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Assessment of parasympathetic functions in children of asthma patients

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ABSTRACT

Asthma patients are known to have increased cholinergic activity. This study aimed at evaluating the parasympathetic functions in children of asthma patients for any occurrence of parasympathetic over activity that is known to occur in asthmatics. The parasympathetic function tests were conducted in children between age group 5 to 10 years. The children were divided into two groups: Group I had children from non-asthmatic parents as Control Group and Group II had children from asthmatic parents as Test Group. Both the groups had healthy children showing no clinical signs and symptoms of asthma, allergy or any illness known to affect autonomic nervous system. In response to various parasympathetic function tests (S/L ratio, 30:15 ratio, valsalva ratio and tachycardia ratio) done, the two groups did not show any statistically significant dissimilarity for any of the parameters. The results of our study showed no parasympathetic over activity found in the children of asthmatic parents. Thus this study indicates that the increased cholinergic activity seen in asthmatics could be secondary to asthma and not because of autonomic aberrations inheritance in asthmatics as shown by earlier few studies supporting the possible role of inherited automatic reactivity in the pathogenesis and progression of asthma.

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1. Introduction

The parasympathetic nervous system is the dominant neuronal pathway in the control of airway smooth muscle tone. Stimulation of cholinergic nerves causes bronchoconstriction, mucus secretion, and bronchial vasodilation. Dysfunction or hyperfunction of this system may be involved in inflammation or hyper-responsiveness observed in asthmatic patients [1,2,3]. Cholinergic nerve activity contributes to airway narrowing in asthma. Reflex vagal activity may be enhanced because of epithelial damage and exposition of sensory nerve endings to nonspecific irritants. Other possible mechanisms include defects in prejunctional receptors that inhibit acetylcholine release, several postjunctional factors that nonspecifically enhance the effect of a given degree of cholinergic muscle contraction on airway caliber, and interactions between inflammatory mediators and the cholinergic system [4].

It has been proposed that increased vagal airway tone resulting in severe bronchoconstriction and mucus plugging responsible for the near-fatal or fatal events in a number of asthmatics. If the airway tone is increased, individuals should be treated with a triple combination of long-acting beta 2 agonists, inhaled steroids, and inhaled anticholinergics to prevent vagally mediated fatal events [5].

Genetic factors are also known to influence not only the occurrence but also the severity of asthma. It has been found that a child's asthma or wheezing is highly associated with mother's or father's asthma, other atopic condition in mother, father or with other siblings. Many of the siblings of asthmatic children who were apparently normal with no overt clinical symptoms of asthma have positive exercise result and are prone develop asthma later in life [6,7].

The present study has therefore been taken to investigate parasympathetic nervous system status in children of asthmatics. As any autonomic nervous system dysfunction in such children may make them more prone to develop asthma under unfavourable circumstances.

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2. Materials and Method

This study was conducted in 84 children (5 to 10 years) divided into two groups: 'Test Group' had 42 healthy children of asthmatic patients that were selected from a private clinic in Mulund, Mumbai. 'Control group' had age matched 42 healthy children from non-asthmatic parents, who volunteered to participate in this study

2.1. Inclusion criteria for test group: The children included in test group had either one or both the parents with moderate to severe persistent asthma diagnosed by as per NHLBI guidelines, with duration of more than three years.

2.2. Exclusion criteria for both test and control group: Children suffering from asthma, allergy or any other illness known to affect the functioning of autonomic nervous system.

All subjects were tested under similar laboratory conditions. Subjects were allowed to acclimatize themselves to experimental and environmental conditions for one hour, as anxiety or stress can affect autonomic function. During this period detailed history and medical examination was conducted with parents help and nature of tests was explained to both parents and children to allay their apprehension. The investigative procedures included two types of measurements: the anthropometric measurements and the autonomic function tests. The tests done are as follows:

2.3. Anthropometric tests

1. Height (in cms): was measured using Park's anthropometric scale. The range of the scale used was 140-190 cm and sensitivity was 0.5 cm.
2. Weight (in Kgs): was recorded using Avery machine. It had maximum measuring capacity of 120 Kgs and sensitivity of 0.05 Kgs.
3. Body surface Area (in Sq m): was calculated from height and weight using Dubois Normogram
4. Body Mass index (Kg/m²) was calculated using Quetelet's index. (BMI = Wt. / (Ht)²).

