

***Chlamydia Pneumoniae* Infection Associated with Uncontrolled Asthma: A Hospital Based Cross Sectional Study**

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Received: 29 November 2011 / Accepted: 24 May 2012
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Abstract

Objectives To evaluate the proportion of anti- *Chlamydia pneumoniae* (Cp) IgM positivity in patients with uncontrolled asthma and partly controlled childhood asthma and their clinical correlates.

Methods This was a hospital based cross sectional study. Children aged 1 to 12 y suffering from asthma were included after written informed parental consent. For diagnosis and classification of uncontrolled and partly controlled asthma, GINA guidelines 2009 were used. Anti-Cp IgM was tested by using an enzyme linked immunosorbent assay (ELISA) and value of antibody index ≥ 0.90 was considered positive. Data was collected on demographic, clinical and investigative variables including chest radiograph posterior-anterior view.

Results From August 2010 through August 2011 44 patients hospitalized with uncontrolled asthma in exacerbation and 45 patients with partly controlled asthma from ambulatory care settings were included. Anti-Cp IgM was positive in 25 % ($n=11/44$) and 6.7 % ($n=3/45$) patients with uncontrolled and partly controlled asthma, respectively (Odds ratio=4.67, $\chi^2=5.64$, 95 % CI 1.20-18.10, $p=0.017$). Among the patients of uncontrolled asthma, duration of hospital stay was longer in anti-Cp IgM positive patients (9 ± 2.19 vs. 7.19 ± 2.10 d, $p=0.02$).

Conclusions Since anti-Cp IgM positivity was associated with age >5 y and radiological consolidation in uncontrolled asthma in exacerbation, specific treatment of *Chlamydia pneumoniae* must be actively considered.

Keywords Asthma · Uncontrolled · *Chlamydia pneumoniae* · Children · India

Introduction

Asthma is a chronic inflammatory disorder of the airways manifesting as recurrent episodes of wheezing, breathlessness, chest tightness and cough. Although childhood asthma is very strongly linked to allergy [1], factors that provoke allergic sensitization and inflammation still remain unclear. Epidemiological studies suggest the possible role of infection in the sensitization and inflammatory process associated with asthma [2]. *Chlamydia pneumoniae*, a respiratory pathogen has been suggested as playing a role in the development of wheezing in both children and adults [3].

Majority of the research linking *Chlamydia pneumoniae* to asthma has been conducted in adult population. However, there is evidence suggesting that *Chlamydia pneumoniae* may play a role in pediatric asthma [4]. Population based longitudinal data suggests that increasing *Chlamydia pneumoniae* prevalence is associated with increasing incidence of asthma attack in all age group [5]. The present study hypothesis was that *Chlamydia pneumoniae* infection is associated with uncontrolled asthma in exacerbation. The objective of present study was to evaluate the proportion of anti-Cp IgM positivity in patients with uncontrolled and partly controlled childhood asthma and their clinical correlates.

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Material and Methods

This hospital based cross sectional study was conducted in the Department of Pediatrics and Department of Microbiology, C.S.M. Medical University, Lucknow, a tertiary care, referral teaching hospital, after approval from institutional ethics committee.

Children aged 1 to 12 y, with asthma were included after written informed parental consent. For diagnosis and classification of uncontrolled asthma and partly controlled asthma, GINA guidelines 2009 were used [6]. A child with any of following measures namely, (1) daytime symptoms more than twice/wk, (2) any limitations of activities (3) any nocturnal symptoms/awakening, (4) need for reliever/rescue treatment more than twice/wk, present preferably over 4 wk was diagnosed as partly controlled and presence of ≥ 3 measures with exacerbation was diagnosed as uncontrolled asthma. Cases in exacerbation were further classified into mild, moderate, severe and imminent respiratory failure according GINA guidelines 2009 [6]. From all the patients 2 ml of venous blood was collected in eppendorf vial with full aseptic precautions. In Department of Microbiology, CSM Medical University, Lucknow, serum was separated and aliquoted and kept at -20°C till it is processed further for detection of anti-Cp IgM.

