Chlamydia Pneumonia Infection and Possible Relationship to Childhood Bronchial Asthma

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Abstract: Background: Asthma is a leading cause of chronic illness in childhood. Respiratory tract infections with viruses and mycoplasma pneumonia are considered the most common triggers of asthma in all age groups. Recently Chlamydia pneumonia infection has been suggested to play a role in pathogenesis of asthma. **Objective**: The aim of this work was to evaluate the possible role of Chlamydia pneumonia in the development or aggravation of childhood bronchial asthma. **Patients and Methods**: This study included 50 asthmatic patients divided into 2 groups; group (1) composed of 20 new wheezier who denied previous wheezing and were evaluated during initial wheezing episode, group (2) composed of 30 chronic asthmatic children who had recurrent episodes of/or persistent wheezing. Also 20 healthy children were included as a control group. Qualitative estimation of Chlamydia pneumonia infection in nasopharyngeal swabs using polymerase chain reaction (P.C.R) technique was done to all cases and controls. **Results**: In the new wheezier group 8 cases (40%) were Chlamydia pneumonia PCR (+ve), in the chromic asthmatic group 9 cases (30%) were PCR (+ve), while in the control group only 2 cases (10%) were PCR+ve. The infection rate of Chlamydia pneumonia among patients were 17 (89.5%) and among controls 2 (10.5%) with a statistically significant difference (P = 0.041) between patients and controls. There was an increase in asthma severity and severity of exacerbation in PCR+ve than in PCR-ve patients for C. pneumonia but it didn't reach statistical significance. Also there was a significant increase in PCR+ve males (58.8%) than PCR+ve females (41.2%), while there were no significant statistical difference between PCR+ve and PCR-ve patients as regards age, residence, seasonal variation, atopic manifestation and family history of atopy. **Conclusion**: The incidence of C. pneumonia infection among new wheezier and chronic asthmatics is high pointing to its possible role as a triggering factor for asthma in new wheezier and continuation of symptoms in spite of proper treatment plan in chronic asthmatic children.

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Key words: Chlamydia pneumonia, Childhood asthma, polymerase chain reaction.

1. Introduction:

Chlamydia are intracellular bacteria that cause infections of the respiratory tract, which is a major clinical problem (Asquith et al., 2011). It is an obligate intracellular parasite with discrete cell wall that is similar to those of gram negative bacteria, it contains both RNA and DNA. It spreads through person to person by droplet and outbreaks of infection have been reported in families, schools, military barracks and nursing homes (Niedzwiadek et al., 2000).

Asthma is a chronic inflammatory airway disease characterized by variable airway obstruction and bronchial hyper responsiveness. There are many factors affecting the development and severity of childhood asthma such as genetic predisposition, atopy, environmental factors, obesity, diet, socioeconomic status, and infectious triggers (Annaqur et al.,2007). It is a leading cause of chronic illness in childhood, responsible for a significant proportion of school days lost. It is the most frequent admitting diagnosis in children's hospital and result nationally in 5 to 7 lost school days/year/child (Martin et al., 2001).

Chlamydia pneumonia has been associated with asthma. It has also been suggested that Chlamydia pneumonia infection may lead to lung remodeling in a subset of asthmatic patients .Although there is no specific symptoms in Chlamydia pneumonia infection, this infection should be suspected in any child with prolonged wheezing for proper diagnosis and treatment (Hahn and Peeling, 2008).

The development of polymerase chain reaction (PCR) test for diagnosis of respiratory tract infection has highlighted the importance of this infection in acute exacerbation of asthma (Johnston et al., 1995).

Aim of the work: Was to investigate the relationship between C. pneumonia in school age children and bronchial asthma. We tried to determine whether previously asymptomatic children presenting

with first ever bronco-spasm would have PCR+ve criteria compatible with Chlamydia pneumonia infection. Another aim was to determine whether patients with established chronic asthma would have C. pneumonia infection.

