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A STUDY OF AUTONOMIC NERVOUS SYSTEM STATUS IN CHILDREN OF ASTHMATIC PARENTS

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Abstract : Asthmatic patients are known to have autonomic abnormalities. This study evaluated the status of autonomic nervous system in children of asthmatic parents for any occurrences of autonomic abnormalities that are known to occur in asthma. In this study autonomic function tests were conducted in children (5 to 10 years of age) divided into two groups: Group A had children from non-asthmatic parents as Control Group and Group B 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) and sympathetic function tests (handgrip test and cold pressor test) done, the two groups did not show any statistically significant dissimilarity for any of the parameters. The results of our study showed that there were no autonomic abnormalities found in the children of asthmatic parents. Thus this study indicates that the autonomic defects 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.

Key words : autonomic function tests asthmatics autonomic abnormalities inheritance autonomic reactivity

INTRODUCTION

The human airways are innervated by autonomic nerves, which regulate many aspects of airway function via its effects on smooth muscle tone, mucus secretion, microvascular permeability, blood flow, migration of inflammatory cells and release inflammatory mediators from them. Thus, autonomic nerves can influence airway calibre (1, 2, 3).

Airways are innervated by four nervous systems: cholinergic, adrenergic, inhibitory nonadrenergic non-cholinergic (i-NANC) and excitatory NANC (e-NANC). Dysfunction or hyperfunction of these systems may be involved in inflammation or hyper-

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responsiveness observed in asthmatic patients. Thus, several types of autonomic defects have been proposed in asthma; enhanced cholinergic, α-adrenergic, excitatory non-adrenergic non-cholinergic (e-NANC) bronchoconstrictor mechanisms and reduced β-adrenergic and inhibitory NANC (i-NANC) bronchodilator mechanisms (4).

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 (5, 6).

The present study has therefore been taken to investigate autonomic 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.

METHODS

This study was conducted in 60 children (5 to 10 years) divided into two groups: 'Test Group' had 30 healthy children of asthmatic patients that were selected from Asthma clinic of Lok Nayak Jay Prakash Narayan Hospital, New Delhi. 'Control group' had age matched 30 healthy children from non-asthmatic parents, who were non-teaching staff of Maulana Azad Medical College, New Delhi.

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 the asthma clinic following NHLBI guidelines, with duration of more than three years.

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 :

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 Mass index (kg/m^2) was calculated using Quetelet's index. ($BMI = Wt./(Ht)^2$.

Autonomic function tests

The following standard autonomic 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.

Standing to Lying Ratio: The standard procedure was followed to conduct this test and S/L ratio was calculated as per Rodrives and Ewing's method (7):

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

30:15 Ratio: Following the standard procedure for this test, this ratio is calculated as given below.

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

Valsalva ratio

Standard procedure for the test was performed.

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

Tachycardia ratio (9)

It was computed from ECG recorded in above mentioned procedure of valsalva manoeuvre.

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

Hand grip test

This test was done with the help of hand grip dynamometer (product of Dr. Reddy's lab) specially designed for children between 5-10 years of age with upper limit of 10 kgs. The upper limit of 10 kgs was deduced by conducting a small pilot study for maximum voluntary effort for 5-10 year old children. The highest rise in the diastolic blood pressure during test is taken as an index of response to hand grip (10).

Cold pressor test

After following the standard procedure of the test, maximum increase in systolic and diastolic blood pressure was determined and results recorded. In any condition where there is deficient sympathetic outflow the cold pressor test will be expected to show a smaller rise (11).

Statistical analysis

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 Students 't'-test.

RESULTS

The physical characteristics of various groups are given in Table I, 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.

Autonomic function tests

Various autonomic function tests performed were standing to lying ratio (S/L ratio), lying to standing ratio (30:15 ratio), valsalva ratio, tachycardia ratio, hand grip test (HGT) and cold pressor test (CPT).

The results of the above tests are depicted in table 1. The data reveals that mean value for S/L ratio and valsalva ratio was found to be slightly higher in Controls than that in Tests. And in HGT, the change in SBP from rest is slightly higher in Tests, while the change in DBP was found to be lower in Tests as compared to that in Controls. In

TABLE I

Parameters	*Tests (n=30)* Mean±SD	*Controls (n=30)* Mean±SD	*P value*
Age (Years)	9.10±1.79	9.23±1.36	>0.5
BMI (kg/m^2)	13.39±3.99	15.3±1.67	>0.5
HR (beats/min)	80.3±8.41	78.63±6.47	>0.5
S/L Ratio	1.05±0.15	1.11±0.13	>0.5
30:15 Ratio	1.12±0.18	1.11±0.09	>0.5
Valsalva ratio	1.45±0.29	1.50±0.30	>0.5
Tachycardia ratio	0.699±0.18	0.701±0.12	>0.5
HGT	Δ SBP 12.29±6.02	Δ SBP 11.53±4.97	>0.5
(in mmHg)	Δ DBP 17.14±6.14	Δ DBP 18.47±4.44	>0.5
CPT	Δ SBP 16.63±8.61	Δ SBP 22.7±4.91	>0.5
(in mmHg)	Δ DBP 16.48±6.88	Δ DBP 12.57±4.34	>0.5

BMI: Basal Metabolic Index
HR: Heart Rate
CPT: Cold Pressor Test
DBP: Diastolic Blood Pressure
S/L Ratio: Standing to Lying Ratio
HGT: Hand Grip Test
SBP: Systolic Blood Pressure
Δ: Change from Basal Blood Pressure

case of CPT the change in SBP from rest was quite lower in Tests, while the change in DBP was higher in Tests as compared to that in Controls.

The results from the statistical analysis done for the two groups using “t” test reveal that the difference in mean values for various parameters between two groups is statistically insignificant.

DISCUSSION

The bulk of evidence indicates that the patients with asthma have both increased cholinergic and α_1-adrenergic sensitivity in conjunction with reduced β_2 adrenergic responses (4). These abnormalities also tend 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 (12, 13, 14, 15, 16).

Whether these autonomic aberrations contribute to pathophysiology of asthma or they are the result of disease process is an important question. The studies of Kaliner etal (17, 18) show a clear correlation between α-adrenergic hypersensitivity and β-adrenergic hyposensitivity 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 (19, 20). 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 (21) in cystic fibrosis where it was found that the autonomic abnormalities present in cystic fibrosis which are similar to those present in asthma (increased α-adrenergic and cholinergic responsiveness and decreased β-adrenergic responsiveness) 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 autonomic nervous system status by comparing it with controls (children of non-asthmatic patients).

The autonomic function tests show that the mean value for 30:15 ratios was higher in children of asthmatic parents, while for S/L ratio, valsalva ratio, and tachycardia ratio is higher in controls. But statistical significance could not be established for any of these parameters. For the handgrip test, the mean Δ SBP was found to be higher, while Δ DBP was found to be lower in Tests as compared to that in Controls. For the cold pressure test, the mean Δ SBP was found to be lower, while Δ DBP was found to be higher in Tests as compared to that in Controls. No statistical significance could be established after analysis for any of the tested parameters for sympathetic tests.

The results of our study reveal that no autonomic abnormalities were 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 autonomic abnormalities. 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 the autonomic aberrations present in asthma are not inherited and are developed secondary to the disease process of asthma.

Therefore results of our study conclude that no autonomic abnormalities are found in children of asthmatic parents and 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 simultaneous PFT is also 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 would be ideal in such

children till their adulthood 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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