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Original Article

Etiologies and Treatment Outcomes of Chronic Cough Diagnosed with a Pathophysiological Diagnostic Procedure: A Single-center Retrospective Observational Cohort Study

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Abstract

OBJECTIVE: We developed a pathophysiological diagnostic procedure to identify etiologies of chronic cough (CC) like cough variant asthma (CVA), atopic cough (AC), cough predominant asthma, sinobronchial syndrome (SBS), and mucoid impaction of small bronchi. After identifying the etiologies of CC through an understanding of its pathophysiological processes, we determined the patient's management outcomes based on the pathophysiological diagnosis.

MATERIAL AND METHODS: In this retrospective observational cohort study, the medical records of CC patients from April 2013 to March 2018 was analyzed to assess the etiologies and treatments based on the pathophysiological diagnostic procedure. The capsaicin cough-reflex sensitivity test, methacholine-induced bronchoconstriction cough response test, bronchodilator reversibility test, bronchial responsiveness test, chest and sinus computed tomography, and sputum investigations were used for pathophysiological diagnosis.

RESULTS: CC etiologies were diagnosed in 289 of the 298 patients who underwent the diagnostic procedures. The remaining nine patients had normal diagnostic findings. The three most common causes of CC were CVA, AC and SBS. Cough disappeared completely in 278 of the 286 patients who completed treatment. The median time to complete symptom resolution was 5.8 weeks.

CONCLUSION: Pathophysiological evaluation may facilitate prompt and objective diagnosis of the etiologies of CC. Our results suggest that pathophysiological diagnosis is better than the conventional diagnostic method in treatment outcomes.

KEYWORDS: Capsaicin, chronic cough, diagnosis, methacholine chloride, pathophysiology

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INTRODUCTION

Chronic cough (CC), i.e., any cough occurring for more than eight weeks without any obvious clinical or radiological evidence of pulmonary disease is one of the most common reasons for referral to a chest physician. Cough variant asthma (CVA), atopic cough (AC), and sinobronchial syndrome (SBS) are the predominant causes of CC in Japan.[1] CVA and AC are associated with non-productive cough, whereas SBS is associated with a productive cough. CVA is primarily characterized by an increased cough response associated with bronchial smooth muscle contraction.[2] The fundamental features of AC include the presence of eosinophilic tracheobronchitis with cough-reflex hypersensitivity;[3] the absence of typical asthma precursors,[1] and the absence of chronic airflow limitation.[1] SBS is indicated by cough receptors stimulated by overproduction of lower respiratory tract secretions.[4]

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Currently, the diagnostic methods for the assessment of presumptive CC etiology are determined by observing improvements following the administration of specific treatments for the CC. There are many concerns regarding the effectiveness of CC therapeutic diagnostic processes.

1. Low specificity of specific treatment regimens leading to false-positive results.

2. Spontaneous cough relief leading to false positive results.

3. Insufficient treatment potency causing false negativity.

4. False negative results in the case of resistance to the therapeutic agents, for example in severe of difficult-to-treat cases.

5. False negative results arising from the occurrence of more than one cause of the CC.

6. Differences between studies in the criteria used to assess response to cough treatment.

7. It takes time to initiate appropriate treatment according to the true pathophysiology.

In addition, treatment is further hampered by drug doses that are often not designed to achieve antitussive effects.[5] Differences in evaluation criteria for cough treatment have also led to different classifications of cough etiologies.[6] Therefore, a new mechanism based on the pathophysiological processes involved in CVA, AC, and SBS may allow us to move from slow and ineffective treatment-based diagnosis to a faster and more reliable pathophysiological diagnosis.

In this study, we successfully developed a pathophysiological diagnostic procedure to determine CC etiologies from 289 CC patients. The diagnostic processes utilized include capsaicin cough-reflex sensitivity test (Cap-Cough test), methacholine-induced bronchoconstriction cough response test (Meth-Cough test), bronchodilator reversibility test, bronchial responsiveness test, chest and sinus computed tomography, and sputum investigations. This study evaluated the patients' clinical outcomes based on our diagnostic procedure.

MATERIAL AND METHODS

Study Subjects

In our institution, all patients presenting for treatment of CC undergo the following tests, after obtaining the patient's informed consent: Cap-Cough test, Meth-Cough test, bronchodilator reversibility test, bronchial responsiveness test, chest imaging, sinus imaging, blood test, and sputum examination. This retrospective observational cohort study included all patients who presented for CC diagnosis and treatment between April 2013 and March 2018. CC etiology was determined from patient records containing diagnostic procedures and treatments. The study was approved by the Ethical Review Board of the National Hospital Organization Nanao Hospital, and conducted in accordance with the revised version of the guidelines in the Declaration of Helsinki (UMIN ID: UMIN000018679, date: 05.11.2015). All patient details have been de-identified. The reporting of the study conforms to the STROBE guidelines.[7]

Main Points

- We developed a pathophysiological diagnostic procedure for identifying chronic cough (CC) etiologies.
- Pathophysiological evaluation may enable prompt diagnosis of the etiologies of CC, leading to better treatment outcomes.
- This procedure may meet the unmet medical needs in CC.

