THE ROLE OF HEREDITARY PROPENSITY, ENVIRONMENTAL FACTORS AND THE POSSIBLE PHENOTYPIC ASSOCIATION IN PHYSICIAN DIAGNOSED ASTHMA

Dissertation submitted to

THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY

in partial fulfillment *of the regulations*
for the award of degree of

M.D DEGREE (PEDIATRICS) BRANCH VII

INSTITUTE OF CHILD HEALTH AND
HOSPITAL FOR CHILDREN
MADRAS MEDICAL COLLEGE

APRIL 2012

CERTIFICATE

This is to certify that the dissertation titled, **"The role of hereditary propensity, environmental factors and the possible phenotypic association in physician diagnosed asthma"** submitted by **Dr.P.Ganesapandian**, to the Faculty of Pediatrics, The Tamilnadu Dr.M.G.R Medical University, Chennai, in partial fulfillment of the requirements for the award of M.D. Degree (Pediatrics) is a bonafide research work carried out by him under our direct supervision and guidance, during the academic year 2009-2011.

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DECLARATION

I, **Dr. P.Ganesapandian**, solemnly declare that the dissertation titled **"The role of hereditary propensity, environmental factors and the possible phenotypic association in physician diagnosed asthma"** has been prepared by me.

This is submitted to the Tamilnadu Dr. M.G.R. Medical University, Chennai in partial fulfillment of the rules and regulations for the M.D. Degree Examination in Pediatrics.

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The Institutional Review Board (Ethical Committee) of Institute of Child Health and Hospital for Children, Chennai-08, was held on 30.01.2010 at 10.00AM at the Deputy Superintendents chamber.

Member Present: Dr.R.Kulandai Kasthuri
Chair Person.

Members: 1.Dr.Gita
2.Dr.P.Jeyachandran
3.Dr.D.Vijaya Sekaran
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Member Secretary: Dr.Luke Ravi Chellaiah

Title: "Study Proposal on the Role of Hereditary Propensity, Environmental Factors and the Possible Phenotypie Association in Physician Diagnosed Asthma in Children".

The Institutional Review Board was satisfied with the revised format submitted by you. Hence the Institutional Review Board is pleased to approve the study.

Director and Superintendent.

To,

Dr.P.Ganesh Pandian

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SPECIAL ACKNOWLEDGEMENT

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CONTENTS

INTRODUCTION

Childhood asthma has emerged perhaps as the commonest chronic medical problem treated by pediatricians all over the world. What was originally thought to be a disorder affecting only adults has emerged as a very significant problem affecting child's lifestyle and day-to-day activities including schooling, sports and recreation. It is responsible for significant social, economic and psychological impact on the family.[1] An estimated 1.9 disability adjusted life yrs (DALYs) are lost every year due to asthma per thousand children under 15 yr of age in India.[2] The incidence of asthma is increasing alarmingly in the past few decades.

Inspite of the intense research efforts, the etiology of asthma and the reason for the increasing trend in prevalence have yet to be established. The exact etiology of asthma is not precisely known. The cause may be multifactorial. The hereditary propensity and environmental trigger factors play a significant role in the possible etiology and in the course of the disease process. Hence the study on hereditary and environmental factors will be useful especially in our population.

Definition of asthma

Asthma is defined as "a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation is associated with airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness and coughing particularly at night or in the early morning. These episodes are usually associated with widespread, but variable airflow obstruction within the lung that is often reversible either spontaneously or with treatment"[3].

Epidemiology

The estimated worldwide prevalence is 7-10% prevalence [4]. The data is limited on asthma epidemiology from the developing world, including India [5]. Although some attempts have been made, studies suffer from several scientific drawbacks including lack of uniformity of methodology and analysis of data[5]. The prevalence of bronchial asthma was found to be 10.3% in India [6]. The prevalence of asthma is higher among boys (12.1%)[6]. There was a significant inverse relationship with increasing age. Childhood asthma among children 13-14 years of age was found to be lower than the younger children (6-7 years of age). It was found that asthma is prevalent in urban and in boys

with wide interregional variation. Burden of bronchial asthma in Indian children is higher than was previously estimated[7]. An increase of more than 50 percent over a period of 4-5 years has been observed[8].

Etiology

Asthma is caused by both genetic and environmental factors[9]. These factors influence the severity of asthma and its response to medication[10]. The interaction is very complex and not yet fully understood[11].

Although the cause of childhood asthma has not yet been established, contemporary research implicates a combination of inherent genetic and biologic vulnerabilities and environmental exposures[12].

Genetics

More than 100 loci have been linked to asthma. Asthma has been consistently linked with loci containing proallergic, proinflammatory genes (the interleukin IL-4 gene cluster on chromosome5) [12].

Environment

Outdoor allergens like environmental tobacco smoke, air pollutants like cold dry air, sulphur dioxide and ozone worsen airway inflammation and increase the severity of asthma.

Indoor factors like dusty home environment, passive smoking, pets, use of mosquito coils, cooking with biofuel, cockroaches, presence of moulds on the walls trigger airway inflammation.

Early risk factors for childhood asthma[12]	
• Allergic rhinitis • Food allergy • Inhalant allergen sensitization • Food allergen sensitization • Pneumonia • Parental asthma	• Allergy • Atopic dermatitis • Wheezing apart from colds • Male gender • Low birth weight • Environmental tobacco smoke

Pathophysiology

Asthma is a disease characterised by chronic airway inflammation. Different inflammatory cells like eosinophils, neutrophils, lymphocytes, predominantly TH-2-mediated response are involved . Interactions between genetic and environmental factors result

in airway inflammation, which limit airflow and leads to bronchospasm, mucosal edema, and mucus plugs.