Anti-Cp IgM was tested by using an enzyme linked immunosorbent assay (ELISA) and value of antibody index ≥ 0.90 was considered positive. Name of kit was Chlamydia pneumonia IgM 96 T Calbiotech, CPG3281, manufactured by Calbiotech Inc., Spring Valley, CA, 91978 and during the testing, manufacturer's instructions were followed.

Data was collected on demographic variables including age, sex, age of first episode of asthma, height, weight, basal mass index (BMI), number of siblings, birth order, and immunization status. Data was also collected on housing conditions, distance from heavy traffic, allergies to food items, smoking habit of parents, family history of allergic dermatitis, allergic rhinitis and other allergies. Clinical variables included respiratory rate, heart rate, difficulty in breathing, night cough, wheeze, headache, chest pain, fever, inability to feed, inability to speak, and disturbed sleep.

In hospitalized patients data in the form of investigative variables including hemogram, arterial blood gas, duration of intravenous (IV) fluids, oxygen therapy, hospital stay and chest radiograph posterior-anterior (PA) view was collected. Data was collected in preformed questionnaires and then entered into excel sheet.

Univariate analysis was done to assess the distribution of baseline variables. Thereafter student "t" test and chi square test were used to compare continuous and categorical variables, respectively between patients who were anti Cp IgM positive and negative. The Odd's ratio with 95 % confidence

limit was also calculated to assess the association of various risk factors with anti Cp IgM positivity.

Results

The study was conducted from Aug 2010 through Aug 2011. Forty four and 45 patients of uncontrolled in exacerbation and partly controlled asthma were recruited, respectively. While all the patients with uncontrolled asthma were in exacerbation and hospitalized, patients with partly controlled asthma were from ambulatory care settings. The mean age of cases of uncontrolled asthma and partly controlled asthma was 52.84 ± 33.76 mo and 63.37 ± 39.68 mo, respectively ($p=0.18$). Table 1 shows demographic characteristics of studied population. Mean weight, height and BMI of cases of uncontrolled asthma and partly controlled asthma was 16.00 ± 6.46 and 17.83 ± 8.36 kg ($p=0.25$), 98.29 ± 18.65 and 102.08 ± 20.51 cm ($p=0.25$), 15.88 ± 2.24 and 15.87 ± 2.44 kg/m² ($p=0.98$), respectively. Anti-Cp IgM was positive in statistically significantly higher proportion of patients with uncontrolled asthma in exacerbation (11/44, 25 %) than partly controlled asthma (3/45, 6.7 %), (Odd's ratio=4.67, $\chi^2=5.64$, 95 % CI 1.20-18.10, $p=0.017$).

On comparing demographic characteristics between anti-Cp IgM positive and negative patients, 78.6 % (11/14) patients who were anti-Cp IgM positive were found to be >5 y of age as compared to 42.7 % (32/75) who were anti-Cp IgM negative (crude OR 4.93, 95 % CI 1.13-24.45, $p=0.014$). There was, however, no difference in BMI of anti-Cp IgM positive and negative patients being 16.73 ± 1.42 and 15.73 ± 2.45 kg/m², respectively ($p=0.14$). There was no difference in gender of patients who were anti-Cp IgM positive and negative.

The clinical features of anti-Cp IgM positive and negative patients were compared (Table 2) and greater proportion of former presenting with headache, chest pain, fever and inability to feed was found. All these symptoms were also statistically significant for a longer duration. The duration of night cough and difficulty in breathing was also longer in anti-Cp IgM positive patients as compared to anti-Cp IgM negative patients even though the proportion having these signs was similar in both study groups. Among the patients of uncontrolled asthma in exacerbation, duration of hospital stay was longer in anti-Cp IgM positive patients (9 ± 2.19 d) in comparison to in anti-Cp IgM negative patients (7.19 ± 2.10 d, p value 0.02).