Study Protocol

Within 4 days of presentation, all patients completed the following investigations: spirometry, bronchodilator reversibility test, Cap-Cough test, Meth-Cough test, and bronchial responsiveness test. A dry wedge spirometer (Chestac 11, Chest Co., Ltd., Tokyo, Japan) was used to determine spirometric indices such as forced vital capacity and forced expiratory volume in the first second (FEV1). Spirometric tests and data interpretation were performed according to the recommendations of the ATS/ERS Task Group.[8] The bronchodilator reversibility test was conducted during the spirometry procedure and involved measurements both before inhalation and 30 minutes after inhalation of 50 μg of procaterol.

Measurements

Methacholine Inhalation Protocol

Methacholine inhalation was performed according to Takishima et al.,[9] using an Astograph (Jupiter 21; CHEST; Tokyo, Japan). Methacholine chloride (FUJIFILM Wako Pure Chemical Industries, Ltd., Osaka, Japan) was diluted in phosphate-buffered saline solution (PBS) to double the concentration (0.0195 to 160 mg/mL). The solutions of PBS and methacholine was inhaled for 1 min. Subjects were examined during quiet breathing while wearing a nose clip.

Assessment of Cough Response to Methacholine-induced Bronchoconstriction

The Meth-Cough test was evaluated as previously documented by Hara et al.[10] An observer counted coughs that occurred during the total time (α + 30 min), consisting of methacholine inhalation (α min, <1 min) and the 30 min after the methacholine inhalation. The cough response to methacholine-induced bronchoconstriction was considered as showing smooth muscle cough hypersensitivity when the Meth-Cough was ≥24 coughs/30+α min.[11]

Assessment of Capsaicin Cough-reflex Sensitivity

The Cap-Cough test was evaluated as previously described by Fujimura et al.[12] The lowest concentration of capsaicin that elicited at least 5 coughs (C5) was defined as the cough threshold. Inhaled capsaicin at a concentration of ≤0.98 μmol/L

for female subjects and ≤3.9 μmol/L for male subjects was used to determine epithelial cough hypersensitivity. The cut-off point was calculated as the geometric mean minus two geometric standard deviations.[13]

The following criteria were used to make the diagnosis: CVA, an increase in cough response to methacholine-induced airway smooth muscle contraction; AC, an increase in cough-reflex sensitivity to inhaled capsaicin; and a combination of CVA and AC, an increase in cough response due to both airway smooth muscle contraction and cough-reflex sensitivity.

Although typical asthma was excluded from CC, asthma patients having isolated CC were assessed in the present study when attending physicians could not identify key symptoms of asthma in patients, including wheeze, chest tightness, rhonchi, and airflow limitation measured by spirometry during the initial presentation. Patients in this study were classified as having cough predominant asthma (CPA) if they had one or more of the following distinctive signs of asthma: bronchial hyperresponsiveness, bronchial reversibility, and/or wheezes on auscultation during the clinical course.

The diagnostic criteria for CVA, AC, SBS, CPA, gastroesophageal reflux (GER), associated CC and mucoid impaction of small bronchi (MISB) syndrome are presented in Table 1. Although MISB syndrome has not been established as a clinical entity, a number of our patients met the diagnostic criteria and, when administered oral corticosteroids (OCS) and antifungal medications, had a successful treatment outcome. Diffuse panbronchiolitis was diagnosed based on the distinctive features observed in the chest X-ray and chest computed tomography. Bronchorrhea was defined as watery sputum production of more than 100 mL per day.

Statistical Analysis

No statistical sample size calculations were conducted. We analyzed all patients with a provisional diagnosis of CC presenting between September 2013 and August 2018. The capsaicin cough threshold was expressed as the geometric mean with geometric standard error of the mean. Statistical differences between the groups were analyzed using the Mann-Whitney U test, Kruskal-Wallis test with Dunn's post-hoc adjusted by Bonferroni, or Wilcoxon signed rank test, as appropriate. The count distributions for the two groups (<65 years and ≥65 years) were compared using Pearson's chi-square test. The relationship between cough threshold to inhaled capsaicin and cough response to bronchoconstriction was evaluated using Pearson's correlation coefficient. All comparisons were two-tailed, and *P* values of <0.05 were considered significant. All analyses were conducted with IBM Statistical Package for the Social Sciences statistics 23 (Japan IBM Co., Tokyo, Japan). Continuous variables were reported as mean±standard deviation.

RESULTS

Overall, 301 patients (121 men, 180 women, mean age 57.0±17.1 years) initially presented to the clinic during the 5-year study period. Three patients (two men and one woman) did not perform the complete diagnostic evaluation. The cause of CC was diagnosed in 289 patients, and the results indicated that the diagnostic values were within normal limits in 9 patients (Figure 1). The median duration of cough in patients was 260.0 weeks (range 10.4-3588.0 weeks). Of the cases analyzed, 83 patients were referred for refractory cough from other facilities, including respiratory clinics.