Bronchoconstriction.

Caused by IgE-dependent release of mediators from mast cells that includes histamine, leukotrienes, prostaglandins and tryptase that cause contraction of airway smooth muscle.

Airway edema.

As the disease becomes persistent and progressive, the following changes occur which include inflammation, edema, mucus hypersecretion and the formation of inspissated mucus plugs.

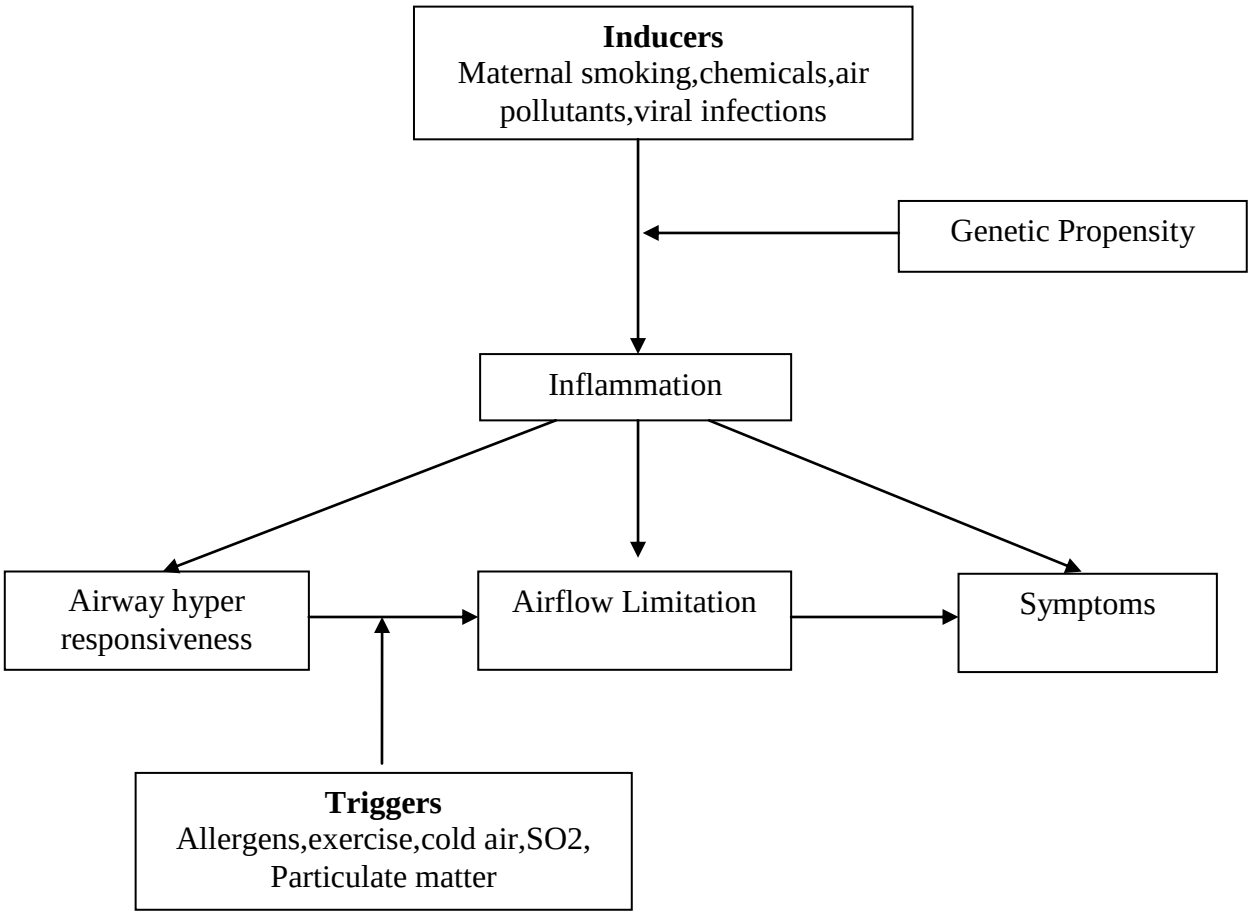
Airway hyperresponsiveness

Airway hyperresponsiveness is influenced by multiple mechanisms which include inflammation, dysfunctional neuroregulation, and structural changes. Major factor in determining the degree of airway hyperresponsiveness is the inflammation.

Airway remodeling

Airway remodeling involves the sub-basement membrane thickening, subepithelial fibrosis, smooth muscle hypertrophy and hyperplasia, neoangiogenesis and mucous gland hyperplasia and hypersecretion.

PATHOGENESIS OF ASTHMA



The pathogenesis occurs in two phases (early phase and late phase)

Early phase	Late phase
• Occurs in 30 min-2 hrs • Mast cell degranulation and release of preformed mediators • Histamine, LTC4, D4, E4, PAF • Bronchoconstriction	• Occurs in 6-8 hrs • Release of cytokines and newly generated mediators • Eosinophilic cationic protein, eosinophilic chemotactic factor • Continued airway hyperresponsiveness, mucus secretion, vasodilatation

Diagnosis

Asthma in children is suspected when they present with symptoms with or without signs of recurrent airflow obstruction.

Symptoms suggestive of recurrent airflow obstruction.

- Recurrent wheeze
- Recurrent isolated dry cough
- Recurrent breathlessness
- Nocturnal cough
- Tightness of chest
- Non focal chest pain

Signs suggestive of generalised airflow obstruction.