Among the patients with uncontrolled asthma ($n=44$) in exacerbation, 16/44 (36.4 %), 26/44 (59.1 %), and 2/44 (4.5 %) patients were in moderate exacerbation, severe exacerbation and imminent respiratory failure, respectively; 11/44 (25 %) were anti-Cp IgM positive, of which 2/11 (18.18 %) and 9/11 (81.81 %) were in moderate and severe

Table 1 Baseline characteristics of patients with uncontrolled and partly controlled asthma

No.	Characteristics		Uncontrolled N=44		Partly controlled N=45		χ^2 , p value
			n	%	n	%	
1.	Age	1-5 y	26	59.1	20	44.44	1.91, 0.16
		>5 y	18	40.9	25	55.55	
2.	Sex	Male	26	59.1	26	57.8	0.02, 0.89
3.	Consanguinity		3	6.8	3	6.7	0.001, 0.98
4.	Religion	Hindu	33	75	35	77.8	0.09, 0.76
		Muslim	11	25	10	22.8	

exacerbation, respectively. ($\chi^2=2.51$, OR=3.71, 95 % CI 0.58-29.77, Fisher exact p value 0.11).

Radiological investigation in the form of digital chest radiograph postero-anterior view was done in all the patients with uncontrolled in-exacerbation asthma ($n=44$). Consolidation was significantly in higher proportion in anti-Cp IgM positive patients in comparison to anti-Cp IgM negative patients (crude OR 18.29, 95 % CI 1.48-507.01, Fisher exact p value 0.01). In hospitalized patients, there were no difference in laboratory values of hemogram and arterial blood gas, duration of intravenous fluid and duration of oxygen therapy in anti-Cp IgM positive and negative cases.

Other factors like housing conditions, distance from heavy traffic, allergies to food items, smoking habit of parents, family history of allergic dermatitis, allergic rhinitis and other allergies were studied, but were found to be similar in both the groups of the present study (data not given). The authors did not find any seasonal variations in the present study (Table 3).

Discussion

The present study was conducted on 89 patients with bronchial asthma who had either uncontrolled asthma ($n=44$,

49.43 %) or partly controlled asthma ($n=45$, 50.56 %). All the patients with uncontrolled asthma were in acute exacerbation and hospitalized for it. Anti-Cp IgM positivity was found to be associated with uncontrolled asthma in exacerbation (Odd's ratio=4.67, $\chi^2=5.64$, 95 % CI 1.20-18.10, p value 0.017).

Association of *Chlamydia pneumoniae* infection with acute attack (exacerbation) of asthma has been reported by other workers also [7, 8]. Infection with *Chlamydia pneumoniae* has also been associated with first ever episode of wheezing [9, 10]. Therefore, it is plausible that infection with *Chlamydia pneumoniae* can trigger bronchospasm both in children with diagnosed asthma as well as those without it. The authors have found that one fourth of patients of uncontrolled asthma in acute exacerbation were having serological evidence of infection with *Chlamydia pneumoniae*. Studies have reported a wide variation in serological evidence of infection with *Chlamydia pneumoniae* ranging from 48.6 % to 5 % from various sites [10–12]. Site to site variation in proportion positivity for anti-Cp IgM in patients with asthma may be due to either a true difference in prevalence or seasonal variation. Epidemiological monitoring for seasonal as well as annual trends in *Chlamydia pneumoniae* infection will assist in deciding when to use specific antimicrobial therapy against *Chlamydia pneumoniae*.

Table 2 Comparison of clinical characteristics of anti Cp IgM positive and negative patients

