Upper airway cough syndrome may be the main cause of chronic cough in Japan: a cohort study

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Research

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Abstract

Background: Upper airway cough syndrome (UACS) is generally considered the main cause of chronic cough, but it is rarely recognised in Japan. This study identified the causes of chronic cough and assessed whether “UACS is the most common cause of chronic cough” in Japan, as it is in other countries. Although signs and symptoms of UACS are described as nonspecific, some items of interviews and examinations might be considered potentially useful in its diagnosis, and were evaluated for their association with it.

Methods: All patients with chronic cough who visited my clinic were preliminarily diagnosed based on interviews and examinations. Bronchial asthma and UACS were preferentially diagnosed. Among the excluded cases, some patients with gastrointestinal symptoms or diet-related cough were diagnosed with gastroesophageal reflux disease, while others were diagnosed with post-infectious prolonged cough. Nasal corticosteroids were administered to the UACS group, and standard treatment to the other groups. The observation period lasted 4 weeks. Subjective cough score at first diagnosis was set at 10, and final diagnosis was made based on the treatment administered when the cough score had decreased to ≤ 2 . The association between the presence or absence of UACS and interview and examination items was statistically evaluated using a logistic regression model.

Results: Among 230 patients with chronic cough, 146 were diagnosed with UACS-only. In the UACS-only group treated with nasal corticosteroids, 110 patients showed a significant improvement in cough scores within 2 weeks. Multivariate logistic regression revealed that assessment items “awareness of mucus accumulating in the back of the throat” (odds ratio [OR]: 4.613; 95% confidence interval [CI]: 1.124–18.928; $P=0.034$), “presence of abnormal echography findings” (OR: 15.725; 95% CI: 1.445–171.101; $P=0.024$), “absence of associated coughing when exercising” (OR: 0.212; 95% CI, 0.055–0.813; $P=0.024$), and “presence of coughing persisting after onset” (OR: 6.470; 95% CI, 1.755–23.843; $P=0.005$) were significantly associated with the presence or absence of UACS.

Conclusions: UACS is the most common cause of chronic cough in Japan, as in other countries, and can be effectively treated with nasal corticosteroids. Diagnosing UACS might be possible by selecting appropriate interview and examination items.

Background

Cough is one of the most common complaints of patients visiting both respiratory and general medicine departments. When cough lasts for 8 weeks or longer, it is considered chronic [1–4]. In 1998, the American College of Chest Physicians (ACCP) stated that postnasal drip syndrome was the most common cause of chronic cough [5]. However, given that the cough associated with postnasal drip syndrome is not simply due to mechanical irritation caused by postnasal drip [6–8], it was termed upper airway cough syndrome (UACS) associated with rhinosinusitis in 2006. According to the ACCP, UACS is the most common cause of chronic cough, and treatments for UACS are recommended for chronic cough of unknown aetiology [1]. The European Respiratory Society (ERS) recommends using the brief term “rhinosinusitis” for UACS [2, 6, 7,

9]. The diagnoses share the same status in terms of upper airway inflammation [9]. Furthermore, recently published ERS guidelines describe UACS as a cause of chronic cough [10].

Meanwhile, in the Japanese cough guidelines, cough variant asthma (CVA) is listed as the most common cause of chronic cough. Gastroesophageal reflux disease (GERD), sino-bronchial syndrome (SBS), and atopic cough (AC) are listed as other causes [3]. Few reports have shown that upper respiratory inflammation, such as UACS or rhinosinusitis, are the major causes of chronic cough in Japan. Niimi contested that racial differences may account for the low prevalence of UACS in Japan [11]. However, numerous studies on UACS have been reported from other Asian countries, and these reports indicate that UACS is a major cause of chronic cough in Asia. [12–19].

The aim here was to evaluate the prevalence of UACS in Japan by identifying the cause of chronic cough and to evaluate whether the ACCP statement that “UACS is the major cause of chronic cough” is valid in Japan. The ACCP also stated that “the symptoms and signs of UACS are nonspecific, and definitive diagnosis of UACS cannot be made from the medical history and physical examination alone” [20]. It was hypothesised that some interview and examination items associated with rhinosinusitis might be useful in UACS diagnosis. To evaluate this hypothesis, these items were compared between a UACS-only group and a group without UACS.