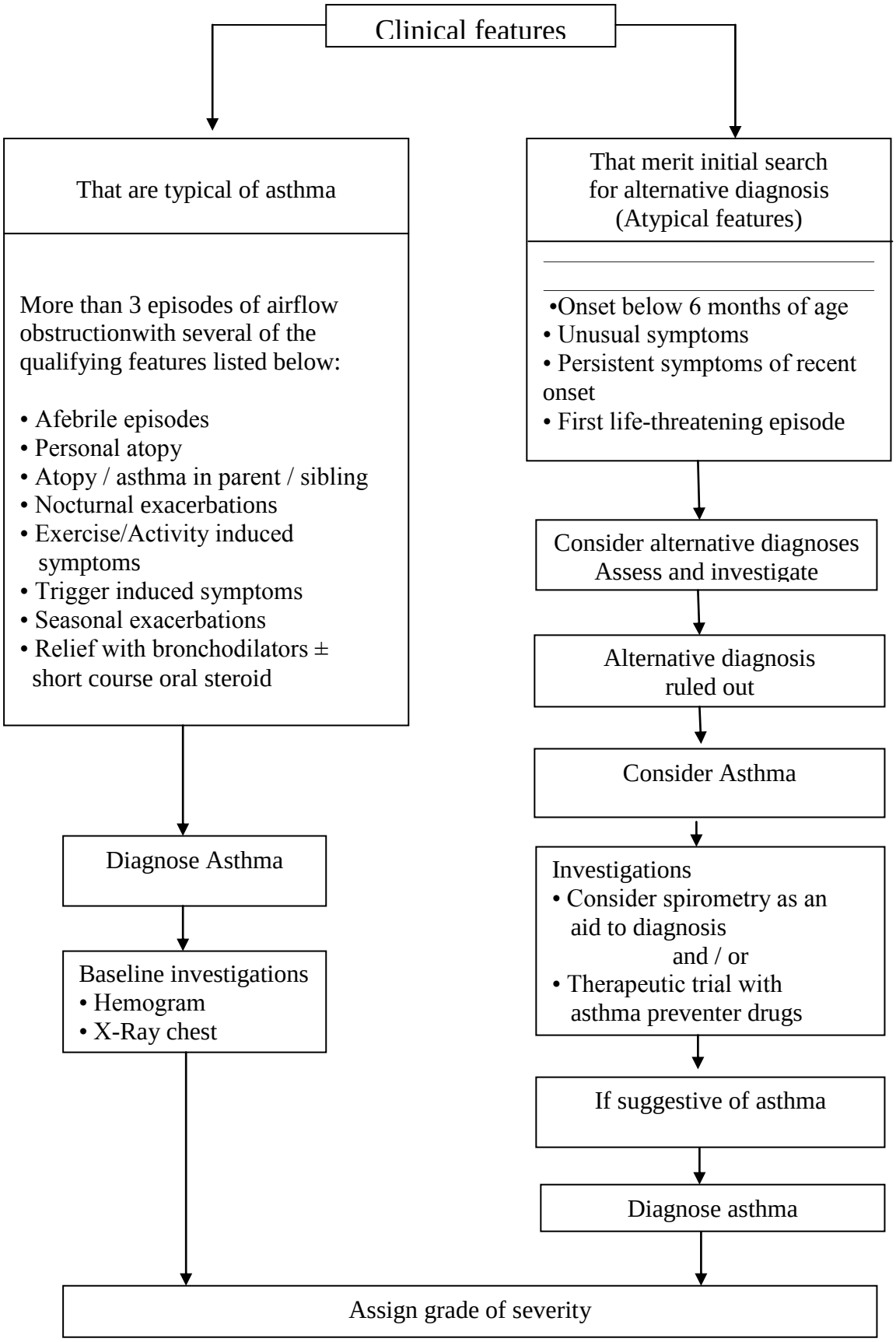
- Generalized rhonchi
- Prolonged expiration
- Chest hyperinflation

Diagnosis of asthma is made mainly by clinical means if episodic symptoms of airflow obstruction (>3episodes per year) with several of the qualifying features listed below[14]

- Afebrile episodes
- Personal atopy
- Atopy / asthma in parent / sibling
- Nocturnal exacerbations
- Exercise/Activity induced symptoms
- Trigger induced symptoms
- Seasonal exacerbations
- Relief with bronchodilators ± short course oral steroid

Flowchart

Assess clinically to qualify the above symptoms



PULMONARY FUNCTION TESTS

Spirometry:

Use is limited to situations where clinical diagnosis of asthma is in doubt, provided:

- the child can perform the test (Age)
- the equipment is available (Availability)
- the cost is permissible (Affordability)

Establishes a diagnosis if:

- FEV1 and FEV1/FVC are reduced (Values relative to reference or predicted. Also examine flow volume curve)
- Improvement in FEV1 by > 12 % after inhaling short acting bronchodilator.

Peak Expiratory Flow (PEF)

A poor tool for diagnosis. May be used when clinical diagnosis of asthma is in doubt (atypical presentation) and spirometry is unavailable, unaffordable or normal at the time of doctor visit.

Establishes a diagnosis of asthma when:

- >15 % increase in PEF after bronchodilator
- >15% decrease in PEF after exercise
- Diurnal variation of >10 % in PEF when not on bronchodilator therapy or diurnal variation of >20 % in PEF when on bronchodilator therapy.