The number of coughs (Meth-Cough) induced in the first 15+α min and the second 15 min after methacholine inhalation is shown in Figure 2. The number of coughs in the first 15+α minutes was overwhelmingly higher than that in the second 15 minutes. This trend was also observed in previous studies in healthy subjects.[10] Twelve patients had a high number of coughs in the second 15 minutes. Details are given below: 4 patients with CVA+SBS (44 in the first; 51 in the second, 14 in the first; 20 in the second, 9 in the first; 30 in the second, 31 in the first; 36 in the second), 2 patients with AC+CVA+SBS (7 in the first; 18 in the second, 25 in the first; 33 in the second), 1 patient with CPA (0 in the first; 1 in the second), 1 patient with AC+CPA (0 in first; 7 in second), 1 patient with AC+SBS (2 in first; 5 in second), 1 CPA+GER (0 in first; 22 in second), 1 patient with CPA+SBS (3 in first; 7 in second), 1 patient with therapeutically diagnosed AC+CVA (0 in first; 11 in second).

The frequency of each CC etiology, demographic characteristics, clinical features, and pulmonary function test results is shown in Table 2. A total of 194/289 patients (67.1%) had two or more causes of CC. CVA (250/289), AC (103/289), and SBS (140/289) were the main etiologies for cough (Table 2). Elderly patients (≥65 years) had significantly more underlying conditions than non-elderly ones (*P* = 0.0484, data not shown). There was no significant relationship between C5 and the Meth-Cough (data not shown).

Of the 289 patients, 10 left our clinic before receiving adequate cough treatment. Also, 271/279 (97.1%) patients had complete symptomatic cough resolution whereas eight patients (2.9%) had incomplete resolution of the cough (Figure 1). The specific treatments of CC based on etiology and additional treatments required for complete cough resolution are shown in Table 3. Of the 279 patients, 49 (17.6%) required additional treatments. Thirty-eight patients required antifungal drugs, and ten patients required additional treatments for GER-related cough: proton-pump inhibitors, ten patients, gastrointestinal promotility drugs, nine patients, and rikkunshito, seven patients (Table 3). The diagnosis of GER-related cough was based entirely on a therapeutic diagnostic procedures.[6]

The median time required for cough resolution in 271 patients, whose cough completely resolved, was median 5.8 weeks [95% confidence interval (CI), 8.0-10.6 weeks]. The time required for cough resolution was significantly different based on the need for additional treatments (*P* = 0.0049, Figure 3).

Table 1. Diagnostic criteria for CVA, AC, sinobronchial syndrome, cough predominant asthma, and mucoid impaction of small bronchi syndrome

All criteria were met for each diagnosis.
CVA
1. Isolated chronic non-productive cough lasting ≥8 weeks
2. No history of wheezing or dyspnea and lack of adventitious lung sounds on physical examination
3. Increase in cough response to methacholine-induced bronchoconstriction
AC
1. Non-productive cough lasting ≥8 weeks
2. Presence of one or more findings indicative of an atopic predisposition, including a history and/or complications of allergic diseases (excluding asthma), peripheral blood eosinophilia (>6% or >400 cells/μL), increased total serum IgE level (>200 IU/mL), presence of IgE antibodies specific to aeroallergens, and positivity of allergen skin testing and/or presence of induced sputum eosinophilia (>2.0%)
3. Increase in cough-reflex sensitivity to inhaled capsaicin
SBS
1. Productive cough lasting ≥8 weeks.
2. One or more of the following:
(i) Symptoms such as postnasal drip and throat clearing
(ii) Signs such as mucous or mucopurulent secretions in the upper and middle pharynx and cobblestone appearance of the mucosa
(iii) Fluid retention and/or mucosal thickening on sinus CT scan
(iv) Increased neutrophil count in nasal secretions
(v) Increased neutrophil count in spontaneous sputum.
3. Cough relief upon treatment with 14-member macrolides. Treatment efficacy was evaluated at 2 months after initiation and was judged as effective when the productive cough diminished to half or less.
Cough predominant asthma (CPA)
1. Isolated chronic non-productive cough lasting ≥8 weeks
2. No history of wheezing or dyspnea and lack of adventitious lung sounds on physical examination and no airflow limitation assessed by spirometry
3. One or more of the following:
(i) Bronchial reversibility, defined as a percentage increase of ≥12% and an absolute volume increase of 200 mL in FEV1
(ii) Presence of bronchial hyperresponsiveness [provocative concentration of methacholine causing a 20% fall in FEV1 (PC20) <10 mg/mL]
(iii) Presence of wheezes on auscultation during clinical course
MISB
1. Productive cough lasting ≥8 weeks
2. Increased eosinophil count in spontaneous sputum
3. Impaction of small bronchi and remarkable thickening of bronchial walls on chest CT
Clinical features of MISB
(i) Cough was relieved upon short-term treatment with oral corticosteroids, but it relapsed soon after treatment termination (intractable).
(ii) Bacteria causing chronic airway infection were seldom detected in purulent sputum, and sputum eosinophil counts were increased.
(iii) Long-term low-dose macrolide therapy was not effective.
(iv) MISB was mostly identified in the lower lobes.
(v) Fungi were seldom culturable in clinically available fungal growth media.
(vi) A combination of oral corticosteroids and itraconazole was effective.
GER-related cough[6]
Characteristic medical history that suggests the cough is due to GER (pre-treatment diagnosis) and signs to consider to make a definitive diagnosis (post-treatment diagnosis) based on the therapeutic effects.
1. Suggestive findings
Suspect that the cough is due to GER when a chronic cough (especially dry cough) has the following characteristics:
(i) Accompanied by esophageal symptoms of GER, such as heartburn and acid reflux
(ii) Accompanied by laryngopharynx symptoms of GER, such as throat clearing, hoarse voice, and abnormal sensation of the laryngopharynx
(iii) Exacerbation of coughing during conversation, eating, immediately after moving the body/going to bed/waking up, while stooping, and with weight gain. Typically, there is none or less coughing during the night
(iv) Intense cough ending in vomiting
(v) Suspect GER disease if drugs that could cause a cough (e.g., angiotensin-converting-enzyme inhibitors) have not been prescribed, and treatment for CVA and SBS is ineffective, particularly if a nocturnal cough is improved by CVA treatment, but a daytime cough persists
2. Post-treatment diagnosis
If the cough is improved by GER treatment (proton pump inhibitor, gastrointestinal prokinetic agents, and obesity/diet improvement), the diagnosis can be confirmed.
Note:
(i) Proton pump inhibitors should be started at higher doses. However, monotherapy may be ineffective (consider adding a gastrointestinal prokinetic agent at an early stage).
(ii) In patients with other comorbidities (especially cough variant asthma), no improvement may be generally expected without sufficient treatment for both diseases.