2. Patients and Methods:

This study was carried on 50 children with reactive airway disease. Their ages ranged from 6-14 years, they were (19) males and (31) females. All cases were selected from Asthma and Allergy Clinic, Children's Hospital, Cairo University. Patients were divided into two groups; group I: new wheezier; a group of 20 children each of whom denied previous wheezing and were evaluated during the initial wheezing episode. All patients in this group reported that wheezing began after an acute respiratory tract illness (described as rhinitis, pharyngitis, bronchitis or pneumonia). Group II: chronic asthmatics; a group of 30 children (who had recurrent episodes of/or persistent wheezing) and who met the American Thoracic Society (ATS) criteria for reversible airway obstruction. All patients in this group were examined during an exacerbation (had prolonged respiratory symptoms and wheezes in spite of proper treatment plan). Also 20 healthy children (age and sex matched) were included as a control group. Cases with chronic illness as chronic liver or kidney disease or diabetes were excluded from the study. All cases and controls were subjected to: thorough medical history and clinical examination, peak expiratory flow rate (PEFR), skin allergy testing, routine laboratory investigations including; CBC, urine and stool analysis, total serum IgE using the IMx micro particle enzyme immunoassay (MEIA) the quantitative measurement of IgE in human serum, chest x-ray and qualitative estimation of Chlamydia pneumonia infection in nasopharyngeal swabs using polymerase chain reaction (P.C.R) technique: the DNA was extracted then PCR was performed using specific primer set which amplifies a 437 bp fragment and consists of the following primers: forward primer HL-1 (5`-GTTGTTCATGAAGGCCTACT-3`) and reverse primer HR-1 (5`-TGCATAACCTACGGTGTGTT-3`). The PCR products (20µl) were analyzed by electrophoresis on a 2 % agarose gel stained with ethidium bromide.

Data was analyzed on an IBM compatible computer using SPSS win version 11 statistical package. Numerical data were described in terms of means, standard deviation, median, minimum and maximum. Nominal data were expressed by frequency distribution and percentage. Chi square test was used to compare groups for categorical data. Mann whitney test was used to compare two groups for numerical data. If P-value is less than 0.05, it is considered to be significant and if it is less than 0.001, it is considered highly significant.

3. Results:

The study patients consisted of 50 children with reactive airway disease. Their ages ranged from 5-14 with mean age of (9) years, and were 19 males (38%) and 31 females (62%).

The characteristics of the studied children as regards age, sex, serum IgE, absolute eosinophilic count (AEC) and atopy are shown in table (1). Table (2) shows comparison of selected data (age, severity of exacerbation, atopy, used inhaled corticosteroids, AEC and IgE) between C. pneumonia PCR-ve (12 case) and PCR+ve (8 cases) in new wheezier. No significant statistical difference could be found between the two groups.

Table (3) shows comparison of selected data between C. pneumonia PCR-ve (21 cases) and PCR+ve (9 cases) in chronic asthmatic patients. No significant statistical difference could be detected between the two groups.

Our results show that there is a significant statistical difference between patients and control group as regards percentage of patients with Chlamydia pneumonia infection using PCR technique for diagnosis, where we have 17 (89.5%) PCR+ve cases in patient group and only 2 (10.5%) PCR+ve cases in control group (P = 0.041) (table 4).

Our results also show that infected boys represent 58.8%, while infected girls 41.2%, with significant difference between both sex, being more in males (P = 0.029) (table 5).

As regards PEFR, there is a significant statistical decrease in PCR+ve than in PCR-ve patients (P= 0.035) (table 5).

Figure 1 shows results of polymerase chain reaction (PCR) of Chlamydia infection.

Table (1): Characteristics of study groups

Characteristic		New wheezier n=20	Chronic Asthmatics n=30	Control n=20
Age (yr.) mean ± SD		9.00±2.90	9.33±2.34	8.45±1.57
	Range	6-14	6-14	7-12
Sex	Male	4 (20%)	15 (50%)	9 (45%)
	Female	16 (80%)	15 (50%)	11 (55%)
Mean serum	IgE (IU/L)	364.70±(239.88)*	421.97±(315.02)*	68±11.2
Mean absolute eosinophilic Count (cells/mm^3)		302.18±224.91	492.70±493.45	137±58.1
Atopy@ atopic		15 (75%)*	22 (73.3%)*	0 (0.0%)
	Non atopic	5 (25%)	8 (26.7%)*	20 (100%)

* Significant difference compared to control (P<0.001).