Comorbid conditions

- Rhinitis
- Sinusitis
- Gastroesophageal reflux

Differential Diagnosis[12]

Upper respiratory tract conditions	**Middle respiratory tract conditions**	**Lower respiratory tract conditions**
Allergic rhinitis Chronic rhinitis Sinusitis Adenoidal or tonsillar hypertrophy Nasal foreign body	Laryngotracheobronchomalacia Laryngeal web or stenosis Vocal cord dysfunction Tracheoesophageal fistula Vascular ring, tumor compressing on the airway Foreign body aspiration Chronic bronchitis	Bronchopulmonary dysplasia Viral bronchiolitis Gastroesophageal reflux Tuberculosis Pneumonia Bronchiolitis obliterans

TREATMENT

Grades	Day Time Symptoms	Night Time Symptoms	Peak Expiratory Flow	Treatment
Mild Intermittent	< Once a week	< Twice per week	>/ = 80% of Personal best < 20% diurnal variation	Inhaled/ oral short acting β2 agonist
Mild Persistent	>Once a week <once a day	>twice a month	>/ = 80% of Personal best 20-30% diurnal variation	Treat Acute Episodes Low dose ICS or LTRA
Moderate Persistent	>Once a day	>once a week	>60% - < 80% of Personal best >30% diurnal variation	Treat Acute Episodes Low dose ICS + inhaled LABA or Medium dose ICS (in <5 Years)
Severe Persistent	Continuous	Frequent	</= 60% of Personal best >30% diurnal variation	Treat Acute Episodes High to medium dose ICS + LABA If needed, add oral steroid

Goals of Asthma Treatment[3]

- Control chronic and nocturnal symptoms
- Maintain normal activity, including exercise
- Prevent acute episodes of Asthma
- Minimise emergency department visits and hospitalisations
- Minimal need for reliever medications
- Maintain near-normal pulmonary function
- Avoid adverse effects of Asthma medication

PREVENTION

Currently, asthma prevention strategies are in their infancy. With recent evidence that chronic airways inflammation may result in pathologic remodeling changes, early intervention with anti-inflammatory medications in young children with recurrent wheezing and persistent asthma risk factors may halt disease progression.

A "hygiene hypothesis" purports that microbial exposures in early life might drive early immune development away from allergen sensitization and allergic inflammation and a lower likelihood of asthma and bronchial hyperresponsiveness in later childhood[(12)].

Current evidence also suggests that several nonpharmacotherapeutic measures -avoidance of environmental tobacco smoke (beginning prenatally), prolonged breast-feeding (greater than 4 months), an active lifestyle, and a healthy diet might reduce the likelihood of asthma development.

REVIEW OF LITERATURE

S Hasan Arshad et al[21], 2005 conducted a cohort study to identify early life factors (<4 years) associated with wheeze, asthma, and bronchial hyper responsiveness at age 10 years, comparing their relative influence for these conditions. in 1,456 children. Information was collected on genetic and environmental risk factors. Results: significant factors were maternal asthma [OR (95% CI)=2.26(1.24–3.73)], paternal asthma [OR (95% CI)= 2.30(1.17 – 4.52)], and sibling asthma [OR (95% CI) = 2.00(1.16 – 3.43)], recurrent chest infections, atopy at 4 years of age [OR (95% CI) = 7.22(4.13 – 12.62)], parental smoking [OR (95% CI) = 1.99(1.15 – 3.45)], and male gender [OR (95% CI) = 1.72(1.01 – 2.95)] and high social class at birth [OR(95% CI) = 2.03(1.16 – 3.53)] proved to be significant.

Conclusion: Asthmatic heredity, predisposition to atopy in early life and early passive smoke exposure and recurrent chest infections are important influences for the occurrence of wheeze and asthma at 10 years of age.

Liebhart et al[22] , 2007 conducted a cross sectional study in Poland to assess asthma prevalence and hereditary and environmental factors. Results were obtained for asthma in 16238 subjects with 3268 children.

Conclusion: risk factors for asthma like family history of asthma, residential exposure to traffic-related air pollution, black smoke in both children and adults, and damp or overcrowded housing in adults. Passive smoking, use of gas stoves, pet ownership, or exposure to air pollution with sulfur dioxide were not found to be significant.

KAW karunasekara et al[36] 2005 conducted a cross sectional study in Srilanka to examine the role of hereditary and environmental factors in childhood asthma. Results: The results obtained with significance were paternal asthma [OR(95% CI) = 6.4(3.2 – 13.2)], maternal asthma [OR(95% CI) = 4.4(2.6 – 7.5)], sibling asthma [OR(95% CI) = 4.3(2.0 – 9.7)], paternal atopy, sibling atopy, breast feeding not more than six months, cockroaches, mosquito coils , firewood smoke, dusty home environment.

Conclusion: This study reinforces that asthma has a multifactorial aetiology. Childhood asthma is influenced by paternal asthma more than maternal asthma. Significant modifiable environmental factors in this study were duration of breastfeeding in infancy and dusty home environment.

Lee YL et al[38], 2003 conducted a cross sectional national survey in Taiwan to identify hereditary and indoor and outdoor environmental factors for physician-diagnosed asthma in Taiwanese schoolchildren. Here 35,036 children of 6- to 15year old schoolchildren were chosen for study. They investigated hereditary and indoor and outdoor environmental factors for childhood asthma by questionnaire. Physician-diagnosed asthma was observed in 8.1% of the boys and 5.6% of the girls. The risk was significantly associated with parental atopy and ambient air pollution in both sexes. Results: The presence of cockroaches [OR(95%CI) = 1.30(1.07 – 1.59)], moulds at home [OR(95%CI) = 1.20(1.01 – 1.41)] and water damage [OR (95% CI)= 1.33 (1.02-1.70)] were also associated with asthma.

Conclusion: Parental atopy, indoor or outdoor environmental factors were significantly related to childhood asthma. Girls may be more susceptible to indoor factors than boys.

Sunil K Chabra et al[42], 1999 conducted a cross sectional study to measure the prevalence of asthma and the predisposing factors in schoolchildren in Delhi. A questionnaire based study was carried out among the children (n = 21,367) for answering by either parent. Results: The prevalence of asthma was 11.9%. Boys had a significantly higher

prevalence of asthma compared with girls (12.8% and 10.7%, respectively).