CVA: cough variant asthma, AC: atopic cough, SBS: sinobronchial syndrome, FEV1: forced expiratory volume in the first second, IgE: immunoglobulin E, CT: computed tomography, MISB: mucoid impaction of small bronchi syndrome, GER: gastroesophageal reflux

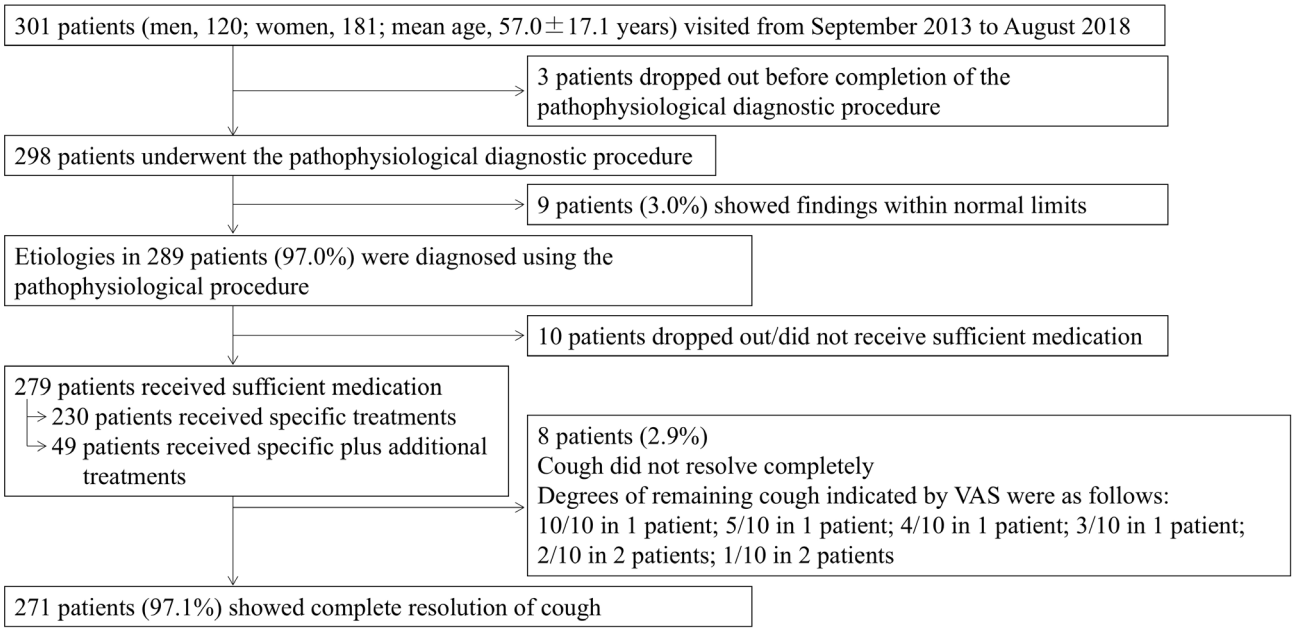

Figure 1. Details of patients who underwent the pathophysiological diagnostic procedure

