because I teach children, but I should have cut my work this year because of coughing.”

UNMET CLINICAL NEEDS

In the European Lung Foundation (ELF) online survey, open-ended questions were used to explore unmet needs of 1,120 patients with chronic cough in Europe. The 2 most outstanding themes were identified: the need for further information relating to the treatment and causes of chronic cough [34]. Similarly, in a previous study of 447 Korean patients using the modified ELF survey protocols, the main unmet needs were identified as the lack of effectiveness of treatment (49.3%) and unclear diagnosis (30.1%), followed by medical costs (6.2%) and adverse effects of treatment (3.5%) [35].

Unmet clinical needs were also explored by our recent qualitative interviews in Korean patients with chronic refractory cough (unpublished data). Three major unmet clinical needs were identified: (1) clear information about disease, (2) effective and curative treatments, and (3) cough specialists. The patients previously got many diagnoses, such as asthma, allergic rhinitis, gastroesophageal reflux, laryngeal reflux, or psychogenic cough; but most treatments were not effective. The lack of clear explanation on the disease or treatment led to poor compliance. Finally, they wanted to know how to locate cough specialists or clinics.

DISEASE BURDEN OF CHRONIC COUGH

Whilst chronic cough impairs life quality and causes socioeconomic loss in individuals, the disease burden has not been formally estimated, probably because chronic cough was just perceived as the consequent symptom from other respiratory conditions, but not as a clinical entity on its own. In previous global burden of disease studies, only whooping cough, but not chronic cough, was assessed [36].

The quality-adjusted life-year (QALY) is a generic measure of disease burden and can be calculated using generic health-related QoL measurement tools such as EuroQoL questionnaires. In the Korean National Health and Nutrition Examination Survey (KNHANES) 2010–2016, chronic cough was significantly associated with health-related QoL, measured by EQ-5D-3L index score [23]. The overall EQ-5D-3L index score was significantly lower in adults with chronic cough than those without chronic cough (0.79 ± 0.01 vs. 0.86 ± 0.00 , $p < 0.001$), and the difference exceeded the minimally important difference score of 0.05 [23]. Notably, the EQ-5D-3L index score was particularly lower among women aged ≥ 65 years (vs. those without chronic cough: 0.55 ± 0.04 vs. 0.70 ± 0.01 , $p < 0.001$) [23]. Among elderly women, the EQ-5D-3L index score of chronic cough was comparable to arthritis, stroke, asthma, angina, and allergic rhinitis, suggesting a substantial disease burden of chronic cough [23]. Similarly to the KNHANES 2010–2016, in the 2019 Japan National Health and Wellness Survey, the EQ-5D-5L index scores were 0.80 in patients with chronic cough vs. 0.87 in matched noncough respondents ($p < 0.001$) [37]. The Japanese study also reported that absenteeism, presenteeism, total work productivity impairment, and total activity impairment (measured by the work productivity and activity impairment questionnaire) were significantly more evident in patients with chronic cough than in controls [37]. Accumulating data from different countries and populations will help to estimate the disease burden of chronic cough on a global scale.

CONCLUSIONS

The impact of chronic cough is diverse and substantial. The disease burden, such as QALY, has not been formally calculated for chronic cough, but it is expected to be considerable, given its high prevalence in the community and its consistent relationships with QoL impairment [20, 28, 38]. The outstanding impact of chronic cough is social isolation. At the time of this writing, the impact is perhaps bigger than ever, due to the coronavirus disease 2019 (COVID-19) pandemic. Cough is one of the most common symptoms of acute COVID-19, and there is a widespread fear of cough in the community. Cough is stigmatizing patients recovered from COVID-19, as it is a frequent symptom of post-COVID syndrome [39]. According to the news and patient group feeds, not a few patients with post-COVID syndrome live with fear of reinfection, remain isolated from family or friends, or have difficulty with returning to the workplace. At the same time, the situation is worse for patients who were suffering from chronic cough; although there is no formal study, we see many patients who are living a more restricted life with the fear of infection and of getting attention from others in the era of COVID-19 pandemic. This situation calls for more social and academic attention to the impact and burden of cough in patients with chronic cough.

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