Methods

Patients with chronic cough who visited my clinic between March 2016 and July 2018 were included. Patients available for follow-up were prospectively treated, and the final diagnosis was evaluated (prospective analysis). The associations between interview and examinations items and UACS diagnosis was retrospectively examined (retrospective analysis).

Interviews and examinations at the first visit

Interviews (including questions in the questionnaire form shown in Table 1), pharynx and nasal cavity assessments, auscultation of the chest, chest radiography, pulmonary function tests, nasal discharge eosinophilic count, and maxillary sinus echography were performed at the first visit. The questionnaire was completed by the patients directly. All items in the list presented in Table 1 were checked.

Table 1

Checklist used at the time of initial visit: characteristics, examination findings, and questionnaire items

Characteristics	Assessment items	Standard
Age	Age	Year(s)
Sex	Male or female	M/F
History of smoking	Has there ever been a history of smoking, including previous smoking?	Y/N
History of asthma	Has there ever been a diagnosis of asthma?	Y/N
Physical and laboratory examination findings	Assessment items	Standard
Auscultation	Can wheezing, rhonchi, or squawking be heard on auscultation?	Y/N
Pharyngeal examination	Are there findings of postnasal drip in the oropharynx?	Y/N
Nasal cavity observation	Is there swelling or purulent nasal discharge in the middle or lower turbinates as observed using a nasal speculum?	Y/N
Pulmonary function test	Are there findings indicative of obstructive changes, such as decreases in FEV1, %FEV1, V50, and V25 or a convex curve below the FVC?	Y/N
Radiographic findings	Are there any findings that may cause coughing?	Y/N
Maxillary sinus echography	Can the posterior wall bone be observed in the maxillary sinus echography?	Y/N
Assessment of eosinophilic count in nasal discharge	Are there at least 1 + eosinophils in nasal swab specimens fixed onto glass slides?	Y/N
Items in the questionnaire form		
Regarding nasal symptoms	Assessment items	Standard
Awareness of runny nose	Is there awareness of runny nose?	Y/N
Awareness of nasal congestion	Is there awareness of nasal congestion?	Y/N
Awareness of postnasal drip	Is there awareness of postnasal drip?	Y/N
History of nasal symptoms	If there are no nasal symptoms, was there awareness of runny nose, nasal congestion, or postnasal drip prior to the onset of coughing?	Y/N
Regarding coughing	Assessment items	Standard
Duration of coughing	How many weeks has it been since you started coughing?	Week(s)

Characteristics	Assessment items	Standard
Coughing at night	Does coughing occur at night?	Y/N
Coughing at bedtime	Does coughing occur at bedtime or when lying down?	Y/N
Coughing at dawn	Does coughing occur at dawn?	Y/N
Choking coughing	Does coughing feel like choking?	Y/N
Coughing that persists after onset	Is there coughing that does not stop for a while after it begins?	Y/N
Coughing after infection	Were there subjective symptoms of infection that triggered coughing (fever, cough, phlegm, runny nose, etc.)?	Y/N
Diet-related coughing	Was coughing particularly frequent before and after or during meals?	Y/N
Coughing upon speaking	Is coughing induced by speaking?	Y/N
Coughing associated with atmospheric changes	Do atmospheric changes induce coughing?	Y/N
Coughing associated with changes in temperature	Do temperature differences (e.g. indoor to outdoor) induce coughing?	Y/N
Coughing upon exercising	Does exercise induce coughing?	Y/N
Coughing associated with warming of the body	Does warming the body induce coughing?	Y/N
Regarding conditions other than coughing	Assessment items	Standard
Presence of phlegm	Is there awareness of phlegm?	Y/N
Feeling of mucus accumulating in the back of the throat	Is there awareness of the feeling of phlegm or mucus accumulating in the back of the throat?	Y/N
Throat irritation	Is there an irritating sensation in the throat?	Y/N
Dry throat	Does the throat feel dry?	Y/N
Difficulty in breathing	Is there any difficulty in breathing or a feeling of tightness in the anterior chest?	Y/N
Wheezing	Is there awareness of wheezing?	Y/N
Clearing the throat	Is there awareness of throat clearing?	Y/N
Hoarse throat	Is there awareness of hoarse throat?	Y/N

