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Clinical diagnosis of current asthma: predictive value of respiratory symptoms in the SAPALDIA study

D. Sistek*, J-M. Tschopp*, C. Schindler#, M. Brutsche*, U. Ackermann-Liebrich#, A-P. Perruchoud¶, P. Leuenberger+ and SAPALDIA team+

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ABSTRACT: Bronchial asthma is a very common disease which often remains underdiagnosed. The aim of this study was to determine the predictive value of the most common respiratory symptoms and to explore the best symptom combinations to predict diagnosis of asthma.

A questionnaire comprising common respiratory symptoms was submitted to 9,651 subjects aged 18–60 yrs, randomly selected from the Swiss population, of whom 225 subjects (2.3%) had current asthma as confirmed by their general practitioner. Based on these data the authors calculated the predictive values of single symptoms and symptom combinations to diagnose asthma.

Wheezing was the most sensitive single symptom (sensitivity 75%). Simple symptoms such as wheezing with dyspnoea, chronic phlegm or chronic cough had specificity greater than 95%. Wheezing with dyspnoea (WD) or nocturnal dyspnoea (ND) had the best positive predictive value (PPV) as isolated symptoms (24% and 21%, respectively). When combining symptoms, wheezing associated with daily dyspnoea at rest or nocturnal dyspnoea showed the best PPV (42% and 39%, respectively), almost double single symptoms such as WD or ND. Wheezing associated with at least two of the three nocturnal symptoms (nocturnal dyspnoea, nocturnal cough or nocturnal chest tightness) had a sensitivity of 80% to diagnose asthma.

In conclusion, respiratory symptoms obtained by medical history are reliable predictors of asthma. The findings suggest that particular combinations of symptoms are clinically useful in the differential diagnosis of asthma.

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*Centre Valaisan de Pneumologie Montana, Suisse, #Institut de Médecine Sociale et Préventive Bâle, Suisse, ¶Dept de Médecine Interne, Hôpital Universitaire de Bâle, Bâle, Suisse and +Division de Pneumologie, Centre Hospitalier Universitaire Vaudois, Lausanne, Suisse.

Correspondence: Dr J. Tschopp PD, Centre Valaisan de Pneumologie, 3962 Montana, Suisse. Fax: 41 27603 81 81

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Asthma is a common respiratory disease which affects more than 5% of the Swiss population [1]. The prevalence of asthma varies considerably among studies due to the lack of well accepted definitions [2] and the different clinical or epidemiological approaches, and underlying population characteristics. Asthma can present with a broad variety of symptoms. Chronic cough may be the sole presenting symptom of asthma [3–5]. The classical triad of dyspnoea, cough and wheezing does not have a sufficient predictive value to diagnose asthma. BAUMANN *et al.* [6] showed that only 36% of asthmatics have these three symptoms simultaneously. Isolated symptoms, such as wheezing or dyspnoea, have been shown to be better predictors of asthma. In a longitudinal study of more than 1,000 subjects, BURROWS *et al.* [7] showed that wheezing was the predominant symptom in recently diagnosed asthma. A European study based on the European Respiratory Survey confirmed the strong correlation between asthma and wheezing or nocturnal dyspnoea (relative risk of 29% and 26%, respectively). The correlation with chest tightness and nocturnal cough was weaker (relative risk of 13% and 3%, respectively) [8]. To the authors' knowledge, no study has previously looked for the best symptom or combination of symptoms that would enable any general practitioner to reliably diagnose bronchial asthma through medical history.

The aim of this study was to determine the diagnostic value of isolated respiratory symptoms in a large cohort of asthma patients drawn from the general population, and to find combinations of symptoms with the best predictive value for the diagnosis of bronchial asthma.

Materials and methods

The data were collected from the SAPALDIA (Swiss Study on Air Pollution and Lung Diseases in Adults) study, a project financed by the Swiss National Research Foundation [9].

