

Evaluation of bronchial challenge test results for use in assessment of paediatric eczema: a retrospective series

KL Hon *, Abraham HY Ng, Chrystal CC Chan, Prisca XY Ho, Emma PM Tsoi, Kathy YC Tsang, Fanny W Ko, TF Leung

ABSTRACT

Background: Atopic dermatitis (AD), asthma, and allergic rhinitis are associated diseases involved in the atopic march. The bronchial challenge test (BCT) is a tool that evaluates airway hyperresponsiveness in patients with asthma. This study aimed to evaluate whether a positive BCT result is useful in assessment of paediatric AD.

Methods: This retrospective case series included 284 patients with AD who had BCT results. Clinical information and laboratory parameters were reviewed, including AD severity (using the SCORing Atopic Dermatitis [SCORAD]), skin hydration, and transepidermal water loss.

Results: Of the 284 patients who had BCT, 106 had positive BCT results and 178 had negative BCT results. A positive BCT result was associated with a history of asthma ($P<0.0005$), sibling with asthma ($P=0.048$), serum immunoglobulin E ($P=0.045$), eosinophil count ($P=0.017$), and sensitisation to food allergens in the skin prick test ($P=0.027$). There was no association between a positive BCT result and personal allergic rhinitis, parental atopy, sibling allergic rhinitis or AD, skin prick response to dust mites, objective SCORAD score, skin hydration, transepidermal water loss, exposure to smoking, incense burning, cat or dog ownership, or AD treatment aspects (eg, food avoidance and traditional

Chinese medicine). Logistic regression showed significant associations of a positive BCT result with a history of asthma (adjusted odds ratio=4.05; 95% confidence interval=1.92-8.55; $P<0.0005$) and sibling atopy (adjusted odds ratio=2.25; 95% confidence interval=1.03-4.92; $P=0.042$).

Conclusions: In patients with paediatric AD, a positive BCT result was independently and positively associated with personal history of asthma and sibling history of atopy, but not with any other clinical parameters.

Hong Kong Med J 2021;27:27-34

<https://doi.org/10.12809/hkmj208453>

¹ KL Hon *, MB, BS, MD

² AHY Ng, MB, ChB

² CCC Chan, MB, ChB

² PXY Ho, MB, ChB

² EPM Tsoi, MB, ChB

¹ KYC Tsang, MPhil, BSc

³ FW Ko, MB, ChB, MD

¹ TF Leung, MB, ChB, MD

¹ Department of Paediatrics, The Chinese University of Hong Kong, Hong Kong

² Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong

³ Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong

* Corresponding author: ehon@hotmail.com

This article was published on 4 Feb 2021 at www.hkmj.org.

New knowledge added by this study

- In paediatric patients with atopic dermatitis (AD), a positive bronchial challenge test (BCT) result was significantly associated with a history of asthma (adjusted odds ratio [aOR]=4.05; 95% confidence interval [CI]=1.92-8.55; $P<0.0005$) and sibling atopy (aOR=2.25; 95% CI=1.03-4.92; $P=0.042$).
- BCT results were independently and positively associated with a personal history of asthma and sibling history of asthma, but not with any other clinical parameters of AD.

Implications for clinical practice or policy

- BCT may have limited usefulness in patients with AD beyond the prediction of asthma prevalence or risk.
- Alternatives to the BCT should be sought with greater clinical predictive strength.

Introduction

Atopic dermatitis (AD) or eczema, asthma, and allergic rhinitis (AR) are associated diseases involved in the atopic march.¹⁻³ Many children with AD develop asthma and/or AR when they reach adulthood. There are a number of clinical and laboratory tools to evaluate atopic status in patients with AD. The

bronchial challenge test (BCT) is an important tool that evaluates airway hyperresponsiveness in patients with asthma. Responsive patients develop acute contraction of smooth muscles lining the bronchi, resulting in sudden narrowing and obstruction of the airway. The extent of airway narrowing can increase during periods of exacerbation and decrease during

支氣管激發測試評估小兒濕疹：回顧系列研究

韓錦倫、吳希仁、何心悅、陳翠清、蔡柏雯、曾燕靜、古惠珊、梁廷勳

引言：異位性皮膚炎、哮喘和過敏性鼻炎是過敏進行曲常見的疾病。支氣管激發測試（BCT）是一種評估哮喘患者氣道高反應性的工具。本研究旨在評估BCT陽性結果可否用於評估小兒異位性皮膚炎。

方法：這項回溯性系列病例研究納入284例具BCT結果的異位性皮膚炎患者。回顧臨床信息和實驗室參數，包括根據SCORAD評估的異位性皮膚炎重度、皮膚水分和表皮水分流失。