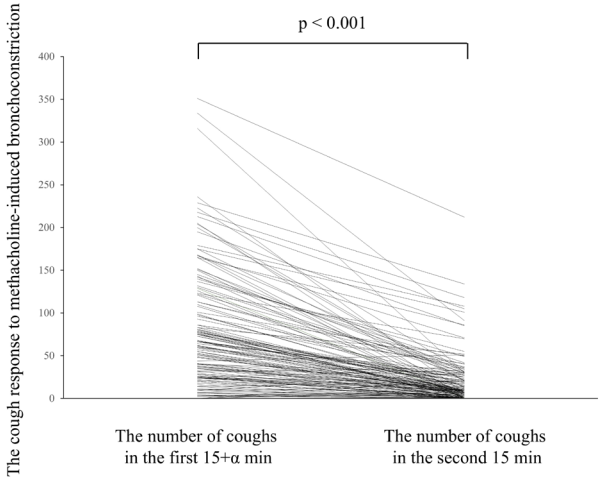

Figure 2. The number of coughs elicited in the first 15+α min and the second 15 min after methacholine inhalation

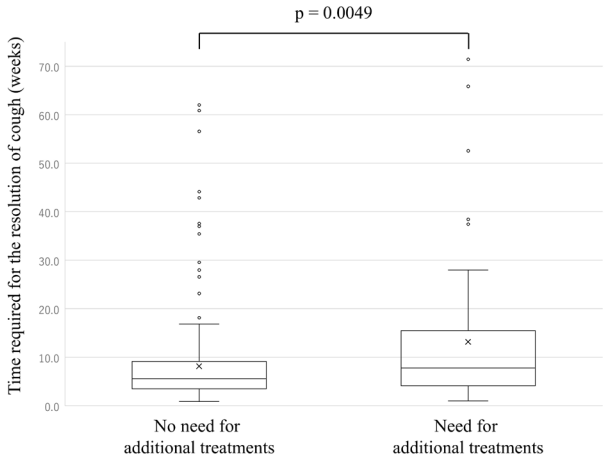

Figure 3. Comparison of cough resolution periods between patient groups with or without additional treatments

DISCUSSION

This study showed that our pathophysiological diagnostic process led to an increased diagnosis of CC and successful outcomes. The findings are unique because we were able to present not only diagnostic procedures and therapeutic measures but also complete CC treatment results.

We found that 97.1% of patients who were diagnosed using the pathophysiological procedures outlined above and who completed the treatment achieved complete cough elimination. The results are noteworthy given that previous studies typically evaluate the efficacy of cough therapy in terms of improvement, not cough elimination when making a diagnosis.[6,14,15] In addition, unexplained CC is found in about 46% of individuals referred to specialty pulmonology clinics.[16]

Because we did not use the therapeutic diagnostic procedures, except 9 patients who had pathophysiological diagnostic results within normal limits in this study, we could not directly compare these two diagnostic procedure outcomes regarding patients' characteristics or cough elimination. On the other hand, Hara et al.[17] have previously shown that complete cough elimination with a therapeutic diagnostic procedure was achieved in only 84.2% of a 36-patient cohort. In prospective studies, the usefulness of our pathophysiological diagnostic procedure should be compared with the conventional therapeutic diagnostic procedure.

Table 2. Etiologies of chronic cough in 298 patients, as determined using the pathophysiological diagnostic procedure and demographic characteristics, clinical features, and pulmonary function tests

	AC	CVA	CPA	SBS	Unknown	AC+CVA	AC+CPA
Number of pts (No. of Fem)	3 (3)	82 (56)	4 (3)	4 (1)	9 (5)	52 (21)	2 (1)
Age (years)	66±14	52±17	64±123	67±17	67±11	50±18	53±13
FVC (%pred.) (%)	124±4	107±15	105±18	106±11	110±14	102±17	90±16
FEV1 (%pred.) (%)	120±8	102±13	102±10	97±29	109±17	96±16	79±17
FEV1/FVC ratio (%)	76±2	80±8	79±7	72±17	80±6	81±9	73±6
Meth-C test	15±3	117±82	11±11	16±9	9±6	124±113	7
C5 (μM)	1±1	7±1	6±2	31±1	17±2	2±1	2±2
Sputum nut (%)	71±16	54±31	32±10	51±30	71±15	70±24	32±7
Sputum eos (%)	0±0	11±24	1±1	25±19	3±2	7±14	26±25
Blood eos (%)	3±2	3±5	2±1	4±3	3±3	3±2	5±1
Total IgE level (IU/mL)	183±31	251±562	26±7	2673±3258	283±577	281±542	173±168
Positive rate of specific IgE (%)	100	51	0	50	22	51	50
	AC+SBS	CPA+SBS	CVA+SBS	AC+CVA+SBS	CVA+MISB+SBS	CPA+MISB+SBS	AC+CVA+MISB+SBS
Number of pts (No. of Fem)	9 (3)	9 (6)	76 (54)	35 (17)	3 (3)	2 (2)	2 (1)
Age (years)	69±4	67±13	59±15	64±14	68±10	61±24	68±4
FVC (%pred.) (%)	91±21	109±12	101±16	105±18	78±7	97±9	100±6
FEV1 (%pred.) (%)	85±12	100±9	95±17	99±21	65±15	767±15	89±4
FEV1/FVC ratio (%)	77±9	74±5	78±8	77±9	66±15	63±11	72±1
Meth-C test	13±7	17±11	123±96	119±87	86±62	16±5	153±102
C5 (μM)	2±1	10±1	8±0	1±1	12±1	16±2	2±2
Sputum nut (%)	79±17	71±16	62±25	67±21	74±11	60±35	95±1
Sputum eos (%)	5±3	11±16	13±21	12±20	11±7	26±25	2.0±0
Blood eos (%)	2±1	3±2	4±4	3±3	2±1	5±5	2±1
Total IgE level (IU/mL)	291±575	107±100	268±687	147±254	104±47	64±33	399±391
Positive rate of specific IgE (%)	22	11	46	46	100	50	50
	Others						
Number of pts (No. of Fem)	6 (3)						
Age (years)	64±15						
FVC (%pred.) (%)	88±15						
FEV1 (%pred.) (%)	82±15						
FEV1/FVC ratio (%)	75±7						
Meth-C test	41±67						
C5 (μM)	14±2						
Sputum nut (%)	74±12						
Sputum eos (%)	3±1						
Blood eos (%)	4±3						
Total IgE level (IU/mL)	59±31						
Positive rate of specific IgE (%)	67						