Patients

Out of 17,500 subjects (aged 18–60 yrs), randomly selected from eight Swiss areas 9,651 (59%) participated

in the study and correctly replied to a standardized and computerized questionnaire on respiratory symptoms. It was based on the questionnaire of the European Community Respiratory Health Survey and used in three languages (German, Italian and French) depending on the investigated area. There were no significant differences in the demographic data (age, race, sex, social status) between the subjects who participated and those who refused to participate [9]. The cohort studied was therefore representative of the selected population.

Respiratory symptoms

The following questions were asked, relating to different symptoms: 1. Wheezing (W): Have you had wheezing or whistling in your chest at any time in the last 12 months? 2. Wheezing with dyspnoea (WD): Have you been breathless when the wheezing noise was present the last 12 months? 3. Wheezing without cold (WwC): Have you had this wheezing or whistling during the last 12 months when you did not have a cold? 4. Nocturnal chest tightness (NCT): Have you woke up with a feeling of tightness in your chest at any time in the last 12 months? 5. Rest dyspnoea (RD): Have you had an attack of shortness of breath when you were at rest at any time in the last 12 months? 6. Exercise dyspnoea (ED): Have you had an attack of shortness of breath that came on following strenuous activity at any time in the last 12 months? 7. Nocturnal cough (NC): Have you been woken up by your coughing at any time in the last 12 months? 8. Nocturnal dyspnoea (ND): Have you ever been woken up by an attack of shortness of breath at any time in the last 12 months? 9. Chronic cough (CC): Do you usually cough during the day or at night in the winter, *i.e.*, do you usually cough during the day or at night, on most days for as much as 3 months each year over at least 2 years? 10. Chronic phlegm (CP): Do you usually bring up any phlegm from your chest during the day or at night in the winter, *i.e.*, do you usually bring up any phlegm from your chest during the day or at night, on most days for as much as 3 months each year over at least 2 years? Chronic bronchitis (CB) corresponds to chronic cough and phlegm.

Definitions of asthma

Current asthma was defined by positive responses to each of the following questions: 1. Do you have or have you ever had asthma? 2. Was asthma confirmed by a medical practitioner? 3. Have you ever had at least one asthma attack during the last 12 months? Asthma was defined as positive responses to the first two questions only. Only subjects with current asthma were considered for this study.

Analysis

All answers to the questionnaire were entered into a computer database by specifically trained staff. Statistical analyses were performed with the SAS program [9].

Definition of diagnostic predictor

These indices were calculated according to GRENIER [10] and WEINSTEIN [11]. A predictor may be a clinical test, a symptom or a combination of symptoms. Sensitivity (S) is the frequency of positive predictor values among subjects with the disease. Specificity (SP) is the frequency of negative predictor values among subjects without the disease. The positive predictive value (PPV) is the probability that a subject has the disease when the predictor is positive. The negative predictive value (NPV) is the probability that a subject does not have the disease when this predictor is negative. The Youden index (J) evaluates the diagnostic efficacy of a test. It is expressed as $J=(S+SP)-1$. If the index is equal or below 0, the diagnostic efficacy of the test is poor. On the other hand, the closer it is to 1, the higher is its diagnostic value.

Search for the best combinations of symptoms

The best combinations of symptoms to predict the diagnosis of asthma were found according to the following method:

Step 1: All the possible combinations of the 11 individual symptoms were investigated. A yes or no answer to each question gives 2^{11}, *i.e.* 2,048 different combinations of individual symptoms. Among these possibilities, the authors only selected combinations which included at least 50% of asthmatics. This reduced the number of combinations to 51. Step 2: Of the asthmatics showing one of the 51 selected combinations, the authors calculated the prevalence of each of the 11 symptoms. The single symptoms with the highest prevalence were thus the most predictive for asthma in these combinations of symptoms. Step 3: A certain number of asthmatics (57/225, 25%) did not have any wheezing, the most prevalent symptom. Therefore, it was crucial to identify the most common symptom among these asthmatics. Using the same method as described in step 2, the authors looked for the prevalence of each of the eight remaining symptoms among the combinations of individual symptoms which do not include the three types of wheezing (W, WD, WwC) in nonwheezer asthmatics. This analysis gave us the prevalence of the most frequent symptoms among subjects with current asthma who had no wheezing at all in the last 12 months. Step 4: Combinations of symptoms were constructed from the individual symptoms selected in steps 2 and 3, and their value as a predictor was calculated.