結果：284例BCT患者中，106例BCT呈陽性，178例BCT呈陰性。BCT陽性結果與個人哮喘病史（ $P < 0.0005$ ）、兄弟姐妹哮喘病史（ $P = 0.048$ ）、血清免疫球蛋白E（ $P = 0.045$ ）、嗜酸性粒細胞數量（ $P = 0.017$ ）以及皮膚點刺測試診斷對食物過敏原敏感（ $P = 0.027$ ）呈相關。BCT陽性結果與以下因素無關，包括過敏性鼻炎、父母過敏、兄弟姐妹的過敏性鼻炎或異位性皮膚炎、皮膚點刺測試診斷對塵蟎敏感、客觀SCORAD評分、皮膚水分、表皮水分流失、吸煙、熏香、貓狗飼養或異位性皮膚炎治療方面（如避免食物和中藥）。邏輯迴歸分析顯示BCT陽性結果與個人哮喘病史（校正比值比=4.05；95%置信區間1.92-8.55； $P < 0.0005$ ）和兄弟姐妹過敏病史（校正比值比=2.25；95%置信區間1.03-4.92； $P = 0.042$ ）顯著相關。

結論：在小兒異位性皮膚炎患者中，BCT陽性結果與個人哮喘病史和兄弟姐妹過敏病史呈相關。

treatment with anti-inflammatory drugs.⁴ The inhalation of histamine or methacholine produces direct airway responses. Histamine maximises bronchial obstruction by directly activating H1 histamine receptors during inhalation challenge. It also stimulates nasal and mucus secretion, promotes vasodilation, and increases vascular permeability. Methacholine is a synthetic derivative of the acetylcholine neurotransmitter, which directly stimulates M3 muscarinic receptors on airway smooth muscles to induce bronchoconstriction.⁴ A low inhaled dose could trigger a high degree of airway hyperresponsiveness in patients with asthma.

In BCT, methacholine and histamine stimulate an increase in cyclic guanosine monophosphate level and a decrease in cyclic adenosine monophosphate level, thus contributing to smooth muscle contraction.⁵ Immediate bronchoconstriction reactions can begin immediately after challenge; the peak is within approximately 30 minutes. The effect is typically reversible within 1.5 to 2 hours with the aid of bronchodilators. This is regarded as a type 1 hypersensitivity reaction mediated by immunoglobulin E (IgE), which is present in patients with hypersensitivity pneumonitis, asthma, and other atopic diseases. Immunoglobulin E has a specific role in the induction of many allergic reactions as evidenced by its high serum level in patients with allergic diseases and those with atopic diseases.^{6,7}

Distinct dosages are used for the inhalation of methacholine and histamine, but the inhalation challenge procedures are identical.⁸ During the test, a diluent is provided via nebulisation for five inhalations, followed by nebulisation of the test compound at low concentrations. A spirometry test is conducted after each dilution to assess the patient's pulmonary function. A reduction in forced expiratory volume in 1 second (FEV_1) of $\geq 20\%$ signifies a positive response and the end of the test. A bronchodilator is then provided to counteract the effects of the test compound. In subsequent tests, the dose that provokes the desirable $\geq 20\%$ reduction of FEV_1 is employed.⁵

There are several contra-indications for the BCT. Patients with reduced lung function as evidenced by a low FEV_1 level in baseline spirometry may be predisposed to a greater risk of serious adverse events.⁹ A prior bronchodilator $FEV_1 < 60\%$ predicted or $FEV_1 < 75\%$ predicted during a single high stimulus (eg, exercise) are relative contra-indications.¹⁰ Airway obstruction in baseline spirometry supplemented with clinical features of asthma is sufficient for diagnosis and the BCT is unnecessary. Furthermore, an inability to follow the instructions of the spirometry test undermines the BCT quality.¹¹ Individuals with a history of cardiovascular problems, increased intracranial pressure, or recent eye surgery may experience enhanced cardiovascular stress as a consequence of bronchoconstriction during the BCT and should not be subjected to this test.^{4,10} In general, patients with asthma respond to methacholine and histamine even at low concentrations, such that 84% and 73% react to the above compounds, respectively.¹²

This study aimed to investigate whether personal characteristics, history of allergen exposure, skin prick test results, clinical assessment scores, laboratory parameters, and personal or family histories of atopic diseases are associated with a positive BCT result in paediatric patients with AD. The result is useful in counselling parents and patients with AD and risks of asthma in the family.