Characteristics	Assessment items	Standard
Gastric symptoms	Is there awareness of gastric symptoms, such as acid reflux, epigastralgia, or nausea?	Y/N
FEV1, forced expiratory volume in 1 second; %FEV1, percent predicted forced expiratory volume in 1 second; V50, flow rate at 50% forced vital capacity; V25, flow rate at 25% forced vital capacity; FVC, flow volume curve		

Diagnosis at the first visit

I excluded patients who were under treatment that could cause coughing, such as with angiotensin converting enzyme inhibitors, or with abnormal shadows on chest radiography that could be indicative of conditions causing cough.

A preliminary diagnosis was made as shown in Fig. 1-A, B. First, the presence or absence of bronchial asthma (BA) was diagnosed based on the diagnostic criteria in accordance with the Global Initiative for Asthma [21]. Simultaneously, patients with symptoms of rhinosinusitis, such as postnasal drip, nasal discharge, and nasal congestion, or with abnormal findings on sinus echography (Fig. 2) were diagnosed with UACS. Patients who were not diagnosed with BA or UACS and had obvious gastric symptoms such as acid reflux, and a feeling of weight in the stomach or diet-related coughing were diagnosed with GERD. Patients who were not diagnosed with BA or UACS or GERD were diagnosed with post-infectious prolonged cough (PIPC). In view that CVA is a BA subtype, diagnosis of BA included both classical BA and CVA. Even if multiple diagnoses were possible, each patient was diagnosed with a single disease at the initial assessment to accurately evaluate the cause of the cough by clarifying the therapy effect of a single diagnosis. However, patients with both BA and UACS were diagnosed with combined conditions according to the concept of “one airway, one disease” [22].

Treatments

Treatment was initiated based on the preliminary diagnoses (Fig. 1-C).

Patients with BA received standard treatment according to the severity grade by combining inhaled corticosteroids, furancarboxylic acid fluticasone 100–200 µg, and long-acting beta agonist, vilanterol 25 µg once daily, and leukotriene receptor agonist, montelukast 10 mg once daily.

Patients with UACS were treated with nasal corticosteroids, beclomethasone dipropionate 50 µg twice daily or mometasone furoate 200 µg once daily, oral carbocysteine 500 mg thrice daily; and herbal medicines, Kakkonto-ka-senkyu-shin-i or Shin-i-seihai-to 2.5 g, thrice daily. Oral bepotastine 10 mg twice daily was added only to patients with strong symptoms of allergic rhinitis including sneezing, nasal discharge, and nasal congestion, and pallor of the middle or lower turbinates observed with a nasal speculum. In patients whose cough score did not decrease to ≤ 2 on first evaluation and whose eosinophilic count in nasal discharge was $\geq 1+$, nasal levocabastine was additionally administered at a dose of 0.2 mg; thrice daily

and/or nasal corticosteroid administration was changed to several drops of betamethasone (0.1%) twice daily as needed. Nasal betamethasone was not administered for longer than 2 weeks.

Famotidine 10 mg or rabeprazole 10 mg twice daily was administered to patients with GERD. Metoclopramide 5 mg thrice daily and domperidone 10 mg thrice daily were administered as needed.

Codeine phosphate 10 mg and Bakumondo-to 3 g, thrice daily were administered to patients with PIPC.

Assessment of cough improvement

The cough score in the initial diagnosis was set at 10; the degree of cough improvement was evaluated by the subjective cough score after the treatment. This assessment method has been shown to be highly correlated with the visual analogue scale score [23, 24].

Evaluation and final diagnosis

The observation period was set at 4 weeks. First evaluation was performed at 2 weeks after the start of treatment. Treatment was completed, continued, intensified, added, or changed based on the cough score (Fig. 1-D). The last evaluation was performed on week 4, final diagnosis was made based on the administered treatment at the time the cough score had decreased to ≤ 2 (Fig. 1-E).