Results

Two-hundred and twenty-five subjects (2.3%) suffered from current asthma at the time of the study, and were therefore included. Out of the initial population of 9,651 subjects, 1,360 (14%) reported

Table 1. – Diagnostic value of isolated symptoms

Symptom	S%	SP%	PPV%	NPV%	J
Wheezing	74.7	87.3	12.4	99.3	0.62
Wheezing with dyspnoea	65.2	95.1	23.9	99.1	0.6
Wheezing without cold	59.8	93.6	18.2	99	0.53
Nocturnal chest tightness	49.3	86.4	8	98.6	0.36
Rest dyspnoea	47.1	94.9	18	98.7	0.42
Exercise dyspnoea	69.3	75.7	6.4	99	0.45
Nocturnal dyspnoea	46.2	96	21.5	98.7	0.42
Nocturnal cough	49.3	72.3	4.1	98.4	0.22
Chronic cough	21.5	95.2	9.6	98.1	0.17
Chronic phlegm	22.7	93.3	7.5	98.1	0.16
Chronic bronchitis	12.5	98.2	14	97.9	0.11

S: sensitivity; SP: specificity; PPV: positive predictive value; NPV: negative predictive value; J: Youden index.

wheezing, whatever the form. Wheezing in any form was the most prevalent symptom (168/225; 75%) in asthmatics. All symptoms, except isolated wheezing (W), nocturnal chest tightness, exercise dyspnoea and nocturnal cough, had a specificity of $>90\%$. Wheezing with dyspnoea and nocturnal dyspnoea had the best positive predictive values (23.9% and 21.5%, respectively). The negative predictive value of all the symptoms was higher than 97.9%. The three types of wheezing (table 1) produced the best Youden index.

Selection of individual symptoms to build up symptom combinations

In step 2, wheezing was present in more than 94% of asthmatics. The three chronic symptoms (CP,CC and CB) were excluded because of their low prevalence (table 2). Of the asthmatics who did not show any form of wheezing (step 3), nocturnal symptoms (ND, NCT and NC) and exercise dyspnoea were the most frequent symptoms. The three chronic symptoms, expectoration, cough and bronchitis (CP, CC and CB, respectively) were also excluded from the selection of symptoms because of their low prevalence (table 3). The remaining symptoms were then systematically combined (step 4), and the diagnostic value of each of the combinations evaluated for the whole cohort.

Table 2. – Prevalence of symptoms in asthmatics (168/225; 75%) who belong to the 51 best combinations of symptoms

Symptom	Prevalence %
Wheezing	94.4
Wheezing with dyspnoea	87.6
Wheezing without cold	79.8
Exercise dyspnoea	82
Nocturnal chest tightness	67.4
Nocturnal dyspnoea	68.5
Rest dyspnoea	71.9
Nocturnal cough	68.5
Chronic phlegm	43.8
Chronic cough	42.7
Chronic bronchitis	24.7

Table 3. – Prevalence of symptoms in nonwheezer asthmatics (57/225; no wheezing, no wheezing with dyspnoea and no wheezing without cold)

Symptom	Prevalence %
Exercise dyspnoea	57
Nocturnal cough	41
Rest dyspnoea	32
Nocturnal dyspnoea	30
Nocturnal chest tightness	30
Chronic chough	16
Chronic phlegm	14
Chronic bronchitis	9

Diagnostic value of symptom combinations

The diagnostic value of symptoms are presented in table 4. The best sensitivity (80%) was obtained by combining wheezing with two nocturnal symptoms (combination 15). The specificity of all the combinations was higher than 92% when combination 15 (wheezing associated with 2 nocturnal symptoms) and combination 16 (which includes only the nocturnal symptoms) were excluded. Combining wheezing with rest dyspnoea (combination 2) produced the best PPV. Wheezing accompanied by nocturnal dyspnoea or rest dyspnoea (combinations 4 and 5, respectively) produced a PPV slightly less than 40%. Combination 16, which combines the three nocturnal symptoms, was particularly mediocre with a specificity of 63.5% and a PPV of less than 5%. Combinations 7, 10 and 15 had the best Youden index. All 16 combinations had a similar NPV close to 100%.