Methods

This retrospective case series included patients with AD who were treated at the paediatric dermatology clinic of a university hospital from January 2000 to November 2017; patients who had undergone the BCT were retrospectively selected for analysis. All selected patients were Chinese and aged > 8 years (the minimum age at which patients can complete the BCT in our hospital pulmonology laboratory).^{4,11,13} Data concerning the following clinical and personal characteristics were obtained from the patients' medical records: AD onset age, history of other atopy (ie, AR and atopic asthma), history of atopy (ie, AD, atopic asthma and AR) in parents and siblings,

potential allergen exposure (ie, pet ownership and tobacco smoking), and AD treatment history (ie, allergen avoidance and use of traditional Chinese medicine). Clinical laboratory parameters obtained from the electronic patient record system included BCT results, highest serum IgE level, highest eosinophil counts (absolute and relative), and skin prick test results for allergic response to dust mite, cockroach, dogs, cats, and food allergens.

Atopic dermatitis severity was clinically scored by the SCORing Atopic Dermatitis (SCORAD), skin hydration, and transepidermal water loss (TEWL) during follow-up visits.¹⁴ The SCORAD is a mathematically derived score that considers the extent, severity, and subjective symptoms of AD.¹⁵ The skin hydration and TEWL were measured using Courage and Khazaka equipment, which indirectly measures the density gradient of water evaporation from the skin by two pairs of sensors that determine the temperature and relative humidity, respectively.¹⁶

The IBM SPSS Statistics (Windows version 20) was used to conduct all statistical analysis. Student's *t* test was conducted to compare continuous variables between groups; these data were expressed as mean ± standard deviation. The Chi squared test (or Fisher's exact test) was conducted to compare categorical variables between groups; these data were expressed as number (%). A *P* value of <0.05 was considered statistically significant. Backward binary logistic regression analysis was then used to analyse the data. The variable with the highest *P* value was removed at each step until the final equation included only variables with *P*<0.05.

The New Territories East Cluster and The Chinese University of Hong Kong ethics committee approved this retrospective study.

Results

Overall patient characteristics

In total, 579 patients with AD were included in this study; 284 had confirmed BCT results. Patient follow-up data were censored as of November 2017 to February 2018. Of the 284 patients with BCT results, 106 had a positive result (BCT-positive group), while 178 had a negative result (BCT-negative group). There were significant differences in current age (*P*=0.039) and the age at BCT performance (*P*=0.004) between groups (Table 1).

Personal and family histories of atopic diseases

A positive BCT result was associated with personal history of asthma (*P*<0.0005) and a sibling with asthma, compared with patients with a negative BCT result (28.6% vs 6.8%; *P*=0.048) [Table 1].

There were no significant associations between BCT results and personal AR, maternal

atopy (specifically, asthma, AR, AD), paternal atopy (specifically asthma, AR, AD), siblings' AR, and siblings' AD. Moreover, BCT results were not associated with a history of skin prick response to allergens, including dust mites (Table 1).

Clinical measures, laboratory results, environmental factors, and previous treatment

There were no significant associations between BCT results and clinical measures of AD severity, in terms of objective SCORAD score, SH, or TEWL. Results of BCT were associated with markers of allergic reactions, including (highest) serum IgE (*P*=0.045), highest eosinophil count (*P*=0.017), and sensitisation to food allergens in skin prick test (*P*=0.027). However, they were not associated with other allergens tested in the skin prick panel, such as aeroallergens from dust mites, cockroaches, dogs, or cats (Table 1). Results of BCT had no significant association with previous exposure to potential environmental irritants, including smoking in the household, incense burning, cat ownership, or dog ownership. There were no significant associations between BCT results and history of AD treatment, including food avoidance and traditional Chinese medicine usage (Table 1).

Regression analysis

Of the 284 patients with AD and confirmed BCT results, 142 patients had all relevant data available. Backward binary logistic regression (*n*=142) showed significant associations between a positive BCT result and a personal history of asthma (adjusted odds ratio [aOR]=4.05; 95% confidence interval [CI]=1.92-8.55; *P*<0.0005) and sibling atopy (aOR=2.25; 95% CI=1.03-4.92; *P*=0.042). However, it did not show associations with AD severity, young age at AD onset, personal history of AR, aeroallergen (including dust mite, cockroach, cat and dog hair) and food allergen sensitisation, parental history of atopy, or highest serum IgE level and blood eosinophil count (Table 2).