Patients who did not respond to any treatment and had a cough score ≥ 8 were diagnosed with cough of unknown aetiology. In some patients who had reached a cough score ≤ 2 prior to week 4, treatment was completed early, and final diagnosis was made based on the administered treatment at that time. Patients with cough scores of 3–7 on week 4 were excluded because they were few ($n = 4$), these patients required continued treatment, and it was considered impossible to properly assess them within the pre-set 4-week follow-up period.

Statistical analysis

The group with a final diagnosis of UACS-only was compared with the group without UACS, and their differences in the items listed in Table 1 were evaluated. Median and 25th and 75th percentiles were obtained for continuous variables, and the Mann–Whitney U test was used to determine significant differences between the groups. The degree and frequency of the variables were obtained, and Fisher's exact test was used to determine significant differences between the groups.

Predictive models were generated to determine whether the final diagnosis of UACS could be predicted by the interview and examination items. Univariate logistic regression models with the final diagnosis of UACS as the dependent variable and individual items as explanatory variables were generated. A multivariate logistic regression model was generated by incorporating variables that achieved $p < 0.1$ in the univariate analyses as the explanatory variables. Model selection based on Akaike's information criterion was performed using the variable-reduction method. To evaluate the discriminatory ability of the generated models, receiver operating characteristic analyses were performed, and the area under the curve was calculated. All statistical analyses were performed using R version 3.3.3 (R Core Team 2017 m, Vienna, Austria). $p < 0.05$ was considered significant.

Results

Patient background

Five hundred and seventy-six individuals with chronic cough visited our clinic between March 2016 and July 2018. One patient who was using an angiotensin converting enzyme inhibitor and three patients with radiographic findings that could have caused the chronic cough were excluded. Two hundred and thirty patients who visited regularly 2 or 4 weeks after their initial visit, so that their clinical course could be followed, were evaluated. Patients who did not return and whose clinical courses could not be followed were excluded. The mean patient age was 43.3 ± 15.4 years; 96 (41.7%) were male, and 80 (34.8%) were smokers (including previous smokers). The median duration of coughing was 12 weeks, the interquartile range was 16 weeks, and the range was 8–500 weeks.

Final diagnosis and breakdown of the number of patients in each disease group by the period to final diagnosis

The final diagnosis in the 230 patients with chronic cough and the number of patients in each disease group broken down by the period until the cough score decreased to ≤ 2 are shown in Fig. 3. Among the 230 patients, 146 (63.5%) were classified in the UACS-only group, of whom 110 patients had achieved a cough score ≤ 2 within 2 weeks.

Characteristics of cough and absence/presence of nasal symptoms in the UACS-only group

Of the 146 patients diagnosed with UACS-only, 108 (74.0%) had productive and 38 (26.0%) had non-productive cough. Of the 108 patients with productive cough, 81 exhibited nasal symptoms, including postnasal drip. Of the 38 patients with non-productive cough, 24 exhibited nasal symptoms, including postnasal drip (Table 2).

Table 2
Characteristics of cough and absence/presence of nasal symptoms in the UACS-only group

	Wet cough (N = 108)	Dry cough (N = 38)
Non-silent UACS: nasal symptom (+) (N = 105)	81	24
Silent UACS: nasal symptom (-) (N = 41)	27	14
UACS, upper airway cough syndrome		

Statistical analyses results

Interview and examination items shown in Table 1 were compared between the group with a final diagnosis of UACS-only (n = 146) and the group without UACS (n = 18: GERD, 4; PIPC, 3; GERD + PIPC, 1; BA, 1; unknown, 9). A significant difference, ($p < 0.05$) was observed in the seven items listed in Table 3.

