

Prevalence of bronchial hyperresponsiveness to 4.5% saline and its relation to asthma and allergy symptoms in Austrian children

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Prevalence of bronchial hyperresponsiveness to 4.5% saline and its relation to asthma and allergy symptoms in Austrian children. J. Riedler, A. Gamper, W. Eder, G. Oberfeld. ©ERS Journals Ltd 1998.

ABSTRACT: The prevalence of asthma in school children has been reported to have increased, with wide variations between countries. To allow comparison of prevalence data, objective markers of asthma should be measured.

Therefore, we assessed the prevalence of bronchial hyperresponsiveness (BHR) to hypertonic saline and its relation to asthma and allergy symptoms in 507 Austrian school children, aged 12–15 yrs in a cross-sectional, community based survey. These children were selected from 3,371 children who had answered a self-administered written questionnaire on asthma, hay fever, eczema and environmental factors.

The prevalence of BHR to hypertonic saline was 14% and the majority (70%) of the children had mild BHR. The prevalence of wheeze in the last 12 months was 12% and of a diagnostic label of asthma was 6%. Fifty three per cent of the children with symptoms in the last 12 months and a diagnostic label of asthma had BHR, and 33% of those with symptoms in the last 12 months regardless of a diagnostic label of asthma showed a positive response to hypertonic saline. Atopic dermatitis, a diagnostic label of asthma, night cough apart from colds, wheeze in the past 12 months (but not "former wheeze") and male gender were significantly associated with increased response to 4.5% saline in the final logistic regression model.

These results show that the prevalence of asthma symptoms in the last 12 months and the prevalence of bronchial hyperresponsiveness to hypertonic saline are twice that of a diagnosis of asthma and that asthma might be underdiagnosed in the present population. The response to hypertonic saline is most strongly associated with current asthma and allergy symptoms. A combination of a "diagnostic label of asthma" and "asthma symptoms in the last 12 months" might best reflect "current asthma" in epidemiological studies in this population.

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More and more studies suggest that the prevalence of symptoms of asthma in school children has increased in recent years and at least some of these studies have been repeated over time with similar methods [1–4]. Besides this increase, the prevalence of reported asthma morbidity and mortality in children varies widely between countries, with high rates reported from countries in the Southern Hemisphere and lower rates in the Northern Hemisphere [5]. However, international comparisons have been hampered by differences in methods including questionnaires and diagnostic criteria of various respiratory diseases. The International Study of Asthma and Allergies in Childhood (ISAAC) has developed a standard questionnaire for use internationally, but this does not overcome the problem of different languages and interpretations of the concepts of wheeze. A questionnaire response may be influenced by the parent's own exposure to the disease, as well as by the general awareness of the condition in the community. Thus, to allow comparison between countries it is important to have an objective marker of asthma. Bronchial hyperres-

ponsiveness (BHR) is strongly associated with asthma and pharmacological challenges with histamine or methacholine [6–8] and physical challenges such as exercise [9], cold air hyperventilation [10] and distilled water [11, 12] have been used in an attempt to provide such an objective marker of asthma. We have recently standardized the hypertonic saline (HS) challenge for use in epidemiological surveys of asthma in children [13].

The aim of the present study was to assess the prevalence of BHR to HS and its relation to asthma and allergy symptoms in Austrian school children.

Methods

Subjects

The study was carried out in Salzburg, Austria between January and July 1995. Subjects selected for the study were part of an ISAAC study. ISAAC was established to

compare prevalence data on asthma and allergy symptoms between countries, using identical methods including written and video questionnaires [5]. In Phase 1 of this survey, all school children in grades 7 and 8 of all secondary schools (*Hauptschule, Gymnasium*) in the city of Salzburg were invited to participate in the written and video questionnaires. Of all 23 schools, seven schools refused to participate. Therefore, another six schools in greater Salzburg within a 20 km radius of the city were randomly selected. The children enrolled in these six schools were comparable to the other children in terms of racial and socioeconomic background, and environmental factors. Altogether, 3,960 schoolchildren were invited to participate.