Discussion

Bronchial asthma is one of the most important chronic respiratory diseases with a continuously rising morbidity [12 – 14]. The costs of asthma are high [15], and it is worthwhile to improve its diagnosis. The prevalence of current asthma in this study was 2.3%. NEUKIRCH *et al.* [8] found a slightly higher prevalence of current asthma between 2.7% and 4.0% depending on the regions they studied (Grenoble and Paris, respectively). A multicentre study from Italy [16] also showed a similarly higher prevalence of asthma between 2.5% and 3.6%. The principal reason for this difference is due to the authors′ more restrictive definition of asthma. To diagnose asthma in this study, subjects had to not only have been previously asthma diagnosed by a physician, but also have suffered from at least one asthma attack within the last 12 months. The aim of this study was not to establish the prevalence of either asthma or its symptoms, though both prevalences were astonishingly similar to those shown in the European Community Respiratory Health Survey (ECRHS) [8, 16, 17] which crossed linguistic barriers. This is not surprising since this study used the same questionnaire as in the ECHRS. There were no significant differences in prevalences between the three speaking areas: French, German and Italian. The authors′ aim was to determine how a clinician could use symptoms drawn from simple medical history to better diagnose asthma. The

Table 4. – Diagnostic value of symptom combinations in the diagnosis of active asthma

Symptom combination	S%	SP%	PPV%	NPV%	J
W and NCT	40.9	97.5	28.1	98.6	0.38
W and RD	38.4	98.7	42	98.5	0.37
W and ED	54.2	95.7	23.1	98.9	0.5
W and ND	37.5	98.6	39.3	98.5	0.36
W and (RD a/o ND)	51.3	98	38.3	98.8	0.49
W and (RD a/o ND a/o NCT)	56.3	96.8	29.4	98.9	0.53
W and (RD a/o ND a/o ED a/o NCT)	65.2	94.5	21.9	99.1	0.6
(W a/o NC) and (RD a/o ND)	57.8	95.8	24.8	99	0.54
(W a/o NC) and (RD a/o ND a/o NCT)	63.1	91.6	15.2	99	0.55
(W a/o NC) and (RD a/o ND a/o ED a/o NCT)	75.1	84.6	10.5	99.3	0.6
(W a/o NCT) and (RD a/o ND a/o NC)	67.9	89.7	13.6	99.2	0.58
(W a/o NCT) and (RD a/o ND)	58	95.6	23.8	99	0.54
(W a/o ND) and NCT	46.2	95.8	20.7	98.7	0.42
(W a/o ND) and RD	43.6	97.9	32.9	98.6	0.41
W a/o 2 nocturnal symptoms	80	85.9	11.9	99.4	0.66
(NC a/o ND a/o NCT)	75.1	63.5	4.7	99.1	0.3

S: sensitivity; SP: specificity; PPV: positive predictive value; NPV: negative predictive value; J: Youden index. W: any wheezing; NCT: nocturnal chest tightness; RD: rest dyspnoea; ED: exercise dyspnoea; ND: nocturnal dyspnoea; NC: nocturnal cough; a/o: and/or; nocturnal symptoms: NCT, ND or NC.

participation rate in the study was slightly lower than that in the European Survey. To ensure the quality of the response, the methodology of the ECHRS was followed and only specifically trained staff were used, who entered the data into the computer immediately and in the presence of the subjects.