Table 1: Anthropometric Data

	Age (Years)		Height (cms)		Weight (Kgs)		BSA (sq. mts)		BMI (Kg/m ²)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Controls	9.15	±1.28	123.13	±7.58	22.75	±3.65	0.91	±0.10	16.8	±1.58
Tests	9.20	±1.67	121.50	±9.65	21.45	±3.90	0.86	±0.09	17.3	±1.77
P Value	>0.5		>0.5		>0.5		>0.5		>0.5	

2.4. Parasympathetic function tests

The following standard parasympathetic function tests were conducted with the help of an ECG machine, Model CARDIART- 406 (BPL product) with automode feature. A standard limb lead II was recorded and R-R intervals were calculated manually.

Table 2: Parasympathetic Function Tests

Parameters	Controls (n=42)		Tests (n=42)		P value
	Mean	SD	Mean	SD	
Heart Rate (beats per min)	79.20	±5.25	80.8	±6.30	>0.5
S/L Ratio	1.15	±0.12	1.11	±0.11	>0.5
30:15 Ratio	1.10	±0.09	1.07	±0.13	>0.5
Valsalva Ratio	1.53	±0.28	1.49	±0.27	>0.5
Tachycardia Ratio	0.711	±0.11	0.702	±0.16	>0.5

a) S/L Ratio: Standing to Lying Ratio

2.5. Standing to Lying Ratio

All subjects were made to stand quietly for two minutes and then lie down quickly without any support while continuous ECG was recorded from 20 beats before to 60 minutes after lying down. The point at which subject started to lie down was marked. The S/L

ratio was calculated as per Rodrives and Ewing's method and that was done by taking longest R-R interval during 5 beats before lying down to shortest R-R interval during 10 after lying down into consideration.

S/L Ratio (8) = $\frac{\text{Longest R-R interval during 5 beats before lying down}}{\text{Shortest R-R interval during 10 beats after lying down}}$

2.6. 30:15 Ratio

In this test each subject laid quietly for three minutes and then stood up and remained motionless. A continuous ECG was recorded and point was marked to identify the point of standing. 30:15 ratio (9) was calculated by taking ratio of R-R interval at beat 30 and beat 15 after standing.

30:15 Ratio = $\frac{\text{R-R interval at beat 30}}{\text{R-R interval at beat 15}}$

2.7. Valsalva ratio

Each subject was told to perform Valsalva manoeuvre (10) by blowing into a mouth piece attached to an anaeroid manometer and maintain a pressure of 40 mm Hg for 15 seconds. A continuous ECG was recorded for one minute before the manoeuvre (resting period), during manoeuvre (strain period, 15 sec.) and 60 seconds subsequent to manoeuvre (post strain). Valsalva ratio is taken as

ratio of maximum R-R interval after the strain to the shortest R-R during the strain.

$$\text{Valsalva Ratio} = \frac{\text{Maximum R-R interval after the strain}}{\text{Shortest R-R interval during the strain}}$$

2.8. Tachycardia ratio

It was computed from ECG recorded in above mentioned procedure of valsalva manoeuvre. It was carried out as supplementary test measure for valsalva ratio as it is more reproducible. Tachycardia ratio is taken as ratio of shortest R-R interval during strain and the longest R-R interval before the strain.

$$\text{Tachycardia ratio (10)} = \frac{\text{Shortest R-R interval during the strain}}{\text{Longest R-R interval before the strain}}$$

3.0. Results

For each variable group, the mean and standard deviation were calculated according to accepted statistical methods. Intergroup mean difference was tested for significance by applying unpaired Student's 't'-test.

The physical characteristics of various groups are given in Table 1, it can be seen that there is no significant difference between age, height, weight, and body mass index (BMI) among the two groups. Statistical analysis was carried out by applying Students "t" test. The resultant p value for the mean difference between the two groups was found to be higher than 0.5, thus suggesting that the two groups are anthropometrically similar.

3.1. Parasympathetic Function Tests

Various parasympathetic function tests performed were standing to lying ratio (S/L ratio), lying to standing ratio (30:15 ratio), valsalva ratio, tachycardia ratio.