Conclusion: Male sex, family history of atopy, and the presence of smokers in the family were significant factors influencing the development of asthma while economic class, air pollution and type of kitchen fuel were not.

Seema Sharma et al[(65),] 2011 conducted a hospital based descriptive study in Punjab, over a period of one year in children (6-15yrs) having asthma. It was done to examine the environmental risk factors in relation to childhood asthma in rural Area. In 200 children studied (boys 64% and 36% girls), asthma attacks were increased during a particular season (86%), after exertional work (70%) and along with ARI (72%). **Conclusion**: The risk of asthma was more in children where smoke producing fuel was used, presence of insects, pets, domestic animals and moisture, moulds in the home, born prematurely or LBW, with family history of atopy, one smoker in family and who belonged to poor socio- economic status. Breast feeding was protective in reducing the incidence.

Han YY et al[66], 2003 conducted a cross sectional study in Taiwan to examine the the relationship between indoor environmental factors and seasonal childhood asthma. 1725 children of age 6 - 15 years with asthma symptoms and 19646 children without asthma were enrolled in this study. Results: Younger age, parental atopy, breast feeding and who perceived air pollution, cockroaches [OR(95%CI) = 1.65(1.12 – 2.25)] and moulds [OR(95%CI)=1.53(1.26–1.85)].

Conclusion: Passive smoking, cockroaches, moulds, pollution each play significant role at particular season.

Maria Helena DA et al[67], 2004 conducted a population based cross sectional survey of 1132 children in SaoPaulo ,Brazil to investigate the prevalence and risk factors of the wheezing disorders in early childhood by obtaining information on recent wheezing and on independent variables such as demographic, socioeconomic, environmental, maternal and nutritional variables and immunization status. Intestinal parasitic infections were diagnosed using standard techniques. Results: They observed the prevalence of recent wheezing was 12.5%. 93% of children with wheezing were also reported to have a medical diagnosis of asthma. Recent wheezing was associated with low per capita income, poor quality of housing, day-care attendance, low birth weight and infection with intestinal helminths.

Conclusion: Wheezing in early childhood in Sao Paulo, although more common than in most developing countries, remains less prevalent than in urban areas of industrialized countries. Low income and conditions associated with poverty (poor housing, low birth weight and parasitic infections) are some of the main risk factors for wheezing disorders among young children in this city.

Stephanie et al[68], 2001 conducted a cross sectional study in California 6259 school children of 9 - 16 years to analyse the relation between family history and asthma.

Conclusion: Parent with asthma and or allergy conferred strongest association with asthma. Sibling asthma was strongly associated even in the absence of parental asthma.

Macedo et al[74]**,** 2009 conducted a study in UK, London to determine whether there were any differences in inflammatory biomarkers between severe and non-severe asthma patients. Nineteen severe and 20 non-severe asthma patients were recruited and underwent collection of induced sputum, bronchoalveolar lavage (BAL) fluid and bronchial biopsies. RESULTS: Biopsy results showed no differences in eosinophils (major basic protein positive), neutrophils, macrophages, T cells and mast cells in the bronchial submucosa. No significant

differences were observed in the induced sputum inflammatory cells. In BAL fluid, there was a significant increase in neutrophils but a significant decrease in macrophages. Eosinophil counts were non-significantly increased threefold in both sputum and BAL in severe asthma.

Conclusion: Differences in inflammatory cells were observed mainly in terms of increased neutrophils and reduction in macrophage numbers in BAL fluid with a trend towards increased eosinophils in severe asthma compared with non-severe asthma. However, the most notable features are the increase in features of airway wall remodelling of SBM thickness and smooth muscle area.

STUDY JUSTIFICATION

- Despite many advances in our understanding of disease, the natural history and the causative factors of asthma are not well defined and vary from place to place. The recent consensus released by various studies questioned the role of precipitating factors for asthma
- A detailed case control study on hereditary and environmental factors may bring out a decision tree which will be useful in early diagnosis and appropriate management.
- Depending upon the cytology and response to therapy the authors distinguished asthma into eosinophilic, non-eosinophilic, neutrophilic varieties(84,85)
- Though assessment of interleukins in BAL will throw more light on this subject, the present study aims to correlate the association of inflammatory cells in various phenotypes like atopic and non atopic asthma.
- Since ICH registers many asthma cases, and it is the only centre where fibreoptic bronchoscopy is routinely done, broncho alveolar lavage could be possible in various types of asthma and correlation of BAL cytology with phenotypes of asthma may throw light on this subject.

AIM OF THIS STUDY

- To study the role of hereditary propensity and environmental factors in physician diagnosed asthma.

- To correlate the phenotypes of asthma (atopic and nonatopic) with inflammatory cells observed in the bronchoalveolar lavage (BAL) fluid.

SUBJECTS AND METHODS

1. Methodology

Study design : Case control study

Study place : Pulmonology department & Outpatient department, ICH & HC

Study period : January 2010 to October 2011

Study population: Children between the age group of 4-12 years

Case definition:

Cases with more than 3 episodes of airflow obstruction in a year with several of the qualifying features listed below [14]

- Afebrile episodes
- Personal atopy
- Atopy or asthma in parent / sibling
- Nocturnal exacerbations
- Exercise/Activity induced symptoms
- Trigger induced symptoms
- Seasonal exacerbations
- Relief with bronchodilators ± short course oral steroid

Cases:

Children between the age group of 4-12 years diagnosed as asthma in asthma clinic.

Inclusion criteria:

All children diagnosed as asthma aged 4-12 years.

