Three clinical signs to distinguish allergies or infections in allergic children with airway symptoms

Rizka Yulianti[1], *Anang Endaryanto[1], Zahrah Hikmah[1], Retno Asih Setyoningrum[1], Kazufumi Shimizu[2,3]

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Abstract

***Background**:* Respiratory disorders are common in children. Symptoms of allergy and airway infection overlap. Simple methods are needed to determine the cause of infection or allergen exposure.

***Objectives**:* To determine the diagnostic value of 3 clinical signs (fever, nasal secretions, and symptom continuation) as a differentiator for infection or allergen exposure in allergic patients who experience airway symptoms.

Method: In this study patients diagnosed with allergies due to food elimination and provocation test, and skin prick test in the Paediatric Allergy Outpatient Clinic Dr Soetomo General Hospital, Surabaya, Indonesia, who experienced airway symptoms, were enrolled. Patients were determined to have 3 clinical signs, by anamnesis and physical examination, and laboratory evaluation (complete blood count, C-reactive protein, and nasopharyngeal swab polymerase chain reaction) as infection markers. Analysis was done using the McNemar and Kappa tests ($p < 0.05$; 95% CI).

***Results**:* A total of 60 patients (60% male) met the inclusion criteria. From laboratory tests, the number of patients who showed infection and non-infection was 26 (43.4%) and 34 (56.6%), respectively. There were 28 (82.4%) patients who met 3 clinical signs of allergy from the results of non-infectious laboratory markers. Sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio and negative likelihood ratio were 82.3%, 80.7%, 84.8%, 77.7%, 4.24 and 0. 22 respectively.

Conclusions: Fever, nasal secretions, and time of symptom continuation can distinguish well between infection and allergen exposure in allergic children who are experiencing airway symptoms

(Key words: Three distinguishing clinical signs, Allergic children, Respiratory infections, Sensitivity, Specificity)

Introduction

Respiratory disorders are commonly experienced by children, with symptoms of cold, nasal congestion, and cough. These symptoms are generally caused by one of the following aetiologies: allergies, viral infections or bacterial infections. Viral infection is the most common condition which has symptoms similar to allergies[1,2]. Reportedly as many as 40% of children in western countries suffer from allergies with symptoms of airway disorders[3]. A study conducted in Georgia found that 53.4% of children with allergies experience respiratory infections 1-2 times per year[4]. Symptoms of allergy and airway infection overlap, clinicians identifying the presence of infection in allergies or vice versa, so a quick and simple procedure is needed to distinguish them and to determine the next step of therapy[1,5]. A simple step to distinguish allergy or bacterial and viral infections in complaints of respiratory symptoms involves three clinical pieces of information: fever, nasal secretion, and symptom continuation[5].

Objectives

This study aimed to determine the diagnostic value of 3 clinical signs as a differentiator for infection or allergen exposure in allergic patients who experience airway symptoms.

Method

A study was conducted from July to September 2019 in the Paediatric Allergy Outpatient Clinic, Clinical Pathology Laboratory of Dr Soetomo General Hospital Surabaya, and Institute of Tropical Disease Surabaya, Indonesia. The study population comprised patients having allergy (diagnosed by the paediatrician), attending the Paediatric Allergy

[1]*Department of Child Health, Faculty of Medicine, Universitas Airlangga / Dr. Soetomo General Academic Hospital, Surabaya, Indonesia,* [2]*Indonesia-Japan Collaborative Research Centre for Emerging and Re-emerging Infectious Disease, Institute of Tropical Disease, Universitas Airlangga, Surabaya, Indonesia,* [3]*Centre for Infectious Diseases, Kobe University Graduate School of Medicine, Japan*
**Correspondence:* aendaryanto.ae@gmail.com
orcid.org/0000-0002-7988-2274
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Outpatient Clinic with respiratory symptoms (cough and rhinorrhoea).

Inclusion criteria were allergic patients attending Paediatric Allergy Outpatient Clinic; patients were diagnosed to have allergy by paediatric immunologist due to clinical signs/ symptoms, food elimination and provocation test, and skin prick test.

Exclusion criteria were congenital anomaly/ anatomical anomaly of airway; history of endocrinological disorder (congenital adrenal hyperplasia, Addison disease, Cushing syndrome etc.), history of other comorbidities that increase C-reactive protein (CRP) and leucocyte (malignancy, autoimmunity, inflammatory disease, rheumatologic disease, drug reaction).

Sample size was 58 based on the sample size formula $n=Z^2P(1-P)/d^2$ where n is the sample size, Z is the statistic corresponding to level of confidence, P is expected prevalence and d is precision.

Patients were asked 3 questions: whether respiratory symptoms were accompanied by fever, whether complaints during the day were more dominant than during the morning and night, and whether nasal secretions were thick or coloured. If all three questions were answered "no" then the respiratory symptoms were very likely due to allergies. However, if one of the three questions was answered "yes", then the respiratory symptoms could be caused by an infection.