In Phase 2 of the survey a bronchial challenge using hypertonic saline was performed. Eight of the 22 schools that participated in Phase 1 were randomly selected for participation. All children who had reported either "wheezing or whistling in the last 12 months" (n=164) or "wheezing or whistling ever" but not in the last 12 months (n=115) or who had a diagnosis of asthma but a negative response to "wheezing or whistling ever" (n=22) were asked to perform an HS challenge test. A control group, equal in number to those who had reported asthma symptoms or a diagnosis of asthma, was selected at random, matched by school, from those who reported no history of wheezing ever and no diagnosis of asthma (n=312). Altogether, 613 children were invited for the HS challenge test.

Questionnaires

The self-administered written questionnaire included 64 questions on respiratory symptoms, a previous diagnosis of asthma, anti-asthma medication, asthma management, allergic rhinitis, eczema and environmental factors.

Details of the video questionnaire and results of the comparison with the written questionnaire will be published elsewhere.

Definitions

"Current wheeze" was defined as a positive response to "have you had wheezing or whistling in the chest during the last 12 months", "former wheeze" as a positive response to "have you ever had wheezing or whistling in the chest at any time in the past" but a negative response to "have you had wheezing or whistling in the chest in the last 12 months". Those children with a positive answer to "have you ever had asthma" were defined as children with a "diagnostic label of asthma". "Current asthma" was defined as a positive answer to "have you ever had asthma" and a positive answer to "have you had wheezing or whistling in the chest during the last 12 months". "Controls" had a negative response to "have you ever had wheezing or whistling in the chest at any time in the past" and a negative response to "have you ever had asthma".

Sensitivity (of the HS challenge) was defined as the proportion of subjects with asthma symptoms (answers to written questionnaire) that had a positive response to the HS challenge.

Specificity (of the HS challenge) was defined as the proportion of subjects with no asthma symptoms (answers to written questionnaire) that had a negative response to the HS challenge.

Hypertonic saline challenge test

A letter issued to the children included a request to withhold the following asthma medication prior to the challenge test: antihistamines, 48 h; theophyllines, 24 h; aerosol beta agonists and cromoglycate, 6 h; and inhaled steroids on the morning of the study day. Before the baseline lung function test was performed, children were asked about the time of last asthma medication and about current or recent respiratory infections. The technician was blinded to the individual subject's "asthma status". Baseline and post-challenge forced expiratory volume in one second (FEV₁) measurements were made using a "hand held" spirometer (Mikroloop 2; Micro Medical Ltd., Rochester, UK) until two successive FEV₁ readings did not differ by more than 5%. Subjects were excluded from the challenge test if their baseline FEV₁ was δ 65% of predicted or if they violated the medication restrictions.

The HS challenge tests were performed using a standardized protocol [13]. Four point five per cent HS was nebulized *via* a DeVilbiss Ultraneb 2000 (DeVilbiss, Somerset, PA, USA) connected to 65 cm of corrugated aerosol tubing (internal diameter 2.2 cm, smooth interior surface) and a two-way nonbreathing valve (Laerdal Catalogue No. 560200 with diverter Catalogue No. 850500; Laerdal, Stavanger, Norway). During the challenge the nebulizer output was kept constant and the dose of saline increased successively by doubling the inhalation time, starting with 0.5 min, then 1, 2, 4 and 8 min, with subjects inhaling at tidal volumes. FEV₁ was measured in duplicate, 60 s after each challenge step and the best of the two readings was used. The challenge ended when the FEV₁ had fallen by 15% or more, or a cumulative inhalation time of 15.5 min had been achieved. If, after the final 8 min challenge time, 23 mL of solution had not been delivered, the challenge was continued to ensure a minimum total of 23 mL had been delivered. The nebulizer canister plus tubing was weighed prior to the challenge and after the final inhalation step on an electronic balance (Mettler BB-3000, Mettler, Greitensee, Switzerland) to assess the total amount of aerosol nebulized and the nebulizer output per minute.

In a previous study, we assessed the repeatability of two or three HS challenge tests within a 10 day period under laboratory conditions [14]. In the present study, repeatability was determined under field conditions in 29 children who had a positive response to HS on the first occasion. The second HS challenge was performed between 48 h and 10 days after the first test, under identical conditions.