Exclusion criteria:

Children with other causes of wheeze like airway anomalies, foreign body aspiration, chronic lung disease and who are severely ill

Controls:

Children between the age group of 4-12 year who are not having wheezing disorder

Case: control ratio :1:1

Sample size : 250: 250

Using the prevalence of asthma 5% and the odds ratio for hereditary factors as 3.42 with alfa error 5% and beta error 20% the sample was calculated as ‘

2) Ethics:

Written informed consent was obtained from the parents and Institution review board clearance was obtained.

3) Maneuver:

- Cases and controls were enrolled on the basis of inclusion and exclusion criteria after obtaining parental consent.
- Using patient data entry form, information was abstracted regarding details and risk factors considered for this study from all cases and controls.

a) Evaluation with detailed questionnaire:

A structured questionnaire was prepared which included data on patient or control hereditary factors, environmental factors, perinatal and epidemiological factors. All the questions were asked subjectively.

- Age
- Sex
- Age of onset
- Residence (rural or urban)
- Birthweight (less than 2.5kg or more than 2.5kg)
- Duration of breast feeding (less than six months or more than six months)
- Presence of personal atopy :
    - Allergic rhinitis
    - Eczema
    - Food allergy
    - Allergic Conjunctivitis

Hereditary factors :

- Family H/O asthma (father, mother, sibling, grandparents and other second degree relatives)
- Family H/O atopy

Outdoor environmental factors

- Nearby factory:

  Presence of the factory within 2kms of radius [15, 16]

- Nearby traffic road:

  Living on heavy traffic roads or streets or more likely to have trucks and trailers passing by within 200 m (656 ft) of their residence[17]

- Automobile exhaust and dust allergy
- Coldair allergy[18]

  Cases:development of asthma symptoms on exposure to cold air

  Controls: development of rhinorrhea or sneezing only exposure to cold air

Indoor environmental factors

- Dusty home environment
- Overcrowding [19]
- Passive smoking
- Cooking fuel (wood, cowdung, kerosene and gas)
- Presence of pets (dogs, cats and fowls)

- ❖ Use of mosquito coils
- ❖ Strong odour allergy
- ❖ Presence of moulds
- ❖ Presence of cockroaches

b) BAL cytology:

Inclusion Criteria

The asthmatic children getting recurrent attacks inspite of bronchodilator therapy, but not yet started on inhaled steroids or who had a short course of oral corticosteroids were subjected for bronchoalveolar lavage.

Exclusion criteria

The asthmatic children who are on inhaled steroids and severely ill

Procedure

- ❖ A brief description of procedure was explained to parents and written informed consent was obtained from parents.
- ❖ Bronchoscopy was done by two pediatric pulmonologists with mutual verification with assistance of pediatric residents and trainees.
- ❖ Bronchoscopy was done transnasally after applying 4% lignocaine gel locally to nasopharynx. During the procedure 2% lignocaine in

the dose of 5mg/kg diluted with equal volume of normal saline was instilled by spray and proceed technique through the working channel.

- Supplemental humidified oxygen was administered by keeping the oxygen catheter close to the other nostril and saturation was monitored by pulseoximetry.
- After wedging the scope into desired subsegmental bronchus, BAL was performed by instilling 2ml/kg of body weight of sterile prewarmed normal saline in three equal aliquots through the suction channel and subsequently aspirating it back into the specimen tray using a suction apparatus.The total amount of saline that can be safely instilled during BAL ranges from 10-40ml.
- The specimen was transported to laboratory within one hour for cytological examination where the differential cell count was done by centrifugation followed by giemsa staining technique.

FIBREOPTIC BRONCHOCOPE

PROCEDURE OF BRONCHOSCOPY FOR BAL CYTOLOGY

4) Statistical analysis:

- Pearson chi-square test was done to compare the proportion of related factors between cases and controls.
- To compare the risk factors among cases and controls, Odds ratio with 95% Confidence Interval was calculated. To adjust for confounding factors, adjusted OR with 95% Confidence Interval was arrived by multivariate analysis.
- Student independent t-test was done to compare the mean cell counts of the BAL cytology results between asthmatics and nonasthmatics.
- Statistical analysis was done using SPSS software.

RESULTS

250 asthmatic children and 250 nonasthmatic children were enrolled in this study.

TABLE 1:

Age and Sex Distribution of Children with Asthma (n=250)

Age	SEX		Total
	Male no (%)	Female no (%)	no (%)
4-8 yrs	72(28.8)	60(24)	132(52.8)
9-12 yrs	58(23.2)	60(24)	118(47.2)
Total	130(52)	120(48)	250(100)

- Most of the children were found in the age group of 4-8 yrs.
- The male: female ratio is 1.08:1 with no statistical significance.