Discussion

Atopic dermatitis and asthma

In our study, backward binary logistic regression analysis showed that a positive BCT result was independently and positively associated with a personal history of asthma in patients with AD. The Global Initiative for Asthma, a medical guidelines organisation, has established a standard for the diagnosis of asthma, which recommends the documentation of variable expiratory airflow limitation. Although asthma is principally a clinical diagnosis, the BCT can aid in this assessment.¹⁷ The sensitivity of the BCT in complementing asthma

TABLE I. Demographics of patients with AD, stratified according to BCT results (n=284)*

	BCT positive (n=106)	BCT negative (n=178)	P value
Patient characteristics			
Current age ± SD, years	20.7 ± 4.1	21.7 ± 4.1	0.039
Male	61 (57.5%)	92 (51.7%)	0.338
Onset age, years (n=256)	2.1 ± 2.9 (n=93)	2.8 ± 3.6 (n=163)	0.098
Age at BCT, years	12.1 ± 3.5	13.4 ± 3.6	0.004
Prematurity (n=140)	1 (2.0%)	3 (3.3%)	>0.999†
Asthma positive (n=271)	64 (63.4%)	63 (37.1%)	<0.0005
Allergic rhinitis positive (n=277)	90 (86.5%)	135 (78.0%)	0.079
Maternal atopy positive (n=269)	38 (40.0%)	71 (40.8%)	0.898
Maternal asthma (n=65)	1 (4.8%)	2 (4.5%)	>0.999†
Maternal allergic rhinitis (n=65)	5 (23.8%)	13 (29.5%)	0.629
Maternal AD (n=65)	3 (14.3%)	7 (15.9%)	>0.999†
Paternal atopy positive (n=270)	51 (53.7%)	91 (52.0%)	0.791
Paternal asthma (n=68)	0	4 (8.7%)	0.296†
Paternal allergic rhinitis (n=68)	6 (27.3%)	14 (30.4%)	0.789
Paternal AD (n=67)	2 (9.1%)	8 (17.8%)	0.478†
Sibling atopy positive (n=261)	59 (64.1%)	89 (52.7%)	0.074
Sibling asthma (n=65)	6 (28.6%)	3 (6.8%)	0.048†
Sibling allergic rhinitis (n=65)	8 (38.1%)	12 (27.3%)	0.377
Sibling AD (n=65)	9 (42.9%)	12 (27.3%)	0.209
Clinical measures for AD			
Objective SCORAD score (n=198)	28.4 ± 17.0 (n=70)	27.4 ± 15.3 (n=128)	0.677
SH (n=182)	30.3 ± 12.7 (n=71)	32.6 ± 12.1 (n=111)	0.227
TEWL (n=182)	10.7 ± 7.0 (n=71)	10.0 ± 6.0 (n=111)	0.503
Laboratory investigations			
Highest serum IgE level, IU/mL (n=223)	7962 ± 11 046 (n=81)	5133 ± 7941 (n=142)	0.045
Highest eosinophil count, 109/L (n=248)	0.96 ± 0.88 (n=89)	0.71 ± 0.75 (n=159)	0.017
Skin prick test result			
Dust mite positive (n=282)	101 (96.2%)	166 (93.8%)	0.384
Cockroach positive (n=281)	48 (45.7%)	60 (34.1%)	0.053
Dog positive (n=282)	20 (19.0%)	23 (13.0%)	0.172
Cat positive (n=282)	41 (39.0%)	67 (37.9%)	0.842
Food allergen(s) positive (n=281)	78 (74.3%)	108 (61.4%)	0.027
Environmental factors			
Smoking exposure (n=244)	19 (21.3%)	34 (21.9%)	0.915
Cat exposure (n=260)	2 (2.1%)	4 (2.4%)	>0.999†
Dog exposure (n=260)	7 (7.4%)	9 (5.5%)	0.536
Previous treatment for AD			
Any TCM (n=264)	64 (66.0%)	101 (60.5%)	0.373
Any food avoidance (n=264)	68 (72.3%)	125 (73.5%)	0.835

Abbreviations: AD = atopic dermatitis; BCT = bronchial challenge test; IgE = immunoglobulin E; SCORAD = SCORing Atopic Dermatitis; SD = standard deviation; TCM = traditional Chinese medicine; TEWL = transepidermal water loss

* Continuous data are shown as mean ± standard deviation and compared by *t* test; categorical data are shown as No. (%) and compared by Chi squared test or Fisher's exact test

† Totals may not be 284 because some data are unavailable

diagnosis is generally believed to approach 100% if a cut point is set at 8 mg/mL or 16 mg/mL, using a non-deep inhalation method.¹⁸ Cockcroft¹⁸ showed that when the PC₂₀ (ie, histamine provocative concentration causing a 20% drop in FEV₁) cut-off was set at ≤8 mg/mL, all individuals with current symptomatic asthma could be identified in a random population with a sensitivity of nearly 100%.¹