Data collection and analysis

Data entry and analyses were made using the Statistical Products and Service Solutions (SPSS) for Windows package (Release 6.0; SPSS Inc., Chicago, IL, USA). Sensitivity and specificity of the HS challenge in regard to different gold standards of asthma were calculated from crosstables. To correct for the sampling method (not all controls were studied), results were weighted to calculate the prevalence of BHR to HS in the population. Factors (categorical and continuous) affecting bronchial reactivity to HS were analysed by univariate and multivariate

logistic regression with reactor status as the categorical dependent variable. Independent variables considered for the modelling were: gender; age; response to respiratory symptoms; rhinitis and eczema core questions; cough; baseline predicted FEV₁; passive smoking; and family history of asthma or allergy.

Repeatability was measured by calculating the 95% limit of agreement between the two measurements of the provocative dose of saline causing a 15% fall in FEV₁ (PD₁₅), as suggested by BLAND and ALTMANN [15].

Approval to conduct the survey was obtained from the Hospital Ethics Committee for Human Studies, from the Landesschulrat Salzburg and from the principals of the schools involved. Informed written consent was obtained from the parents of all children.

Results

Response rates

Three thousand nine hundred and sixty children were invited to answer the questionnaire. Of these, 3,371 agreed to participate, a response rate of 85%. Details about participation in the HS challenge test are shown in figure 1. Eighty three per cent (507 out of 613) participated in the challenge and there were no significant differences in participation between the four groups ("current wheeze", "former wheeze", "diagnostic label of asthma, but no symptoms", and controls). In six of the 507 (1.2%) participating children the challenge test could not be successfully completed due to nausea (n=5) and baseline FEV₁ less than 65% (n=1).

Age and gender

Of the 3,371 participants, three children were aged 10 yrs and 11 children were aged 16 yrs. These outliers were excluded and all further analyses considered the remaining 3,357 children. The mean age of these participating children was 13.3 yrs (range 12–15 yrs) of whom 51% were boys.

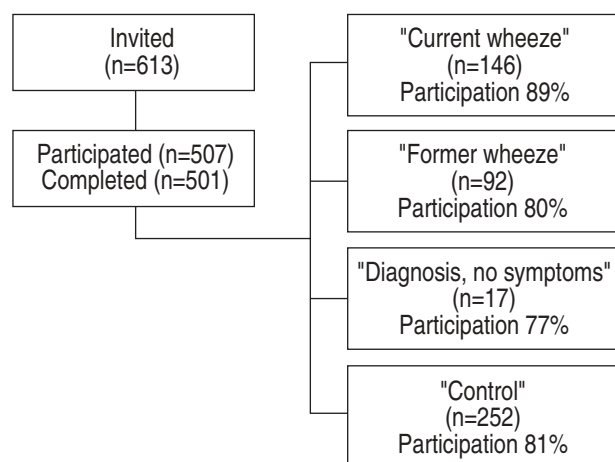


Fig. 1. – Flow chart showing participation of children with different respiratory conditions and asymptomatic children in the hypertonic saline challenge.

Prevalence, sensitivity, and specificity

The calculated prevalence of BHR to HS in the population was 13.7% (95% confidence interval (CI) 10.7–16.7%).

Eight per cent of 99 children who responded positively to HS had severe BHR (PD₁₅ <2 mL), 22% had moderate BHR (PD₁₅ 2.01–6.0 mL) and 70% had mild BHR (PD₁₅ >6.0 mL). According to our definitions, 47 of 143 (33%) subjects with "current wheeze", 21 of 90 (23%) with "former wheeze", 38 of 84 (45%) with the "diagnostic label of asthma" and 24 of 45 (53%) with "current asthma" had a positive response to HS. This gives a sensitivity for the HS challenge of 53% and a specificity of 84% (367 out of 437) to identify "current asthma". Twenty five of 248 (10%) of the controls responded positively. Of these control subjects who had a positive response to HS, 83% had mild BHR. Table 1 gives information on symptom prevalences by level of bronchial responsiveness to HS and table 2 shows the relationship between degree of BHR and severity of asthma symptoms assessed as frequency of wheeze attacks in the last 12 months.