@ Atopy defined as +ve skin prick test reaction to at least one of tested allergens (Dreborg, 1987).

Table (2): Comparison of selected data between Chlamydia pneumonia PCR(-) and PCR(+) patients in new wheezier group.

Data		PCR(-) (12)	PCR(+) (8)	P-value
Age (yr.) 6-14		9 (3.015)	9 (2.927)	0.741
Severity of exacerbation				
	Mild	5 (41.7%)	4 (50%)	0.535
	Moderate	7 (58.3%)	4 (50%)	
Atopy	atopic	9 (75%)	6 (75%)	0.693
	Non atopic	3 (25%)	2 (25%)	
Inhaled corticosteroids				
	Not used	6 (50%)	3 (37.5%)	
	Low dose	1 (8.3%)	0 (0.0%)	
	Medium dose	5 (41.7%)	5 (62.5%)	0.535
Mean serum IgE (IU/L)		363.58 (253.38)	366.58 (253.38)	0.938
Mean absolute eosinophilic Count (cells/mm^3)±SD		632.17±(273.76)	213.75±(66.415)	0.216

P<0.05 is considered significant.

Table (3): Comparison of selected data between Chlamydia pneumonia PCR(+) and PCR(-) patients in chronic asthma group.

Data		PCR(-) (21)	PCR(+) (9)	P-value
Age (yr.) 6-14		9.5 (2.3)	8.7 (2.4)	0.334
Age of onset				
	< 5 yr.	16 (76.2%)	5 (55.5%)	0.275
	> 5 yr.	5 (23.8%)	4 (44.5%)	
Severity of asthma				
	Mild	11 (52.4%)	3 (33.3%)	0.40
	Moderate	10 (47.6%)	6 (66.7%)	
Severity of exacerbation				
	Mild	12 (57.1%)	3 (33.3%)	0.427
	Moderate	9 (42.9%)	6 (66.7%)	
Atopy	atopic	14 (66.7%)	8 (88.9%)	0.3
	Non atopic	7 (33.3%)	1 (11.1%)	
Inhaled corticosteroids				
	Not used	6 (28.6%)	2 (22.2%)	
	Low dose	3 (14.3%)	0 (0.0%)	0.50
	Medium dose	12 (57.1%)	7 (77.8%)	
Mean serum IgE (IU/L)		356.85±(314.03)	573.88±(275.84)	0.090
Mean absolute eosinophilic Count (cells/mm^3)		535.04±(366.37)	393.88±(254.98)	0.928

P<0.05 is considered significant.

Table (4): Infection rate of Chlamydia pneumonia among patients and controls.

	PCR-ve n=51	PCR+ve n=19	Total n=70	P-value
Patients group	33 (64.7%)	17 (89.5%)	50 (71.4%)	0.041
Control group	18 (35.3%)	2 (10.5%)	20 (25.6%)	
Total	51 (100%)	19 (100%)	70 (100%)	

P<0.05 is considered significant.

Table (5): Statistical comparison between PCR-ve and PCR+ve patients as regards sex distribution and median value of PEFR.

	PCR-ve n=33	PCR+ve n=17	P-value
Male (n=19)	9 (27.3%)	10 (58.8%)	0.029 (s)*
Female (n=31)	24 (72.7%)	7 (41.2%)	
PEFR (M±SD)	76.97 (9.38)	71.06 (9.22)	0.035 (s)

P<0.05 is considered significant.