Others including the following patients, DPB 1 patient, MISB 1 patient, CPA+MISB 1 patient, SBS+Bronchorrhea 1 patient, AC+CVA+DPB 1 patient, AC+CVA+MISB 1 patient.

AC: atopic cough, CPA: cough predominant asthma, CVA: cough variant asthma, DPB: diffuse panbronchiolitis, eos: eosinophils, Fem: female, FVC: forced vital capacity, FEV1: forced expiratory volume in 1 s, FeNO: fractional exhaled nitric oxide, MISB: mucoid impaction of small bronchi, nut: neutrophils, pts: patients, pred.: predicted, SBS: sinobronchial syndrome, IgE: immunoglobulin E

Table 3. Etiologies and treatments of 279 chronic cough patients. Diagnosis and treatment were based on pathophysiological diagnosis. Additional treatments for complete cough resolution are listed separately although there is some overlap with original treatment in some cases

Etiology	N	Specific treatments	Additional treatments (n = number of cases)
Single cause	86		
AC	3	H1-RA, ICS, OCS (n = 1)	
CVA	75	Beta-2, ICS, LTRA, LAMA, OCS (n = 24), seratrodast	Antifungal drug (n = 10) Gastrointestinal promotility drugs (n = 2) H1-RA (n = 1) PPI (n = 3) Rikkunshito (n = 2)
CPA	4	Beta-2, ICS, LTRA, OCS (n = 1), seratrodast	Gastrointestinal promotility drugs (n = 1) PPI (n = 1) Rikkunshito (n = 1)
SBS	4	Macrolides	Beta-2 (n = 4) ICS (n = 4) LTRA (n = 4)
Dual causes	145		
AC+CVA	51	Beta-2, ICS, LTRA, LAMA, OCS (n = 25), seratrodast	Antifungal drug (n = 7) Gastrointestinal promotility drugs (n = 3) PPI (n = 3) Rikkunshito (n = 3)
AC+CPA	2	Beta-2, H1 RA, ICS, LTRA, OCS (n = 1)	
AC+SBS	9	H1 RA, ICS, macrolides, OCS (n = 3)	Antifungal drug (n = 1) Beta-2 (n = 1)
CPA+SBS	9	Beta-2, ICS, LTRA, macrolides, OCS (n = 5)	Antifungal drugs (n = 1)
CVA+SBS	74	Beta-2, ICS, LAMA, LTRA, macrolides, OCS (n = 37), seratrodast	Antifungal drugs (n = 11)
Triple causes	40		
AC+CVA+SBS	35	Beta-2, H1-RA, ICS, LAMA, LTRA, macrolides, OCS (n = 12), seratrodast	Antifungal drugs (n = 8) Gastrointestinal promotility drugs (n = 3) PPI (n = 3) Rikkunshito (n = 1)
CVA+MISB+SBS	3	Antifungal drugs, beta-2, ICS, LTRA, OCS (n = 3)	
CPA+MISB+SBS	2	Beta-2, ICS, LTRA, macrolides, OCS (n = 1)	
Quad causes	2		
AC+CVA+MISB+SBS	2	Antifungal drugs, beta-2, H1-RA, ICS, LTRA, macrolides, OCS (n = 1)	
Others	6		
			Beta-2 (n = 2) ICS (n = 2) LTRA (n = 1)

Others including the following patients, DPB 1 patient, MISB 1 patient, CPA+MISB 1 patient, SBS+Bronchorrhea 1 patient, AC+CVA+DPB 1 patient, AC+CVA+MISB 1 patient.