Multivariate analyses

The following variables showed significant association with increased response to HS in the final multivariate

Table 1. – Numbers and percentages of subjects with asthma symptoms in relation to the level of bronchial responsiveness (BHR) to hypertonic saline

Symptom/Diagnosis Prevalences	BHR to 4.5% saline			
	None	Mild	Moderate	Severe
Subjects n	402	69	22	8
Current wheeze	98 (67.1)	31 (21.2)	12 (8.2)	5 (3.4)
Diagnostic label of asthma	46 (54.8)	22 (26.2)	8 (9.5)	8 (9.5)
Wheeze after exercise	114 (65.5)	39 (22.4)	17 (9.8)	4 (2.3)
Night cough last 12 months	69 (69.0)	20 (20.0)	9 (9.0)	2 (2.0)
Wheeze ever	169 (71.0)	45 (18.9)	18 (7.6)	6 (2.5)
Current asthma	21 (46.7)	15 (33.3)	5 (11.1)	4 (8.9)
Controls	223 (89.9)	21 (8.5)	4 (1.6)	0 (0.0)

Values are presented as number of subjects, and within row percentages in parentheses. For definitions of symptoms and diagnosis, see text. Mild BHR: provocative dose of saline causing a fall in forced expiratory volume in one second of 15% (PD₁₅) >6 mL; Moderate BHR: PD₁₅: 2.01–6.0 mL; Severe BHR: PD₁₅ ≤2 mL.

Table 2. – Numbers and percentages of subjects in each group of frequency of wheezy episodes in the last 12 months in relation to the level of bronchial responsiveness to hypertonic saline (r=0.33, p=0.02)

Wheezy episodes*	BHR to 4.5% saline			
	None	Mild	Moderate	Severe
None	314 (84.2)	43 (11.5)	13 (3.5)	3 (0.8)
1–3	71 (74.0)	19 (19.8)	5 (5.2)	1 (1.0)
4–12	13 (65.0)	5 (25.0)	2 (10.0)	0 (0)
>12	4 (36.4)	2 (18.2)	2 (18.2)	3 (27.3)

Values are presented as number of subjects, and within row percentages in parentheses. *: in the last 12 months. For definitions of categories and abbreviations, see table 1.

Table 3. – Factors associated with increased response to 4.5% saline in the final multivariate logistic regression model

	OR	95% CI	p-value
Male gender	1.97	1.08–3.59	0.026
Wheeze			0.015
Former	1.74	0.84–3.65	0.139
Current	2.67	1.37–5.20	0.004
Night cough in last 12 months	2.17	1.15–4.08	0.016
Atopic dermatitis	4.73	1.91–11.70	0.001
Diagnostic label of asthma	3.51	1.84–6.71	0.001
FEV ₁ % pred	0.97	0.74–1.29	0.072

A total of 424 subjects were included (72 exposed "cases", 25 nonexposed "cases", 178 exposed "noncases" and 223 nonexposed "noncases"; the difference between these 498 and the 424 included arose because of missing data for one or more variables included in the model). A response was defined as a fall in forced expiratory volume in one second (FEV₁) of greater than 15%. 95% CI: 95% confidence interval; OR: odds ratio; % pred: percentage of predicted value.

logistic regression model: atopic dermatitis; diagnostic label of asthma; night cough apart from colds; wheeze in the past 12 months (but not "former wheeze"); and male gender. There was a trend for decreased baseline FEV₁ to be associated with increased response to HS. A family history of atopy, a personal history of allergic rhinitis and passive smoking did not show significant association with BHR to HS in this study. There were no significant interactions between the independent variables (table 3).

Repeatability

Two challenges were performed at the same time of day within a period of 48 h to 10 days. None of the children had a respiratory infection or had taken any medication prior to the tests.

Of the 29 randomly selected children who had a positive response to HS on the first occasion, 24 children responded again with a fall in FEV₁ of more than 15% when challenged a second time. Thus, 83% of children retained the same classification.