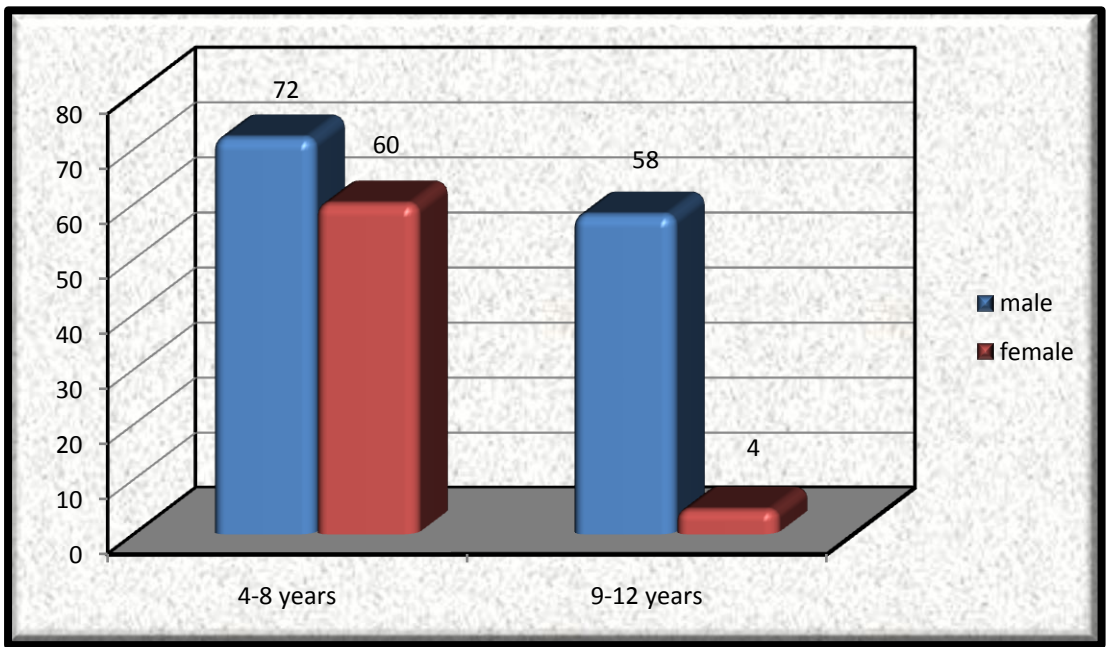


Figure 1: Age and sex distribution of children with asthma

TABLE 2:

Age of onset of asthma in study population (n=250)

Age	No	%
0-3 yrs	172	68.8
4-8 yrs	71	28.4
9-12 yrs	7	2.8
Total	250	100

- Around 69% of the asthmatic children started having their symptoms at their 0-3 yrs of age
- 28.4% of the children started their symtoms at the age of 4-8yr
- 2.8% of the children started their symtoms after 9yrs

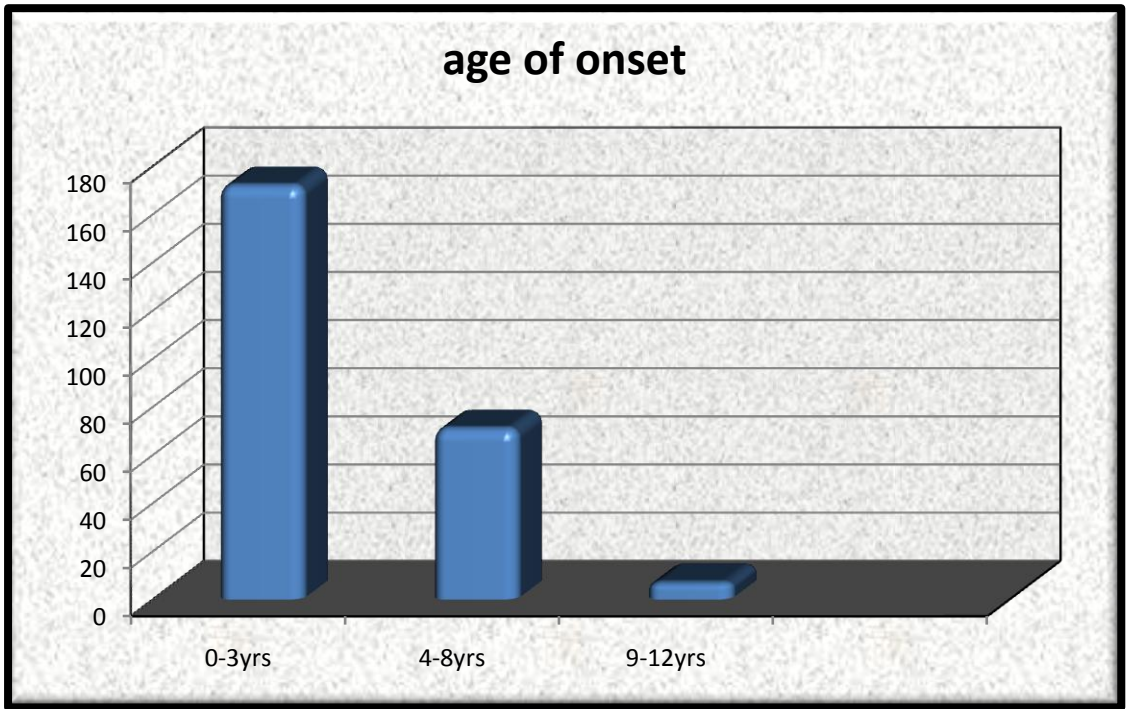


Figure 2: Age of onset of asthma in study population

TABLE 3:

Personal atopic manifestations among children with asthma and controls – univariate analysis (n=250)

Personal Atopy	Cases no (%)	Controls no(%)	OR (95%CI)	X^2	p value
Eczema	22(8.8)	1(0.4)	24.02(3.21-179)	20.09	<0.000
Food allergy	33(13.2)	1(0.4)	37.7(5.1 - 278)	68.91	<0.000
Allergic rhinitis	51(20.4)	9(3)	6.86(3.29-14.2)	33.4	<0.000
Conjunctivitis	3(1.2)	1(0.4)	3.02 (0.3 - 29.2)	1.008	<0.15
Total	109(43.6)	12(4.8)	15.33(8.7 – 28.8)	102.6	<0.000

- Some form of personal atopy is noted in 43.6% of asthmatic children compared to nonasthmatics(4.4%). Asthmatic children were 15 times more likely to be having various atopic manifestations when compared to to those children without asthma [OR (95%CI)=15.33(8.7-28.8)].
- Allergic rhinitis accounted for 20% which was observed in asthmatic children 7 times more than nonasthmatic children with statistical significance [OR(95% CI)= 6.86(3.29-14.2)]
- Food allergy was observed in33(13.2) asthmatics compared to 1(0.4%) nonasthmatics with statistical significance [OR (95% CI)= 37.7(5.1 - 278)]