AC: atopic cough, Beta-2: beta-2 agonists, CPA: cough-predominant asthma, CVA: cough-variant asthma, DPB: diffuse panbronchiolitis, GER: gastroesophageal reflux, H1-RA: histamine H1 antagonists, ICS: inhaled corticosteroids, LAMA: long-acting muscarinic antagonists, LTRA: leukotriene receptor antagonists, MISB: mucoid impaction of small bronchi, OCS: oral corticosteroids, PPI: proton-pump inhibitors, SBS: sinobronchial syndrome

An accurate pathophysiological investigative process may dramatically improve therapeutic efficacy for chronic cough (CC) because the initial treatment period for a suspected cough etiology can last between 1 and 8 weeks.[6,18,19] In addition, without rapid treatment, cough damaging the airway quickly becomes self-perpetuating, resulting in exacerbated airway inflammation and worsening cough.[20] Fujimura et al.[3] showed that therapeutic diagnosed AC resistant to H1 receptor antagonist had higher degree of eosinophil infiltration in the biopsied bronchi and this result implicated that pathological feature influenced the therapeutic effect of CC.

Ideally, the efficacy of our therapeutic regimens used in this study should be examined in a prospective clinical trial. However, the drugs used in this study are primarily described in the 2021 Japanese guidelines.[6] Therefore, we do not believe that our therapeutic regimens in this study deviate from general routine medical care. On the other hand, we consider the possibility that the administration of OCS may have affected the therapeutic efficacy should be considered. Doan et al.[21] reported that short-term oral prednisolone dramatically improved cough in CVA, and all cases were subsequently controlled primarily with inhaled corticosteroids (ICS).[21] The 2020 German guidelines stated that some CC patients respond only to systemic corticosteroids, because of the tussive effect of ICS, which also prevents proper deposition of medication in the airways.[22] Furthermore, Puente-Maestu et al.[23] showed that physicians were reluctant to prescribe OCS for patients with refractory or unexplained CC, probably because of the safety profile of OCS, even though they recognize their effectiveness.

In this study, the main additional treatment for cough was antifungal drugs which were used to eliminate cough that was resistant to specific cough treatments, including corticosteroids. Fungus-associated CC (FACC) is a relatively new clinical concept defined as CC with the following findings: the presence of environmental fungi in sputum, especially filamentous basidiomycetes (f-BM); and response to antifungal drugs. FACC may have been diagnosed with unexplained CC because FACC did not respond to the general cough medications[24] and specialized facilities to isolate f-BM were not available.[6]

We found that few patients needed additional treatment for GER-related cough. Kanemitsu et al.[25] reported that GER-related subacute cough CC were increasing in Japan also, and they recently reported that 11.9% (37/312) of subacute and CC patients had GER-related cough. Globally, the proportion of GER-related cough in CC is extremely variable, ranging from 2 to 86%.[26] In this study, only 10 out of the 279 CC patients (3.6%) were diagnosed with GER-related cough. We do not fully know the reasons for the discrepancy between the proportion of GER-related cough of the previous studies and those of the present study, but it is possible that adequate cough treatment based on pathophysiological diagnostic procedures suppresses further reflux induced by cough and the cough-reflux vicious cycle. It has been reported that the evidence for the diagnosis of GER-related cough is insufficient,[27] and that a powerful placebo effect influences the efficacy of treatment for cough,[28] including GER-related cough.[27]

This study diagnosed two or more etiologies in 67.1% of CC patients. In such cases, treatment-based diagnostic processes are challenging and time-consuming. Guidelines have indicated that the accuracy of treatment-based diagnostic processes for CC with multiple etiologies is limited.[6] Our findings indicate that cases with multiple etiologies accounted for a substantial proportion of the CC cases. This was because we could use a pathophysiological diagnostic procedure, and determine the final diagnosis at the point when the cough was completely resolved. We found that the elderly had a greater incidence of multiple etiologies compared to non-elderly individuals. On average, the participants of this study were over 5 years older than those from several past studies.[29]

The main causes of CC in our patients were AC, CVA, and SBS. According to a 2005 study, three leading causes of CC in Japan were AC, CVA, and SBS.[29] As a result, the etiologies of CC may have remained relatively the same over the past 15 years. During that time two guidelines for cough management were published in Japan,[1,6] and several advances in cough research and diagnostic procedures occurred.[19] In Western countries, increased bronchial hyperresponsiveness is considered important for the diagnosis of CVA, while Chinese and Japanese guidelines recommend confirming the efficacy of bronchodilators. It has long been known that the efficacy of bronchodilators does not always coincide with increased bronchial hyperresponsiveness. The studies from China reported that 23.6% to 37.5%[30] of patients with CC diagnosed with CVA based on increased bronchial hyperresponsiveness or diurnal variation in PEF greater than 20% were refractory to bronchodilators. Also, in Japan, when patients with chronic or subacute/CC were diagnosed with CVA based on increased bronchial hyperresponsiveness and response to bronchodilators, the prevalence of CVA was reported up to 67.0%,[25]. Considering these results, it is possible that the proportion of patients diagnosed with CVA increased with physiological or our pathophysiological diagnostic criteria compared to CVA based solely on the efficacy of bronchodilators. Furthermore, the findings of this study, in which 86.5% of CC, were diagnosed with CVA, were considered consistent with the results of the above-mentioned Japanese studies. It is necessary to validate the efficacy of bronchodilators in patients with pathophysiologically diagnosed CVA.