However, a recent study indicated that the prevalence of a positive BCT result in children with asthma is approximately 70%.¹⁹ This is attributed to the potential effects of several factors associated with a positive BCT result, especially using the methacholine challenge test; these factors include AR, respiratory infections, and chronic respiratory conditions (eg, bronchitis and chronic obstructive pulmonary disease).¹⁹ Despite its limitations, including that the test can only be used in older children, the BCT remains a useful tool for the diagnosis of asthma (Table 2). Clinical usage of the BCT in the diagnosis of asthma is based on its high sensitivity and negative predictive value, but a positive BCT result itself is not confirmatory for asthma.^{17,20}

In this study of 284 patients with BCT results, the aOR of a positive BCT result for asthma in patients with AD was 4.05, implying that patients with AD who have a positive BCT result are fourfold more likely to have asthma. This is consistent with the findings of a 2015 meta-analysis that included 31 studies conducted in 102 countries; the risk ratio of AD to other two atopic disorders, including AR and asthma, was 4.24 (95% CI=3.75-4.79). The results demonstrated a clear relationship between the skin and the airways.²¹ Riiser et al²² followed 530 children who completed the BCT at the age of 10 years and underwent structured reviews and clinical examinations at the age of 16 years; they examined the predictability of BCT results for active asthma in adolescence. The investigators concluded that the presence of bronchial hyperreactivity (BHR), especially severe BHR, was a significant risk factor and that provocative dose 20 resulting in 20% decrease in FEV₁ in a positive test alone explained 10% of the variation in active asthma.²² Another study showed similar findings, in that airway hyperresponsiveness independently predicted asthma symptoms in childhood (aOR=2.6; 95% CI=1.8-3.7).²³ Our results concurred with those of the above studies, indicating that BHR could develop before active asthma symptoms appear and that BCT might indeed predict asthma incidence in children with AD.

Sibling history of atopy

Atopy is known to have a strong hereditary component. A family study of 188 Caucasian patients and their family members demonstrated a twofold

TABLE 2. Clinical asthma diagnosis and bronchial challenge test (BCT) status (n=271)

	Asthma positive (n=127)	Asthma negative (n=144)
BCT positive (n=101)	True positive: 64	False positive: 37
BCT negative (n=170)	False negative: 63	True negative: 107

Sensitivity of BCT = true positive/asthma positive = 50.4%

Specificity of BCT = true negative/asthma negative = 74.3%

Positive predictive value = true positive/BCT positive = 63.4%

Negative predictive value = true negative/BCT negative = 62.9%

increase in risk of developing AD and atopy with each additional first-degree relative who exhibited atopy.²⁴ Furthermore, a maternal history of atopic disease was associated with an elevated IgE level among infants. For maternal asthma, this association was only evident in infant girls.²⁵ Hong Kong has a relatively high prevalence of single-child families; however, among patients with siblings, positive relationships with sibling atopy have been found.^{1,2} In our study, among 106 patients with a positive BCT result, rates of maternal, paternal, and sibling atopy were 40.0%, 53.7%, and 64.1%, respectively. A positive BCT result was independently and positively associated with sibling atopy (aOR=2.25; 95% CI=1.03-4.92; P=0.042), which includes asthma, AR, and/or AD. However, no associations with parental atopy were found. Patients with positive BCT results are presumably more likely to have siblings with atopy, in that 64.1% of patients with positive BCT results had siblings with atopy, compared with 52.7% of patients with negative BCT results. The most likely explanations of the association with siblings involve genetic heredity and similar epigenetic factors in childhood. Siblings of patients with atopy are predisposed to an inherited tendency to developing IgE antibodies to specific allergens, with subsequent hypersensitivity reactions. Several twin studies were conducted to demonstrate the roles of genetic and environmental factors on atopy. A multivariate genetic analysis with a total of 575 twin participants revealed that atopic conditions were associated with genetic and environmental factors; it also showed that different phenotypic conditions shared common genetic backgrounds.²⁶ Family and twin studies have shown that genetic inheritance plays an important role in the development of atopy; they identified 79 genes associated with asthma or atopy in more than one population.²⁷ Despite genetic involvement, atopic conditions are highly heterogeneous and involve complex epigenetic factors. The atopic state is presumably related to a pre-existing genotype that is activated by environmental factors.²⁸ Both the factors themselves and duration of exposure are important. Several epigenetic factors with an impact on atopy have been established; these can be further subcategorised into prenatal, infancy, childhood,

and adulthood types.²⁹ Affected children and their siblings are exposed to common environmental factors in their childhood, such as tobacco smoke, allergic sensitisation, infections, and diet.