Three ml of blood was drawn from a peripheral vein for complete blood count (CBC) (flow cytometry with Sysmex XN-1000) and CRP (ELISA method with measuring device The Quantikinine human hs-CRP immunoassay), and for viral nasopharyngeal swab polymerase chain reaction (PCR) tests with multiplex technique using primary xTAG® Respiratory Virus Panel FASTv2 produced by Luminex Molecular Diagnostic Inc., Ontario, Toronto, Canada by trained staff at ITD, Airlangga University, Surabaya. Non-infection was diagnosed if all three tests showed negative results (leucocyte count on CBC within normal limits, negative CRP, and negative PCR), and infection was diagnosed if one or more of the three tests shows positive results.

Ethical issues: Approval for e study was obtained from the institutional ethics committee of Dr Soetomo General Academic Hospital, Surabaya, Indonesia (No. 1211/KEPK/V/2019). Written informed consent was obtained from parents of the participants.

Statistical analysis for diagnostic tests (sensitivity, specificity, false positive, false negative, positive predictive value, negative predictive value, likelihood ratio) and inferential analysis (Kappa association and McNemar test).

Results

The total sample was 64 children; 60 of them fulfilled the inclusion criteria and 4 of them were excluded because they refused to do blood tests.

Table 1: ***Characteristics of subjects***

Baseline characteristic	%
Sex	
Male	60
Female	40
Age	
<5 years old	38.3
5-10 years old	46.7
>10 years old	15
Clinical symptom	
Fever	
Negative	75
Positive	25
Nasal secretion'	
Watery, clear	75
Thick, coloured	25
Symptom continuation	
Negative during the day	60
Night and day	40

A total of 10% of subjects did not fulfil 3 clinical signs of allergy (positive fever, thick and coloured nasal secretions, time of symptom continuation during the day) and 55% of subjects met 3 clinical signs of allergy (negative fever, runny and clear nasal secretions, negative daytime symptoms). (Table 2)

Table 2: ***Combined distribution of clinical symptoms of subjects***

Clinical symptoms	Yes	No	%
Fever positive, nasal secretion thick, coloured and symptom continuation positive during the day - n (%)	6 (10)	54 (90)	60 (100)
Fever positive, nasal secretion thick, coloured and symptom continuation negative during the day - n (%)	0 (0)	60 (100)	60 (100)
Fever positive, nasal secretion watery, clear and symptom continuation positive during the day - n (%)	6 (10)	54 (90)	60 (100)
Fever positive, nasal secretion watery, clear and symptom continuation negative during the day - n (%)	3 (5)	57 (95)	60 (100)
Fever negative, nasal secretion thick, coloured and symptom continuation positive during the day - n (%)	9 (15)	51 (85)	60 (100)
Fever negative, nasal secretion thick, coloured and symptom continuation negative during the day - n (%)	0 (0)	60 (100)	60 (100)
Fever negative, nasal secretion watery, clear and symptom continuation positive during the day - n (%)	3 (5)	57 (95)	60 (100)
Fever negative, nasal secretion watery, clear and symptom continuation negative during the day - n (%)	33 (55)	27 (45)	60 (100)

From laboratory tests, 26 (43.4%) subjects showed infection with details viral PCR positive 77%, CRP positive 11.5%, and leucocytosis 11.5%, while 34 subjects (56.6%) showed non-infection.

Table 3 shows the distribution of virus types of subjects from the PCR.

Table 4 shows the distribution of three clinical signs of allergy with laboratory markers.

Table 3
Distribution of virus types of subjects from PCR

Virus types	%
Rhinovirus	80
Respiratory syncytial virus	05
Parainfluenza virus	05
Corona virus	05
Boca virus	05

PCR: Polymerase chain reaction

Table 4: ***Distribution of three clinical signs of allergy with laboratory markers***

	Non-infection - n (%)	Infection - n (%)
Fever		
No	29 (85.3)	16 (61.5)
Yes	05 (14.7)	10 (38.5)
Nasal secretion		
Watery, clear	31 (91.2)	14 (53.8)
Thick, coloured	03 (08.8)	12 (46.2)
Symptoms' continuation		
Negative during the day	29 (85.3)	07 (26.9)
Positive during the day	05 (14.7)	19 (73.1)
Fulfil 2 clinical signs of allergy		
Yes	01 (02.9)	05 (19.2)
No	33 (97.1)	21 (80.8)
Fulfil 3 clinical signs of allergy		
Yes	28 (82.4)	05 (19.2)
No	06 (17.6)	21 (80.8)

Subgroups that fulfil all three clinical signs of allergy have higher sensitivity and specificity values than the sub-groups of each clinical sign of an allergy (Table 5).