There are few reports analyzing the length of treatment needed to achieve complete resolution of cough. In 2017, a study in a tertiary care clinic reported that it took more than 14 weeks for the cough to improve (complete or partial resolution).[31] In that study, 65/155 (41.9%) patients attending a tertiary care clinic and 67/193 (34.7%) individuals attending a secondary care clinic had a complete resolution of their cough, and 76/155 (49.0%) patients in tertiary care clinics and 97/193 (50.3%) patients in secondary care clinics had at least 50% improvement in their cough. The longitudinal CC prognosis has been investigated in two retrospective cohort studies. Kang et al.[32] reported that 64/323 individuals with (19.8%) had persistent cough 4 years after evaluation and management in a Korean tertiary clinic, and Koskela et al.[33] reported that 31 of 68 CC patients (46%) still had persistent cough five years post-initial evaluation at a Finnish University. We found that the median time to complete symptomatic resolution of cough was 5.8 weeks (95% CI: 8.0-10.6) and that the number of etiologies did not affect the time to complete resolution of cough. Thus, our findings suggest that the assessment and management of CC based on pathophysiological investigative processes may help to improve prognosis.

The use of ICS to treat eosinophilic airway diseases, like CVA, AC, and CPA, is problematic. For example, CVA may lead to future airway remodeling and typical asthma, which requires long-course ICS treatment, whereas AC does not lead to these conditions, and ICS treatment can be stopped after the resolution of the cough. Therefore, differentiating CVA from AC before starting treatment is essential, even though it is not recommended by some guidelines due to specific reasons

that may need further explanation.[6,18,19] In addition, long-term use of ICS is known to increase the risk of pneumonia and mycobacterial infection among individuals with chronic obstructive pulmonary disease. Although there are currently no data on risks associated with the use of ICSs in CC patients, we suggest that the routine use of ICSs in individuals with cough is not recommended.

In the present study, we used C5, which indicated the cough threshold for cough-reflex sensitivity evaluation. Several studies have shown that this traditional index, C5, displayed overlaps between healthy subjects and patients with CC,[34] and there is also a need for standardization of the methodology regarding the equipment and protocols in assessing cough-reflex sensitivity to inhaled capsaicin. Hara et al.[10] previously found that the median Meth-Cough was 7 (range, 0-71/30+α min) in 41 healthy young subjects. Problems with this previous study include that only young, healthy subjects were included and that their number was too small to establish reference values. Therefore, the results of this previous study alone cannot be used to develop pathophysiological diagnostic criteria for CVA. Nor, can the overlap between the Meth-Cough in healthy subjects and in cough variant asthma (CVA) be assessed. The Clinical and Laboratory Standards Institute in the USA stipulates that a sample size of at least 120 persons is required for the establishment of reference values by the percentile method. We are currently reassessing the Meth-Cough in healthy subjects of various age groups. In the evaluation of Meth-Cough, we compared the number of coughs elicited in the first 15+α min and the second 15 min after Meth inhalation; the most of the cough symptoms occurred within 15+α min, suggesting that these were not spontaneous but induced by bronchoconstriction. This trend was also observed in previous studies in healthy subjects.[10]

This study had several limitations. First, it was a single-center retrospective study, while multicenter prospective studies are necessary to confirm our findings and develop the methods and endpoints as diagnostic tools. Second, most of the patients included in the study had CC that did not improve with cough treatment at other institutions. That is, CC improvements reported in the current study may be influenced by previous treatments.

CONCLUSION

In conclusion, more effective diagnoses and treatments are needed for CC patients. Poor treatment efficacy and unclear diagnosis are major challenges and unmet needs in CC management.[35] Pathophysiological CC diagnostic procedures only require 2 days, compared to more than 1 week for traditional CC diagnostic procedures.[18,19] Our diagnostic procedure included the Cap-Cough test, and the Meth-Cough test before the commencement of therapy. We found that the median treatment time required for complete resolution of cough based on our pathophysiological diagnosis, was only 5.8 weeks, compared to therapeutic diagnoses, which typically take multiple years for resolution.[6,32,33] Thus, a pathophysiology-based evaluation procedure may dramatically improve the management of CC.

Ethics

Ethics Committee Approval: The study was approved by the Ethical Review Board of the National Hospital Organization Nanao Hospital and conducted in accordance with the revised version of the guidelines in the Declaration of Helsinki (UMIN ID: UMIN000018679, date: 05.11.2015).

Informed Consent: Retrospective study.

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Footnotes

Authorship Contributions

Concept: J.H., M.F., Design: J.H., Data Collection or Processing: J.H., M.F., Analysis or Interpretation: J.H., Literature Search: J.H., M.F., M.Y., R.T., N.O., S.Y., Writing: J.H.

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