There was minimal information concerning birth order and family size in the present study, although these factors may have substantial impacts on allergic disease susceptibility. Asthma prevalence is reportedly inversely related to family size in families with ≥ 4 children.³⁰ An inverse relationship between birth order and asthma risk has also been suggested. Compared with younger siblings, stronger associations with older siblings with asthma have been demonstrated.³⁰ However, family size was not specified in those studies; thus, there is a need to determine whether family size or birth order exerts a greater impact upon the risk of atopy. The mechanism by which younger children are protected against atopy is unknown. One possible explanation is the hygiene hypothesis, which suggests that children with less exposure to pathogens and other microorganisms in early childhood are more susceptible to allergic diseases. An implication is that the attempt to create dust-free and pathogen-free clean environment leads to increased atopy prevalence. The presence of older siblings and larger family size is presumed to protect children from atopy through greater exposure in early childhood, thus modulating their immune systems.

Food and aeroallergen sensitisation

Univariate analysis showed that food sensitisation, but not aeroallergen sensitisation, was significantly associated with a positive BCT result in patients with AD ($P=0.027$). The association was not statistically significant following regression analysis. It has been reported that 40% of patients with food allergy, but no diagnosis of asthma, have a substantial degree of bronchial hyperactivity (measured by the BCT).³¹ Another small study ($n=22$ patients with allergic asthma) showed no relationship between skin prick test sensitisation and inhaled reactivity (measured by the methacholine BCT).³² Skin allergen sensitisation does not accurately predict airway allergen response.^{32,33} This result was confirmed by several other studies,^{34,35} which showed no relationship between methacholine responsiveness and the presence or degree of atopy. Hence, food and aeroallergen sensitisation are generally not associated with BCT results.

Serum immunoglobulin E level and blood eosinophil count

Univariate analysis showed significant associations of serum IgE level ($P=0.045$) and blood eosinophil count ($P=0.017$) with a positive BCT result. These findings were consistent with the results published by Liu et al³⁶ concerning significant relationships

of BHR to methacholine and increased total serum IgE to a positive BCT result ($P=0.001$). Sears et al³⁷ showed that BHR was related to serum IgE level in children not diagnosed with asthma; this relationship persisted despite the exclusion of children with a history of AR or AD. Hence, BHR is dependent on serum IgE level and is unrelated to the presence of AD. Nevertheless, IgE can be measured in young children when BHR is difficult to demonstrate; notably, IgE is a simple blood marker of AD severity and asthma risk.^{7,38}

Personal history of allergic rhinitis

The “one airway” hypothesis (ie, “united airway disease”) is based on the bidirectional interaction between asthma and rhinitis, with the implication that both upper and lower airways should be treated for optimal symptomatic control.^{39,40} However, our study showed no association between the presence of AR and a positive BCT result in children with AD ($P=0.079$). Although several studies have shown an association between AR and BHR, they did not equate a positive BCT result with the diagnosis of AR.^{20,41,42}

Atopic dermatitis severity

In our study, there was no association between AD severity (based on objective SCORAD score, SH, and TEWL) and a positive BCT result. Liu et al³⁶ found that BHR to methacholine was related to atopy ($P=0.0063$), while the degree of BHR was not significantly associated with the severity of any atopic disease.

Strengths and limitations of this study

The strengths of this study included collection and review of the data over 10 years, which enabled the addition of follow-up assessments for many of the patients. The Prince of Wales Hospital is a public hospital; the family cost of healthcare service is relatively low, which supports a low dropout rate and consistent long-term follow-up. Our relatively large sample size enabled examination of various atopic phenotypes. Patients with AD who exhibited both skin and airway manifestations confirm the presumed atopic march with progression from AD to AR and asthma, or co-expression of asthma and AD phenotypes (ie, skin sensitivity plus wheeze).

The primary limitation of the present study was that data were missing for some factors, notably family atopic conditions and laboratory tests. Regarding the family history, many parents did not provide clear information concerning their own atopic conditions. Those with mild symptoms may fail to seek medical advice, although they reported self-diagnosed atopic conditions. Although only physician-diagnosed conditions were included in

the data analysis, there was difficulty confirming the validity of those family histories. A substantial number of patients were only children in their families and had no siblings. Additionally, the BCT is a medical test that provokes airway narrowing. It is physically demanding and can cause severe discomfort (eg, violent coughing) which makes the measurement difficult. The irritating nature of the BCT makes it suitable solely for older children and causes high failure rates; thus, the number of patients with a positive BCT result was relatively low. Our observations concerning the usefulness of the BCT should be confirmed in a prospective study.