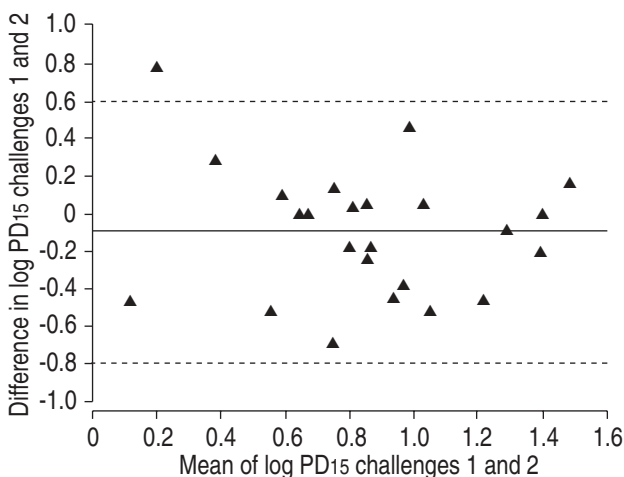


Fig. 2. – Relationship between the difference of log provocative dose of saline causing a 15% fall in forced expiratory volume in one second (PD₁₅) in challenge 1 and 2 and the mean of log PD₁₅ in challenge 1 and 2 in 24 children. The dotted lines represent the range of ± 2 SD of the difference.

As log PD₁₅ values were normally distributed (fit of normality tested by using normal plots), all the values were log transformed prior to statistical analysis. Figure 2 shows a plot of the difference between the two PD₁₅ measurements as a function of their average.

The five of the 29 children who had a fall in FEV₁ of greater than 15% on only one occasion all had mild BHR. Their PD₁₅ values ranged 9.43–25 mL. None of these children had received any asthma medication in the last 12 months and all had only trivial to mild asthma symptoms.

Discussion

The results of the present study show that 14% (95% CI 10.7–16.7%) of all 12–15 yr old school children in Salzburg, Austria demonstrated BHR to inhaled 4.5% saline. According to responses to the written questionnaire, the prevalence of "current asthma" was 3.5%, of "a diagnostic label of asthma" 6.4% and of "current wheeze" 11.6%. A diagnostic label of asthma, night cough apart from colds, wheeze in the past 12 months (but not "former wheeze"), atopic dermatitis and male gender were significantly associated with increased response to 4.5% saline in a multivariate logistic regression model.

The prevalence of BHR to HS was shown to be 20.4% (95% CI 16.4–24.4%) in Australian school children of similar age, using an identical challenge protocol. One of the authors (JR) was a member of both study teams [13]. This is the only other epidemiological study in which an HS challenge in children has been performed. In the same survey, the prevalence of "a diagnostic label of asthma" was 27.1% and of "current wheeze" 26.5%. In contrast to these Australian results, the prevalence of "current wheeze" was almost twice the prevalence of "a diagnostic label of asthma" in the present study, suggesting a labelling bias. Since BHR to HS has been shown to be strongly associated with asthma, the relationship between the prevalence of BHR and the prevalence of asthma symptoms on the one hand and of the diagnostic label of asthma on the other, might be of value in comparisons of questionnaire responses between different countries. The higher prevalence of BHR in Australia as compared to Austria (20.4 versus 13.7%) was probably due to the higher prevalence of asthma (symptoms and diagnosis) in Australia. However, in the present study the ratio of the prevalence of BHR to the prevalence of the diagnosis of asthma is twice as high as the ratio of the prevalence of BHR to the prevalence of asthma symptoms, whereas these two ratios did not differ from each other in the Australian study. We think that this supports the speculation that asthma might be underdiagnosed in the present population. This low prevalence of a diagnostic label of asthma in Austria might be due to the fact that parents of children with asthma symptoms do not seek adequate medical help, do not adequately perceive the asthma symptoms or that doctors in Austria use different diagnoses for asthma symptoms. This latter hypothesis is supported by clinical observations that asthma in this population is often referred to as "spastic bronchitis", "asthmatic bronchitis" or just "bronchitis" by doctors and parents. It appears that there is a relatively high threshold for the use of the diagnostic label of asthma in the age group studied in this population.