The results of the above tests are depicted in table 2. The data reveals that mean value for S/L ratio, 30:15 ratios, valsalva ratio and tachycardia ratio was lower in test group while mean value for HR is lower in controls. The results from the statistical analysis done for the two groups using students "t" test reveal that the difference in mean values for various parameters between two groups is statistically insignificant

4. Discussion

There is profound evidence indicating that the patients with asthma have increased cholinergic activity [5]. This abnormality tends to increase bronchial smooth muscle tone, increase mucous secretion, increase release of inflammatory mediators from mast cells and increase release of proteolytic enzymes from inflammatory cells. All of these results would clearly be deleterious in obstructive pulmonary diseases [11,12,13,14,15]. Since parasympathetic system is most dominant neuronal pathway that controls airway calibre, parasympathetic over activity could be inferred as the most significant autonomic aberration causing airway narrowing in asthma.

Whether this increased cholinergic activity contributes to pathophysiology of asthma or it is the result of disease process is an important question. The studies of Kaliner et al [16,17] show a clear correlation between autonomic aberrations and airway reactivity

as assessed by methacholine challenge. This is inferred evidence that inborn abnormalities in autonomic reactivity are risk factors for increased airway reactivity. In epidemiological studies, the airway reactivity has been shown to be one of the risk factors for development and progression of obstructive pulmonary disease [18,19]. Thus these studies support the hypothesis that the autonomic reactivity might predispose to development and progression of obstructive pulmonary disease. However, there is some additional interaction with environmental factors (allergens, infection or irritants such as cigarette smoke) or with other genetic traits is necessary in order for the disease to occur.

If these hypotheses are true, the first degree relatives of persons with clear autonomic abnormalities (such as allergic asthma patients) will also have demonstrable asthma symptoms and a subgroup of patients with obstructive pulmonary disorders (such as intrinsic asthma and chronic bronchitis/emphysema) will also have abnormal autonomic reactivity. All of these predictions can be tested experimentally.

Nothing much has been done in this regard specially in asthma. Interestingly, a similar study has been done by Davis & Kaliner [20] in cystic fibrosis where it was found that the autonomic abnormalities present in cystic fibrosis which are similar to those present in asthma also occur in asymptomatic heterozygotes for cystic fibrosis (parents of patients). So it was suggested that autonomic abnormalities may be inherited characteristic and not secondarily acquired.

Therefore the present study is an endeavour to reveal similar findings in case of asthma. In our study, we have taken non-asthmatic children whose at least one parent is asthmatic, as their first degree relatives and have assessed their parasympathetic nervous system status by comparing it with controls (children of non-asthmatic patients).

The parasympathetic function tests show that the mean value for S/L ratio, 30:15 ratios, valsalva ratio and tachycardia ratio was lower in children of asthmatic parents while mean value for HR is lower in controls. But statistical significance could not be established for any of these parameters.

The results of our study reveal that no parasympathetic abnormality was found in the children of asthmatic parents that are not in accordance with the above mentioned hypothesis (Abnormal autonomic reactivity might predispose to development and progression of obstructive pulmonary disease). Though such children are prone to develop asthma but it would be due to hereditary and other factors and not due to parasympathetic overactivity. Above study is also not in accordance with the cystic fibrosis study (The study suggested the autonomic abnormalities may be inherited characteristics and not secondarily acquired) as no autonomic abnormalities were found in these children whose asthmatic parents do have autonomic abnormalities. So our study goes in favour of the possibility that increased cholinergic activity present in asthma is not inherited and is developed secondary to the disease process of asthma.

5. Conclusion

The results of our study conclude that no parasympathetic over-activity was found in children of asthmatic parents and probably the autonomic defects found in asthmatics are developed

secondary to disease process. Hence, it does not favour the possibility that these autonomic aberrations present in asthma being inherited and having a possible role in pathogenesis and progression of asthma.

For future studies it would be highly acceptable if sympathetic function tests are also done to evaluate overall autonomic nervous system in children having asthmatic parents. In addition, a simultaneous PFT could also be done in such children to know their bronchial lability. PFT tests would further corroborate the findings and conclusions of the study. Moreover, a follow-up in such children till their adulthood would be ideal to reveal any ANS imbalance or asthma if developed later. A similar study can also be conducted in the children whose both parents are asthmatics, as in such cases chances of developing asthma are of higher degree. Such studies may give more definitive conclusions on the nature of ANS abnormalities in asthma being primary or secondary to the disease process.

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