Conclusions

In patients with paediatric AD, a positive BCT result was independently and positively associated with personal history of asthma and sibling history of atopy, but not with any other clinical parameters.

Author contributions

Concept or design: KL Hon, AHY Ng, CCC Chan, PXY Ho, EPM Tsoi, TF Leung.

Acquisition of data: AHY Ng, CCC Chan, PXY Ho, EPM Tsoi. Analysis or interpretation of data: KL Hon, AHY Ng, CCC Chan, PXY Ho, EPM Tsoi, KYC Tsang.

Drafting of the manuscript: KL Hon, AHY Ng, CCC Chan, PXY Ho, EPM Tsoi, FW Ko.

Critical revision of the manuscript for important intellectual content: KL Hon, FW Ko, TF Leung.

Conflicts of interest

As the editor of the journal, KL Hon was not involved in the peer review process. Other authors have disclosed no conflicts of interest.

Funding/support

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Ethics approval

This study was approved by The Joint Chinese University of Hong Kong–New Territories East Cluster Clinical Research Ethics Committee (The Joint CUHK-NTEC CREC).

References

- Hon KL, Liu M, Zee B. Airway disease and environmental aeroallergens in eczematics approaching adulthood. *Pediatr Respirol Crit Care Med* 2017;1:81-5.
- Hon KL, Wang SS, Leung TF. The atopic march: from skin to the airways. *Iran J Allergy Asthma Immunol* 2012;11:73-7.
- Hon KL, Yong V, Leung TF. Research statistics in atopic eczema: what disease is this? *Ital J Pediatr* 2012;38:26.
- Coates AL, Wanger J, Cockcroft DW, et al. ERS technical standard on bronchial challenge testing: general considerations and performance of methacholine challenge tests. *Eur Respir J* 2017;49:1601526.
- Dixon C. The bronchial challenge test: a new direction in asthmatic management. *J Natl Med Assoc* 1983;75:199-204.
- Pepys J, Hutchcroft BJ. Bronchial provocation tests in etiologic diagnosis and analysis of asthma. *Am Rev Respir Dis* 1975;112:829-59.
- Ng C, Hon KL, Kung JS, Pong NH, Leung TF, Wong CK. Hyper IgE in childhood eczema and risk of asthma in Chinese children. *Molecules* 2016;21:E753.
- Miller MR, Crapo R, Hankinson J, et al. General considerations for lung function testing. *Eur Respir J* 2005;26:153-61.
- Ramsdale EH, Morris MM, Roberts RS, Hargreave FE. Bronchial responsiveness to methacholine in chronic bronchitis: relationship to airflow obstruction and cold air responsiveness. *Thorax* 1984;39:912-8.
- Crapo RO, Casaburi R, Coates AL, et al. Guidelines for methacholine and exercise challenge testing-1999. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. *Am J Respir Crit Care Med* 2000;161:309-29.
- Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J* 2005;26:319-38.
- Spector SL, Farr RS. A comparison of methacholine and histamine inhalations in asthmatics. *J Allergy Clin Immunol* 1975;56:308-16.
- Schulze J, Smith HJ, Fuchs J, et al. Methacholine challenge in young children as evaluated by spirometry and impulse oscillometry. *Respir Med* 2012;106:627-34.
- Hon KL, Kung JS, Tsang KY, Yu JW, Cheng NS, Leung TF. Do we need another symptom score for childhood eczema? *J Dermatolog Treat* 2018;29:510-4.
- Severity scoring of atopic dermatitis: the SCORAD index. Consensus Report of the European Task Force on Atopic Dermatitis [editorial]. *Dermatology* 1993;186:23-31.
- Hon KL, Wong KY, Leung TF, Chow CM, Ng PC. Comparison of skin hydration evaluation sites and correlations among skin hydration, transepidermal water loss, SCORAD index, Nottingham eczema severity score, and quality of life in patients with atopic dermatitis. *Am J Clin Dermatol* 2008;9:45-50.
- Rothe T, Spagnolo P, Bridevaux PO, et al. Diagnosis and management of asthma—the Swiss guidelines. *Respiration* 2018;95:364-80.
- Cockcroft DW. Direct challenge tests: Airway hyperresponsiveness in asthma: its measurement and clinical significance. *Chest* 2010;138(2 Suppl):18S-24S.
- Huang SJ, Lin LL, Chen LC, et al. Prevalence of airway hyperresponsiveness and its seasonal variation in children with asthma. *Pediatr Neonatol* 201;59:561-6.
- Davis BE, Cockcroft DW. Past, present and future uses of methacholine testing. *Expert Rev Respir Med* 2012;6:321-9.
- Pols DH, Wartna JB, van Alphen EI, et al. Interrelationships between atopic disorders in children: a meta-analysis based on ISAAC questionnaires. *PLoS One* 2015;10:e0131869.
- Riiser A, Hovland V, Carlsen KH, Mowinckel P, Lødrup Carlsen KC. Does bronchial hyperresponsiveness in childhood predict active asthma in adolescence? *Am J Respir Crit Care Med* 2012;186:493-500.
- Toelle BG, Xuan W, Peat JK, Marks GB. Childhood factors that predict asthma in young adulthood. *Eur Respir J* 2004;23:66-70.
- Küster W, Petersen M, Christophers E, Goos M, Sterry W.