As shown by TOREN *et al.* [2], diagnosis of asthma cannot be based exclusively on functional criteria. There are still no gold standard specific markers to diagnose asthma. Bronchial hyperreactivity (BHR) could have been used as a marker in the diagnosis of asthma, as discussed in a previous publication [18]. However, as WOOLCOCK pointed out [19], BHR is not at all specific for asthma. It can be found in patients with other diseases, especially chronic obstructive pulmonary diseases [20] or can be absent in patients with asthmatic symptoms [21, 22], probably indicating episodic asthma. The present authors therefore decided not to use BHR, despite the fact that most of our subjects participated in the methacholine test.

PEKKANEN and PEARCE [23] recently produced a review on the definition of asthma in epidemiological studies. They showed poor agreement between objective laboratory measurements such as BHR and clinical asthma. They suggested that although clinical asthma cannot be considered to be a true gold standard of asthma, it currently represents the most appropriate standard for use in validating instruments for epidemiological studies. JENKINS *et al.* [24] tried to validate an asthma questionnaire with or without BHR to diagnose asthma. Interestingly, they concluded that adding BHR to an asthma symptom questionnaire would dramatically decrease the sensitivity to detect clinical asthma and miss the majority of asthmatics involved in this epidemiological study. Since there is no gold standard to define asthma, the diagnostic approach was limited to current asthma as confirmed by a medical doctor, as used by BURROWS *et al.* [7].

In medical practice any physician will make a diagnosis of asthma on a collection of symptoms and not on the basis of an isolated symptom or diagnostic tests such as methacholine challenge. However as far as the authors are concerned, no other study has ever addressed the diagnostic value of combinations of symptoms when making a diagnosis of asthma.

Wheezing, in whatever form, has a high diagnostic value as single symptom, with not only a good sensitivity and a well conserved specificity, but an excellent PPV and was associated with the best Youden index (table 1). The combination of wheezing, in whatever form, associated with two nocturnal symptoms (cough, dyspnoea or chest tightness) had the best Youden index with well conserved sensitivity and specificity (combination 15, table 4); these symptoms can also be seen in combinations 8 and 12 of table 4.

The results show that it would be advantageous for any clinician to look more systematically for the presence of wheezing when attempting to make a diagnosis of asthma and to ask the patient about nocturnal symptoms. As shown by GROSS [25] many years ago, there is no universally accepted definition of asthma. None of the definitions which have been put forward over time [26 – 31] relate its diagnosis only to respiratory symptoms. There are also pitfalls in epidemiological questionnaires. For example, answers to the various questions on respiratory symptoms depend on many factors: patient′s memory and understanding of the questions, over and underreporting of symptoms, *etc.* will all influence the answers to the questionnaire [29]. The authors have attempted to avoid as many imprecisions as possible: the questionnaire was conducted by a trained technician using a computer to record answers immediately. The SAPALDIA questionnaire is an extended version of the questionnaire used in the European Community Respiratory Health Survey [1, 17]. Other studies have used the same questionnaire but have not attempted to calculate the sensitivity and specificity of the different symptoms in asthmatics [8, 16].

It remains to be seen whether the symptomatic profile found in the present study is coherent with other epidemiological studies on bronchial asthma. Many

authors have been interested in asthmatic symptoms. Using a questionnaire distributed to 1,444 subjects recruited by medical practitioners around London, LITTLEJOHNS *et al.* [32] determined that of 33 diagnosed asthmatics, 94% suffered from wheezing, 91% from cough, 94% from dyspnoea and 89% from production of phlegm. This last symptom was only present in 22% of our asthmatics. Nocturnal symptoms are equally frequent. Two studies have shown that more than 90% of asthmatics are woken up at least once per month by these symptoms [33, 34]. Guidelines of the International Asthma Management Project, 1992 [35] include nocturnal symptoms not only in the diagnosis but in the classification of asthma severity. However the present study showed that isolated nocturnal symptoms are poor predictors of asthma (table 1).

Many authors *i.e.* refs. [3–5] have confirmed that cough may be the only symptom of asthma, although there are only a few studies published on this topic, with small numbers of subjects, hence questioning whether serious conclusions may be drawn. For general medical practice, the present study allowed identification of more than 200 asthmatics from a cohort of about 10,000 subjects, and showed that nocturnal and chronic cough are neither sensitive nor specific enough to predict the diagnosis of asthma.