No.	Clinical Characteristics (A)	Anti Cp IgM Positive N=14		Anti Cp IgM Negative N=75		p value χ^2 statistics (B vs. D)	P value "t" statistics (C vs. E)
		No. (%) (B)	Mean $\pm$ SD (d) (C)	No. (%) (D)	Mean $\pm$ SD (d) (E)		
1.	Difficulty in breathing	14 (100)	10.21 $\pm$ 11.15	75(100)	4.57 $\pm$ 5.79	NA	<0.01
2.	Night cough	14 (100)	9.57 $\pm$ 11.24	70 (93.3)	4.05 $\pm$ 5.40	0.98, 0.32	<0.01
3.	Wheeze	12 (85.7)	2.79 $\pm$ 2.38	69 (92)	3.13 $\pm$ 5.23	0.57, 0.45	0.81
4.	Headache	3 (21.4)	4.35 $\pm$ 10.86	3 (4)	0.40 $\pm$ 0.19	5.70, 0.01	<0.01
5.	Chest pain	5 (35.7)	4.57 $\pm$ 10.79	6 (8)	0.11 $\pm$ 0.42	8.36, <0.01	<0.01
6.	Fever	5 (35.7)	5.86 $\pm$ 11.08	6 (8)	0.16 $\pm$ 0.62	8.36, <0.01	<0.01
7.	Inability to feed	9 (64.3)	2.28 $\pm$ 3.43	22(29.3)	0.44 $\pm$ 0.74	6.34, 0.01	<0.01
8.	Inability to speak	5 (35.7)	0.43 $\pm$ 0.65	21(28)	0.36 $\pm$ 0.65	0.33, 0.56	0.72
9.	Disturbed sleep	3 (21.4)	0.29 $\pm$ 0.47	19 (25.3)	0.26 $\pm$ 0.51	0.09, 0.75	0.97

Table 3 Month wise recruitment of cases of asthma

Month	Uncontrolled Asthma (n=44)		Partially Controlled Asthma (n=45)	
	n	%	n	%
Jan	3	50.0	3	50
Feb	2	66.66	1	33.33
March	3	37.5	5	62.5
April	6	60.0	4	40.0
May	8	50.0	8	50.0
June	4	50.0	4	50.0
July	0	-	0	-
August	0	-	0	-
September	3	42.85	4	57.14
October	5	45.45	6	54.54
November	3	42.85	4	57.14
December	7	53.84	6	46.15

in children with wheeze in different settings. Thus, the authors recommend further research in this field.

The authors identified that in patients with severe exacerbation, anti Cp IgM is likely to be raised. ($\chi^2=2.51$, OR= 3.71, 95 % CI 0.58-29.77, Fisher exact *p* value 0.11). Therefore screening in this group for anti Cp IgM may prove cost effective and thus further research in this field is recommended.

A statistically significant higher proportion of children >5 y of age were found to have serological evidence of *Chlamydia pneumoniae* infection. This is in collaboration on the similar reports by other workers [4, 13, 14]. While no gender preference for *Chlamydia pneumoniae* infection was found in the present study, male dominance has been reported from elsewhere [13].

The authors found that radiological evidence of consolidation was associated with *Chlamydia pneumoniae* infection, as reported by others. They also found that *Chlamydia pneumoniae* infection tends to result in higher proportion of cases in severe exacerbation, which was reflected by increased duration of hospital stay in cases who were hospitalized with acute attack of asthma. If anti *Chlamydia pneumoniae* treatment is started early in older patients (> 5 y) or those with radiological evidence of consolidation or in severe exacerbation, this may probably reduce the duration of symptoms and hospital stay. However, further research is needed in this issue.

There is no simple gold standard test for diagnosis of *Chlamydia pneumoniae* infection. *Chlamydia pneumoniae* is an obligate intracellular bacterium and must be cultivated within eukaryotic host cell. It is a slow growing organism which is difficult to culture. PCR is a rapid and sensitive process for detection of *Chlamydia pneumoniae*. Serology can be done relatively easily by ELISA and can be used for presumptive diagnosis of *Chlamydia pneumoniae* infection.

However, in primary infection, IgM antibody appears 2–3 wk after the onset of illness and is generally undetectable after 2–6 mo. In cases of re-infection, IgM antibody may not appear [15]. Thus IgM may not pick early infection and miss re-infection. This is an intrinsic weakness of the present study. The authors did not plan for culture of *Chlamydia pneumoniae*. They did not assess for viral pathogen which also may result in exacerbation but did assess for anti Cp IgM positivity in children with uncontrolled and partly controlled asthma. Therefore, viral co-infection was not excluded.

Conclusions

Since anti-Cp IgM positivity was associated with age >5 y and radiological consolidation in patients with uncontrolled asthma in exacerbation, it is hypothesized that treating such children for *Chlamydia pneumoniae* may result in earlier resolution of symptoms and faster recovery. However, further research is needed in this regard.

Conflict of Interest None.

Role of Funding Source None.

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