Table 5: ***Diagnostic test of 3 clinical signs of allergy with non-infectious laboratory markers***

	Sn (%)	Sp (%)	PV (%)	NPV (%)	LRP (%)	LRN (%)	McNemar	Kappa	V
No fever	85.29	38.46	64.44	66.67	1.37	0.39	0.027	0.035	nv
Watery, clear nasal secretion	91.18	46.15	68.89	80	1.68	0.19	0.013	0.001	nv
Negative during the day	85.29	73.08	80.56	79.17	3.15	0.21	0.774	0.000	v
Fulfil 2 clinical signs of allergy	2.94	80.77	16.67	38.89	0.1	1.23	0.000	0.037	nv
Fulfil 3 clinical signs of allergy	82.35	80.77	84.85	77.78	4.24	0.22	1.000	0.000	v

Sn: Sensitivity; Sp: Specificity; PPV: Positive Predictive Value; NPV: Negative Predictive Value; LRP: Likelihood Ratio Positive; LRN: Likelihood Ratio Negative; V: Validity; v: valid; nv: nonvalid

Discussion

An estimated 10% of the total child population and 5% of the entire adult population suffer from airway hypersensitivity which is characterized by symptoms of recurrent chronic cough[5]. Reportedly as many as 40% of children in western countries suffer from allergies with symptoms of airway disorders[3]; 53.4% of allergic children experience respiratory infections 1-2 times per year[4]. In this study, all subjects were patients with a history of allergies suffering from cold and cough, which would be analysed as causative of airway symptoms due to infection or allergic recurrence.

In upper respiratory tract infections, examination of bacterial and viral cultures with throat swab specimens is the standard for diagnosing pharyngitis, epiglottitis, and laryngotracheitis[6,7]. In this study, 77% subjects were positive for virus PCR results; most types were rhinovirus. Upper respiratory tract infections are generally caused by one of the aetiologies of allergies, viral infections or bacterial infections. Viral infection is the most common condition, which has symptoms similar to allergies[1,2]. The most common viral aetiology are rhinovirus, parainfluenza virus, coronavirus, adenovirus, RSV, coxsackievirus, and influenza virus[8]. There is a complex interaction between allergies and respiratory tract infections, and there is evidence to suggest that viral respiratory infections can trigger, sustain and activate exacerbations of allergic conditions in the respiratory tract. In addition, studies have shown that allergies can increase the expression of rhinovirus receptors on mucosal epithelial cells and can also increase the expression level of influenza virus receptors. This

shows that respiratory allergies and viral infections have a reciprocal interaction[2].

Fever is one of the clinical markers to distinguish infections or allergies examined in this study. In the non-infection group 14.7% subjects had fever. The sensitivity for clinical markers of non-fever was 85.3% and specificity was 38.5%. In patients with allergies, symptoms of fever do not appear, because antigen exposure will only cause a local inflammatory response and not kill microbes[9,10].

In this study, thin and clear nasal secretions were found as much as 91.2% in non-infectious laboratory markers. Sensitivity for thin and clear nasal secretions was 91.2% but it has a low specificity of 46.2%. Nasal secretions tend to be thick because they have been mixed with inflammatory cells, micro abscesses, and necrotic focus[11]. Production of coloured nasal secretions is commonly found in influenza infections. Influenza viruses damage the airway epithelium and cause a substantial inflammatory response by involving white blood cells. Purulent discharge has also previously been found to be a common clinical feature of uncomplicated influenza[12].

In this study, clinical signs of negative daytime symptoms were 85.3% in non-infectious laboratory markers. The sensitivity and specificity of the continuation of symptoms that are not daytime are quite high, namely 85.3% and 73.1%, respectively. Allergy is known to vary in symptom severity throughout the day/night cycle. This rhythm is also observed in mast cell function and response. Mast cells are key effector cells from allergic reactions and release cytokines, chemokines, and important inflammatory mediators such as histamine, which have been shown to display diurnal variations[13]. Allergy symptoms can disappear or decrease during the day because humans naturally have a diurnal cycle, in which the body produces more hormones adrenaline and cortisol during the day and decreases at night, while adrenaline and cortisol can eliminate or reduce allergy symptoms[5].

This study has provided information that 3 clinical signs of allergy (no fever, thin and clear nasal secretions and negative daytime symptoms) are indeed associated with non-infectious laboratory results. The sensitivity and specificity of the three clinical signs indicate that 3 clinical signs can be used to diagnose allergies because they can give positive results of 82.4%. In addition, these 3 clinical signs have quite a good specificity so as to determine non-allergic subjects as much as 80.8%. In this study, the examination of three clinical signs that distinguish allergies and infections had PPV values of 84.9% and NPV of 77.8%, LRP values 4.24, and LRN 0.22. The weakness of this study is subjective clinical symptoms based on parents' reports, but there are still not many similar studies that can be superior to this study.

Conclusions

Three clinical signs (fever, nasal secretions, time of symptom continuation) can distinguish between infection and allergen exposure in allergic children who are experiencing airway symptoms.

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