Results of polymerase chain reaction (PCR)of Chlamydia infection

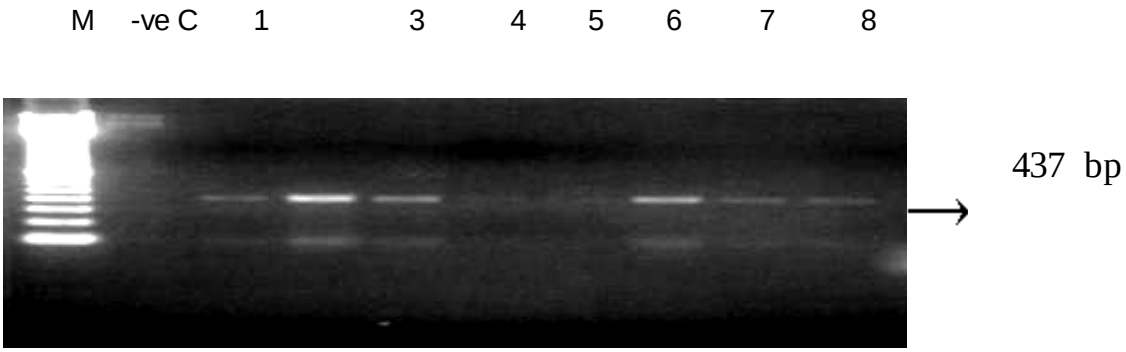

Figure (1): An agarose gel electrophoresis 2% stained with ethidium bromide.

M: DNA marker (100 bp each). **-ve C:**Negative control. **Lanes 1-3,6-8**: Positive samples. **Lanes 4,5:**Negative samples.

4. Discussion:

Asthma is a major health problem, it is the most common chronic childhood disease, it affects an estimated 5 to 10% of population and as such it is a major health care issue in most countries (Timothy, 2000).

Respiratory tract infection is considered one of the common risk factor. Infections with viruses such as respiratory syncytial virus, para influenza virus, influenza A and B virus, corona virus, adenovirus and rhino virus have been identified in 10% to 60% of children and adults with asthma. Another atypical respiratory pathogen, Chlamydia pneumonia, has been established as an important cause of acute respiratory infection in 1% to 11% of children as well as adults (Specjalski , 2010).

In our study we investigated the relationship between C. pneumonia in school age children and bronchial asthma. First we tried to determine whether previously asymptomatic children presenting with first ever bronco-spasm would have PCR+ve criteria compatible with Chlamydia pneumonia infection. We found (40%) of those children (new wheezier) to have evidence of C. pneumonia infection diagnosed by PCR technique.

Our finding are in agreement with the results of Zaitsu , (2007) who found that C. pneumonia infection triggers asthma in wheezy infants. Also Mostafa and Arnout, (2000) found that (27.3%) of

children with first ever wheezing and with objective measure of obstructive airway disease, had evidence of acute C. pneumonia infection diagnosed by serological criteria.

On regular follow up of the new wheezier at allergy clinic (87.5%) of children with first ever-wheezing episode and PCR+ve for C. pneumonia subsequently developed chronic persistent asthma based on clinical data and PEFR regular measurements, this provide evidence that acute wheezing illness due to C. pneumonia infection can develop into chronic asthma in previously asymptomatic individuals. In accordance with our observation Sato et al.,(2007) found C. pneumonia IgM- positive results in 48.4% of patients with asthma. Also Hahn and Mc Donald, (1998) found persistent C. pneumonia infection diagnosed by cultures of nasopharyngeal secretions after clinical resolution of acute respiratory illness and during development of chronic asthma symptoms.

Another aim of our study was to determine whether patients with established chronic asthma would have C. pneumonia infection. Nine of thirty (30%) children with established asthma were PCR+ve for C. pneumoniae. This result are in agreement with a study done by Agarwal and Chander, (2008) found IgG anti Chlamydia antibody-positively rate in the patients with bronchial asthma(80%) was significantly higher in all age groups than that in the healthy age and sex matched controls(59%).Also Thrumerelle et al., (2003) confirmed that persistent features of childhood asthma was more frequently associated with atypical bacterial infection (C. pneumonia and mycoplasma pneumonia). Bestou et al., (2003) showed the presence of anti Chsp 10 (children heat shock protein 10) antibodies in adult onset asthma (73%). In contrast to our results Dejsomritrutai et al., (2009) could not support the speculative theory that C. pneumonia is a cause of bronchial asthma, they found no difference between asthmatic and control as regards C. pneumonia specific IgA, IgG and IgM in the sera.