Table 3
Comparison of patient characteristics in the UACS-only group and without UACS group

	UACS-only (N = 146)	Without UACS (N = 18)	P-value
Swelling of the middle and lower turbinates (Yes)	92 (63.0%)	6 (33.3%)	0.021*
Runny nose (Yes)	70 (47.9%)	3 (16.7%)	0.012*
Existence of a possible trigger for infection (Yes)	86 (58.9%)	4 (22.2%)	0.005*
Awareness of postnasal drip (Yes)	43 (29.5%)	1 (5.6%)	0.045*
Presence of abnormal maxillary sinus echography findings (Yes)	144 (98.6%)	15 (83.3%)	0.010*
Cough that persists after onset (Yes)	99 (67.8%)	7 (38.9%)	0.020*
Awareness of wheezing (Yes)	13 (8.9%)	5 (27.8%)	0.031*
*P < 0.05 UACS, upper airway cough syndrome			

Ten items with $p < 0.1$ in the univariate analysis are shown in Table 4.

Table 4

Items with $P < 0.1$ in univariate logistic regression analysis (with presence/absence of UACS as objective variable)

	Odds ratio	95% lower limit	95% upper limit	P-value
Duration of coughing (weeks)	0.995	0.990	1.001	0.082
Existence of a possible trigger of infection (Y/N)	5.017	1.704	18.372	0.006*
Runny nose (Y/N)	4.605	1.445	20.489	0.019*
Awareness of the presence of postnasal drip (Y/N)	7.097	1.389	129.869	0.060
Awareness of the presence of sputum from the nose that accumulated at the back of the throat (Y/N)	5.963	2.022	21.871	0.002*
Findings of middle and lower turbinate swelling (Y/N)	3.407	1.248	10.274	0.020*
Coughing upon exercise (Y/N)	0.406	0.147	1.186	0.086
Cough that does not stop after onset (Y/N)	3.31	1.226	9.511	0.020*
Awareness of the presence of wheezing (Y/N)	0.254	0.081	0.89	0.022*
Presence of abnormal findings on maxillary echography (Y/N)	14.4	2.224	116.126	0.005*
* $P < 0.05$ UACS, upper airway cough syndrome				

A full model incorporating these 10 items was generated, and selection of variables using the variable-reduction method based on Akaike's information criterion was performed. After reconstructing the model, a significant association with the presence or absence of UACS ($p < 0.05$) was found with the following assessment items: "awareness of mucus accumulating in the back of the throat" (odds ratio [OR]: 4.613; 95% confidence interval [CI], 1.124–18.928; P -value = 0.034), "presence of abnormal echography findings" (OR: 15.725; 95% CI, 1.445–171.101; P -value = 0.024), "absence of associated coughing when exercising" (OR: 0.212; 95% CI, 0.055–0.813; P -value = 0.024), and "presence of coughing persisting after onset" (OR: 6.470; 95% CI, 1.755–23.843; P -value = 0.005) (Table 5).

Table 5

Results of multivariate analysis using a binomial logistic regression model: after backward stepwise model selection

	Odds ratio	95% CI lower limit	95% CI upper limit	P-value
Existence of a possible trigger for infection (Y/N)	4.011	0.984	16.355	0.052
Awareness of mucus accumulating in the back of the throat (Y/N)	4.613	1.124	18.928	0.034*
Presence of abnormal maxillary sinus echography findings (Y/N)	15.725	1.445	171.101	0.024*
Coughing upon exercise (Y/N)	0.212	0.055	0.813	0.024*
Cough that persists after onset (Y/N)	6.47	1.755	23.843	0.005*
Awareness of postnasal drip (Y/N)	4.627	0.43	49.774	0.206
Swelling of the middle and lower turbinates (Y/N)	2.543	0.712	9.088	0.151
*P < 0.05; CI, confidence interval; UACS, upper airway cough syndrome				

Receiver operating characteristics analyses were performed to evaluate the discriminatory ability of the multivariate model, and the area under curve was 0.863. The sensitivity was 72.60%, the specificity was 94.44%, the positive predictive value was 99.07%, and the negative predictive value was 29.82%.

Discussion

UACS is widely recognized as a cause of chronic cough. However, its prevalence is considered low in Japan [3, 11]. As it is unlikely that Japan constitutes the only exception, this study was conducted to examine the actual UACS prevalence in Japan. In this study, UACS was the most common cause of chronic cough. It was effectively treated by nasal corticosteroids. Some interview and examination items were useful for UACS diagnosis.