Fifty three percent of subjects with "current asthma" responded positively to the HS challenge in the present study. This is similar to the Australian survey where "current asthma" was defined as "a paediatric respiratory physician's diagnosis of asthma", established in a separate interview. However, only 33% of subjects with "current wheeze" had a positive HS challenge in Austria compared to 47% in Australia [13]. Most likely, this is related to differences in the meaning of "wheeze" in various languages. Another explanation for this difference could be related to the different treatment of asthma in the two countries. Long-term use of inhaled steroids can block or at least attenuate the response to HS even in the presence of asthma symptoms and more use of these drugs in Austria could be responsible for the lower prevalence of a positive HS challenge in children with "current wheeze". However, only two of 88 children with a negative response to HS and reported asthma symptoms in the last 12 months had been on inhaled steroids, making different treatment modalities rather unlikely to account for this difference. Sensitivity and specificity of the HS challenge were not different, whatever 'gold standard' of asthma or wheeze was used in the Australian survey, suggesting that all these definitions equally and carefully defined the patients with asthma. In the present study, however, sensitivity increased significantly when diagnostic labelling and asthma symptoms were combined (from 33 to 53%). Thus, "wheeze in the last 12 months" alone may not be a good indicator of "current asthma" in this community as compared to other communities [13]. This might be related to the fact that, in German, there is no real expression corresponding to wheeze that is widely understood and used by children and their parents [16]. Thus, "wheeze" in English might provide a much better description of "asthma" than any similar expression in German.

The final multivariate logistic regression analysis revealed a significant association between increased response to HS and a history of "wheeze in the last 12 months" (but not "former wheeze"), atopic dermatitis, male gender, night cough apart from a cold and a diagnostic label of asthma. Of special interest is that "former wheeze" showed no significant association with a positive response to HS, since this is in contrast to challenges using pharmacological agents such as histamine or methacholine [17, 18]. Unlike pharmacological challenges, nonpharmacological challenges such as HS or cold air challenge involve inflammatory cells in the airways, a key pathophysiological feature of current asthma, but most likely not of former asthma [19]. Thus, one might speculate that a nonpharmacological challenge, such as the HS challenge, is more specific for current asthma than a pharmacological challenge. The association between male gender and HS reactivity was weak but significant. This is in contrast to the Australian survey, where a weak, but significant, association with female gender was found [13]. In younger children there is usually a male predominance of asthma and BHR which is, however, usually absent by the age of 12 yrs [3]. Furthermore, atopy and allergic symptoms have shown a close association to bronchial responsiveness to various stimuli. We did not perform skin prick tests in this study, but did however, assess allergy symptoms and diagnoses in the questionnaire. Hay fever (diagnosis and symptoms) was significantly associated with BHR to HS in the Australian population. This association narrowly failed to reach sig-

nificance in the present study, in which atopic dermatitis was strongly associated with BHR to HS.

Unlike others, we did not find cigarette smoking or passive smoking to be related to BHR to HS in this age group in the present study. However, these factors were only assessed by a questionnaire and no objective measure, such as cotinine, was used. Some other diseases such as cystic fibrosis, bronchopulmonary dysplasia or chronic obstructive pulmonary disease and current respiratory viral infections can lead to increased response to HS, but no subject with such a condition took part in this study.

In a recent laboratory study, we were able to show good repeatability for the HS challenge [14]. The present study is the first to assess repeatability of the HS challenge under field conditions. Again, we found that the test yields a good repeatability within 10 days, under less optimal conditions in the field.

In conclusion, the results of this study show that the hypertonic saline challenge is a useful, well-accepted and reproducible test to assess bronchial hyperresponsiveness in epidemiological studies in children and that it might serve as an objective marker of asthma in international studies. Furthermore, we speculate that asthma might be underdiagnosed in the population studied and that a combination of a "diagnostic label of asthma" and "asthma symptoms in the last 12 months" might best reflect "current asthma" in this population.

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