Investigators suggested that the immune response to organism might play a pathological role in asthma. C. pneumonia infects the human bronchial tree causing ciliary's dysfunction and epithelial damage. It also generates inflammatory cytokines, production of C. pneumonia IgE, and capacity during re infection to produce T cell mediated immune pathogenic disease considering this association between immune response to C. pneumonia and asthma symptom frequency, it seems logical to suggest that C. pneumonia infection may act as a cofactor, possibly rendering asthmatic children more susceptible to other stimuli such as allergens or viruses or both (Hironos et al., 2003).

In our study there was no significant difference between PCR-ve and PCR+ve patients as regards age distribution, residence, seasonal variation, atopic manifestation and family history of atopy. This is in concordance with that of Kercsmiar ,(1998).

Sex distribution of our asthmatic patients was 38% males and 62% females, we found a significant statistical difference between males and females as regards PCR+ve for C. pneumonia (more in males). This difference may be secondary to other factors such as the increased ability to produce IgE, airway caliber that has a clear gender difference, or the possibility of inherited vulnerability of boys than girls to the injurious effect of aeroallergens. In quite similarity to this result Kaledy et al., (2001) showed that prevalence of antibodies to C. pneumonia was more common in males than in females, a difference that increased with age.

As regards asthma severity and type of medication, we followed the National Heart, lung and blood institute classification. There was an increase in asthma severity and severity of exacerbation in PCR+ve than in PCR-ve patients for C. pneumonia but it didn't reach statistical significance. Liberman et al., (2003) reported that Chlamydia pneumonia is not responsible for acute exacerbation of bronchial asthma. On the contrary Thrumerelle et al., (2003) and Niedzwiadek et al., (2000) reported that persistent Chlamydia pneumonia infection has occurred more frequently in-patient with moderate and severe asthma than in ones with mild asthma, also persistent clinical features were more frequently associated with atypical bacterial infection. This conflict in the results between studies can be attributed to the fact that serological test is not accurate way to diagnose Chlamydia. The only accurate way is by identification of organism by polymerase chain reaction which is known to be almost 100% sensitive and specific. Using PCR technique, one is able to detect the presence of C. pneumonia organism either due to acute infection, re infection or chronic infection (Shi et al., 2003).

In our study we didn't find significant statistical difference between PCR+ve and PCR-ve patients for C. pneumonia as regards total eosinophilic count. This can be attributed to the fact that eosinophilic count in sputum and markers of eosinophil degranulation (such as eosinophilic cationic protein) can reflect the disease severity rather than blood eosinophilic count (Pifferi et al., 2001).

In the current study there was significant statistical difference between PCR+ve and PCR-ve for C. pneumonia as regards the median values of PEFR, this reflected increase severity of airway

obstruction in PCR+ve patients. Ten Brink et al., (2001) suggested that C. pneumonia infection might promote the development of persistent airflow limitation in patients with non atopic adult onset asthma. In contrast Strachan and Carrington (2000) showed a lack of significant association between COPD and level of C. pneumonia antibody titer of IgE and IgA.

Inhaled steroids have now become the main stone of chronic asthma treatment (Barnes, 1997). In our results, there was no significant statistical difference between PCR+ve and PCR-ve patients for C. pneumonia as regards use of inhaled corticosteroids. In contrast Black et al., (2000) reported high titer of antibodies to C. pneumonia in asthmatic being treated with high dose inhaled steroids. This difference may be attributed to steroid dose and duration of therapy.

It is worth to mention that the present study failed to find any peculiar clinical or laboratory characteristics distinguishing PCR+ve asthmatic patients from PCR-ve ones. In quite similarly to our results, Patel et al., (2010) diagnosed C. pneumonia in 33% of their studied asthmatics, with no significant difference in clinical signs, symptoms or laboratory data between patients with and without C. pneumonia infection.

5. Conclusion:

We can conclude that incidence of C. pneumonia infection among new wheezier and chronic asthmatics is high pointing to its possible role as triggering factor for asthma in new wheezier or continuation of symptoms in spite of proper treatment plan in chronic asthmatic children. We recommend that children with chronic asthma, not well controlled with conventional anti-asthma therapies, must be evaluated for C. pneumonia infection especially by PCR technique. Also it seems appropriate to do the test during the earlier stages of asthma onset especially if it begins during or after acute respiratory illness and once infection is verified proper antibiotic must be given.

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