According to the ACCP guidelines, antihistamines/decongestants are recommended for UACS treatment, and the diagnosis should be based on the response to antihistamines in addition to symptoms and examinations [1]. The concept of "silent UACS" without nasal symptoms, diagnosed only by the efficacy of antihistamine treatment was also presented [20, 25]. First-generation antihistamines are recommended for UACS treatment [1]. The mechanism of action is considered to be mainly anticholinergic (suppression of cholinergic vagal reflex); the binding affinity of histamine receptors may not be highly correlated, but no definite conclusion has been reached [26]. This medicine may have strong sedative–hypnotic side effects, which can cause antitussive activity [6]. Therefore, instead of first-generation antihistamines, nasal corticosteroids were administered, as recommended by the European and American guidelines for rhinosinusitis, in this study [27–32]. Because UACS and rhinosinusitis share the same pathophysiological

status, treatment with nasal corticosteroids for UACS is appropriate and has been previously reported [33, 34]. In this study, in 110 (75.3%) of the 146 patients with a final UACS-only diagnosis, cough scores significantly improved (from 10 to ≤ 2) within only 2 weeks with nasal corticosteroid administration. Although ERS cough guidelines state that there is no evidence of localised treatment being effective against UACS [10], this finding indicates that inflammation in the nasal cavity plays a central role in the pathophysiology of UACS. Compared with antihistamines, nasal corticosteroids constitute a potent therapeutic option for UACS in terms of efficacy, side effects, and clarification of the location of the primary pathophysiology. The efficacy and mechanism of action of herbal medicines used for treating rhinosinusitis have been demonstrated in Japan, China, and Korea [35–42].

UACS is described only briefly in the Japanese cough guideline [3] and is poorly recognised [11]. It would be interesting to examine why this is the case. The Japanese Cough Guidelines state that CVA, SBS, AC, and GERD are the major causes of chronic cough [3]. SBS, which is defined as chronic recurrent neutrophilic inflammation of the upper and lower airways, is described as a cause of chronic cough only in the Japanese guidelines. Macrolides are effective in treating SBS, and the therapeutic effect is determined based on improvements within 4–8 weeks after administration [3]. Although the concept of SBS differs from that of UACS in that it defines the presence of lower-airway as well as upper-airway lesions (rhinosinusitis), its clinical status largely overlaps with that of UACS [25]. In other words, rhinosinusitis as a cause of chronic cough has been incorporated into the SBS concept and is not recognized as a separate causative disease in Japan. AC had been reported mostly from Japan [43–45]. The condition has been defined as dry cough that can be effectively treated with inhaled corticosteroids or antihistamines and is characterised by eosinophilic central airway inflammation [3, 43, 44]. The concept of AC pathophysiologically overlaps with those of CVA and non-asthmatic eosinophilic bronchitis, and whether AC is an independent disease remains controversial [2, 11, 25, 46]. Niimi and Yu noted that AC may overlap with silent UACS, which is not associated with nasal symptoms and the associated cough symptoms can be improved in this case with antihistamine administration [11, 25]. Additionally, UACS associated with allergic rhinitis that can be ameliorated by antihistamines may overlap with AC. As these diseases overlapping with UACS are recognized as causes of chronic cough, UACS may not be recognized as a cause in itself in Japan.

ACCP reported that “the symptoms and signs of UACS are nonspecific, definitive diagnosis cannot be made from the medical history and physical examination alone” [1]. Several interview and examination items associated with rhinosinusitis were useful in diagnosing UACS in this study. The questions shown in Table 1 refer to common cough-related patient complaints and the major rhinosinusitis guidelines in the United States and Europe [27–32]. These guidelines utilise both clinical symptoms and objective findings for rhinosinusitis diagnosis. Given that UACS shares the same status with rhinosinusitis, it is reasonable to refer to the features of rhinosinusitis for the diagnosis of UACS. All guidelines recommend computed tomography, but echography might be a useful diagnostic tool, as it is economical, convenient, and does not involve radiation exposure [47–49].