Many studies have shown that wheezing is a symptom that is equally frequently found in asthmatics and the general population. DODGE *et al.* [36] found that the prevalence of wheezing accompanied by dyspnoea is 10% and depending on the age group considered, wheezing represents up to 30% of all respiratory symptoms. They did not examine the diagnostic value of symptoms in asthma. MORTAGY *et al.* [37] found a wheezing prevalence of 27% in more than 2,200 subjects. PEAT *et al.* [38], in a study using more than 5,000 subjects, showed a wheezing prevalence of 24.2% and LITTLEJOHNS *et al.* [32] found a prevalence of wheezing of 21% (313/1,444). In the study of NEUKIRCH *et al.* [8], prevalence of wheezing was 14% in the general population. It can be concluded from this study that 25% of asthmatics do not wheeze, and that the prevalence of wheezing in the general population is very similar to previous studies. All these studies underline the importance of wheezing in asthma, but also that it is not necessarily present in this disease.

It is interesting to note that DODGE *et al.* [36], using a different statistical approach, found that of 36 newly diagnosed asthmatics, the PPV of the combination of dyspnoea with wheezing, cough and chronic bronchitis was 29%. NEUKIRCH *et al.* [8] showed that the relative risk of having bronchial asthma is markedly elevated for subjects who suffer from nocturnal dyspnoea or wheezing (associated either with or without dyspnoea).

Medical textbooks describe dyspnoea as a diagnostic symptom of asthma, an observation which is confirmed in the present study, taking a cohort of 225 asthmatics from a normal population. Wheezing accompanied by nocturnal dyspnoea or dyspnoea at rest has a very good diagnostic value (combinations 2, 4 and 5, table 4). One has to be aware that in the combinations drawn from the present study, subjects may show the different symptoms at different times, a fact which must be distinguished from the isolated symptom (WD) where wheezing and dyspnoea were simultaneously present. When combining these two symptoms, PPV almost doubles from 23% to 40%. The other combinations of symptoms, though more complex, do not improve the diagnostic value of the history and are therefore not very useful in clinical practice for the diagnosis of asthma.

In conclusion, this study showed that wheezing with dyspnoea is the best isolated symptom for the diagnosis of asthma. As for the combinations of symptoms, the association of wheezing with two of the three nocturnal symptoms (nocturnal dyspnoea, chest tightness and cough) is the best anamnestic tool to diagnose asthma. It needs to be emphasised that these results have been obtained from an epidemiological study which may possibly limit its clinical value. However, the data suggest that clinicians should focus on particular combinations of symptoms in the differential diagnosis of asthma prior to confirmation by paraclinical objective tests.

SAPALDIA (Swiss Study on Air Pollution and Lung Diseases in Adults) Team: Study director: P. Leuenberger (p); Program director: U. Ackermann-Liebrich (e); Members: P. Alean (am), K. Blaser (a), G. Bolognini (p), J.P. Bongard (p), O. Brändli (p), P. Braun (p), C. Bron (l), M. Brutsche (l), C. Defila (m), G. Domenighetti (p), S. Elsasser (1), L. Grize (s), P. Guldimann (1), P. Hufschmid (1), W. Karrer (p), H. Keller-Wossidlo (o), R. Keller (p), N. Künzli (e), J.C. Luthy (1), B.W. Martin (e), T. Medici (p), C. Monn (am), A.G. Peeters (pa), A.P. Perruchoud (p), A. Radaelli (1), C. Schindler (s), J. Schwartz (s), G. Solari (p), M. Schöni (p), J.M. Tschopp (p), P. Villiger (p), B. Wüthrich (a), J.P. Zellweger (p), E. Zemp (e). (a): allergology, (am): air pollution monitoring, (e): epidemiology, (1): local assistant (MD), (m): meteorology, (o): occupational medecine, (p): pneumology, (pa): pathology, (s): statistics.

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