- A family study of atopic dermatitis. Clinical and genetic characteristics of 188 patients and 2151 family members. *Arch Dermatol Res* 1990;282:98-102.
25. Johnson CC, Ownby DR, Peterson EL. Parental history of atopic disease and concentration of cord blood IgE. *Clin Exp Allergy* 1996;26:624-9.
 26. Thomsen SF, Ulrik CS, Kyvik KO, Ferreira MA, Backer V. Multivariate genetic analysis of atopy phenotypes in a selected sample of twins. *Clin Exp Allergy* 2006;36:1382-90.
 27. Ober C, Hoffjan S. Asthma genetics 2006: the long and winding road to gene discovery. *Genes Immun* 2006;7:95-100.
 28. Sublett JL. The environment and risk factors for atopy. *Curr Allergy Asthma Rep* 2005;5:445-50.
 29. Subbarao P, Mandhane PJ, Sears MR. Asthma: epidemiology, etiology and risk factors. *CMAJ* 2009;181:E181-90.
 30. Goldberg S, Israeli E, Schwartz S, et al. Asthma prevalence, family size, and birth order. *Chest* 2007;131:1747-52.
 31. Kivity S, Fireman E, Sade K. Bronchial hyperactivity, sputum analysis and skin prick test to inhalant allergens in patients with symptomatic food hypersensitivity. *Isr Med Assoc J* 2005;7:781-4.
 32. Bowton DL, Fasano MB, Bass DA. Skin sensitivity to allergen does not accurately predict airway response to allergen. *Ann Allergy Asthma Immunol* 1998;80:207-11.
 33. Turner KJ, Stewart GA, Woolcock AJ, Green W, Alpers MP. Relationship between mite densities and the prevalence of asthma: comparative studies in two populations in the Eastern Highlands of Papua New Guinea. *Clin Allergy* 1988;18:331-40.
 34. Lúdvíksdóttir D, Janson C, Björnsson E, et al. Different airway responsiveness profiles in atopic asthma, nonatopic asthma, and Sjögren's syndrome. BHR Study Group. Bronchial hyperresponsiveness. *Allergy* 2000;55:259-65.
 35. Suh DI, Lee JK, Kim CK, Koh YY. Methacholine and adenosine 5'-monophosphate (AMP) responsiveness, and the presence and degree of atopy in children with asthma. *Pediatr Allergy Immunol* 2011;22:e101-6.
 36. Liu SF, Lin MC, Chang HW. Relationship of allergic degree and PC20 level in adults with positive methacholine challenge test. *Respiration* 2005;72:612-6.
 37. Sears MR, Burrows B, Flannery EM, Herbison GP, Hewitt CJ, Holdaway MD. Relation between airway responsiveness and serum IgE in children with asthma and in apparently normal children. *N Engl J Med* 1991;325:1067-71.
 38. Hon KL, Lam MC, Leung TF, et al. Are age-specific high serum IgE levels associated with worse symptomatology in children with atopic dermatitis? *Int J Dermatol* 2007;46:1258-62.
 39. Haccuria A, Van Muylem A, Malinovschi A, Doan V, Michils A. Small airways dysfunction: the link between allergic rhinitis and allergic asthma. *Eur Respir J* 2018;51:1701749.
 40. Lluncor M, Barranco P, Amaya ED, et al. Relationship between upper airway diseases, exhaled nitric oxide, and bronchial hyperresponsiveness to methacholine. *J Asthma* 2019;56:53-60.
 41. Shaaban R, Zureik M, Soussan D, et al. Allergic rhinitis and onset of bronchial hyperresponsiveness. *Am J Respir Crit Care Med* 2007;176:659-66.
 42. Ciprandi G, Signori A, Cirillo I. Relationship between bronchial hyperreactivity and bronchodilation in patients with allergic rhinitis. *Ann Allergy Asthma Immunol* 2011;106:460-6.