More than half of patients presenting with chronic cough were excluded because they did not revisit the clinic for various reasons, and their clinical course could not be followed up. Many of them did not visit the clinic because their symptoms improved. On the other hand, some patients may not have been able to visit the clinic because their symptoms did not improve. There are no data on the extent and duration of cough improvement in these cases. Nevertheless, patients who did not return should have been followed up over the phone or by other means. More patients were diagnosed with UACS than with BA in this study. In general, outpatients often consult a physician before their cough becomes chronic. CVA is generally recognised among general practitioners because the Japanese guidelines specify CVA as the major cause of chronic cough [3]. Therefore, in many cases, inhaled corticosteroids had been empirically administered before the patients visited my clinic (data not shown). Thus, the possibly high number of cases that had not improved with inhaled corticosteroid use may have inflated the prevalence UACS over CVA as a cause of chronic cough. In addition, most patients with BA presented with nasal symptoms or abnormal echography findings and received UACS treatment. Although some patients should have been diagnosed with BA only, they may have been over-diagnosed with complicated UACS. The diagnosis of BA and UACS should have been separated. However, even when all these patients were diagnosed with BA only, the prevalence of UACS in patients with chronic cough was 63.5%. This result indicates that UACS remained the most common cause of chronic cough. The large difference in the number of patients with UACS-only and those without UACS may have biased the statistical results regarding the diagnostic items. This bias may be avoided by equalising the number of patients. This correction may lead to more accurate identification of diagnostic items for UACS. The interview and examination items were limited, and there might be additional items that could be useful for diagnosis. In this study, nine patients were diagnosed with cough of unknown aetiology. In 2016, a systematic review of randomized controlled trials of unexplained chronic cough showed that gabapentin was the only recommended treatment [50]; hence, gabapentin should have been considered to treat cough of unknown aetiology in this study.

Conclusions

“UACS is the most common cause of chronic cough,” as stated by the ACCP, appears to also apply to the Japanese population based on our findings, and it can be effectively treated with nasal corticosteroids. Some interview and examination items may be able to increase the diagnostic accuracy of UACS.

Abbreviations

AC
atopic cough
ACCP
American College of Chest Physicians
BA
bronchial asthma
CI
confidence interval;

CVA
cough variant asthma
ERS
European Respiratory Society
GERD
gastroesophageal reflux disease
OR
odds ratio
PIPC
post-infectious prolonged cough
SBS
sino-bronchial syndrome
UACS
upper airway cough syndrome

Declarations

Ethics approval and consent to participate and consent for publication

This clinical study was performed in accordance with the Declaration of Helsinki, with the approval of the institution's ethics review board (#15-06-01). Informed consent was not required because, instead of obtaining direct consent from patients, Information such as research purposes, methods, and handling of personal information was posted in the clinic and on the website. Participants were provided with the opt-out opportunity to refuse or drop out of the study. I ensured that patient anonymity was respected by removing any detail that may have led to patient identification.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Competing interests

The author declare that I have no competing interests.

Author information

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Supplementary Information

Additional file 1. Table S1: Comparison of all items of interviews and examinations between the UACS-only group and without UACS group. Table S2: Univariate logistic regression analyses using the presence or absence of UACS as an objective variable. Table S3: Results of multivariate analysis using a binomial logistic regression model to determine whether UACS is present or not. Table S4: Discriminant performance evaluation results of the final built model; discrimination result. Figure S1: Discriminant performance evaluation results of the built model: ROC curve

Figures

Figure 1

Flow chart of diagnosis and treatment. GINA, global initiative for asthma; BA, bronchial asthma; UACS, upper airway cough syndrome; GERD, gastroesophageal reflux disease; PIPC, post infectious prolonged cough; ICS, inhaled corticosteroids; LABA, long-acting beta agonist; LTRA, leukotriene receptor agonist;

Figure 2

Abnormal maxillary sinus echography. The sector probe was moved vertically to the horizontal line of the maxillary sinus to confirm whether the posterior wall bone could be observed. The posterior wall bone is usually not visible.

Figure 3

Diagnosis and breakdown of patient number in each disease group by period till final diagnosis. UACS, upper airway cough syndrome; BA, bronchial asthma; GERD, gastroesophageal reflux disease; PIPC, post infectious prolonged cough

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