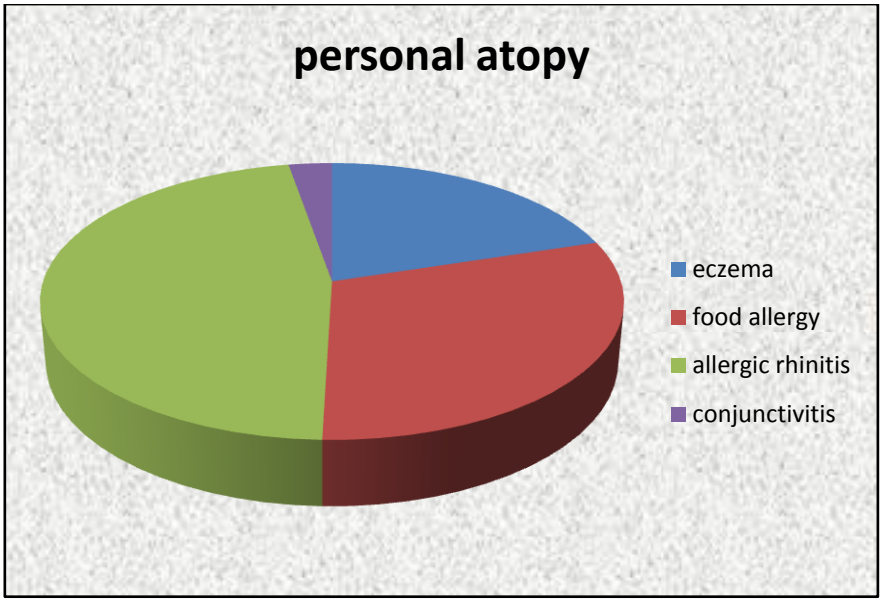


Figure 3: Distribution of personal atopic manifestations

- Eczema was noted in 22(8.8%) asthmatic children with statistical significance [OR (95% CI)= 24.02(3.21-179)]
- Conjunctivitis had no statistical significance.

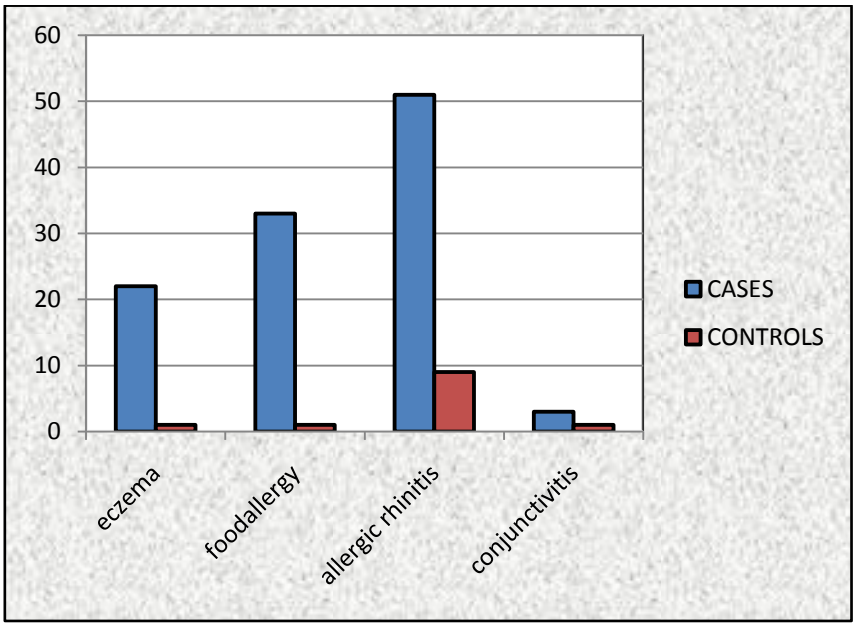


Figure 4: comparision of personal atopic manifestations among children with asthma and controls

TABLE 4:

Family H/O Asthma among asthmatics and nonasthmatics – Univariate analysis (n=250)

Family H/O Asthma	Cases no (%)	Controls no (%)	OR (95%CI)	X^2	p Value
Father	24(9.6)	2(0.8)	13.1 (3.07 - 6.34)	19.64	<0.000
Mother	30(12)	3(1.2)	11.23 (3.38 - 7.3)	23.65	<0.000
Sibling	21(8.4)	3(1.2)	7.55 (2.22 - 5.65)	14.18	<0.0001
Grandparents	31(12.4)	3(1.2)	11.65 (3.5 - 8.65)	24.74	<0.000
Relatives (second degree)	8(3.2)	1(0.4)	8.23 (1.02 - 66.3)	5.54	<0.018
Total	114(45.6)	13(5.2)	15.2(8.2-28.1)	107.7	<0.000

- Among the asthmatics, 45.6% had family history of asthma and the likelihood of having family members with asthma is 15 times more compared to the nonasthmatics . [OR (95% CI)=15.2(8.2-28.1)]

- Paternal asthma accounted for 9.6% [OR (95% CI) =13.1(3.0-56.3)] has more influence in development of asthma than the maternal asthma which accounted for 12% but with [OR (95% CI)= 11.2(3.3-37.3)].

- Presence of asthma in sibling is 8.4% in asthmatics with 1.2% in nonasthmatics with statistical significance.

- History of asthma in grandparents is 12.4% in asthmatics is with only 1.2% in nonasthmatics with statistical significance.

- Presence of asthma in second degree relatives is only 3.2% but with statistical significance.

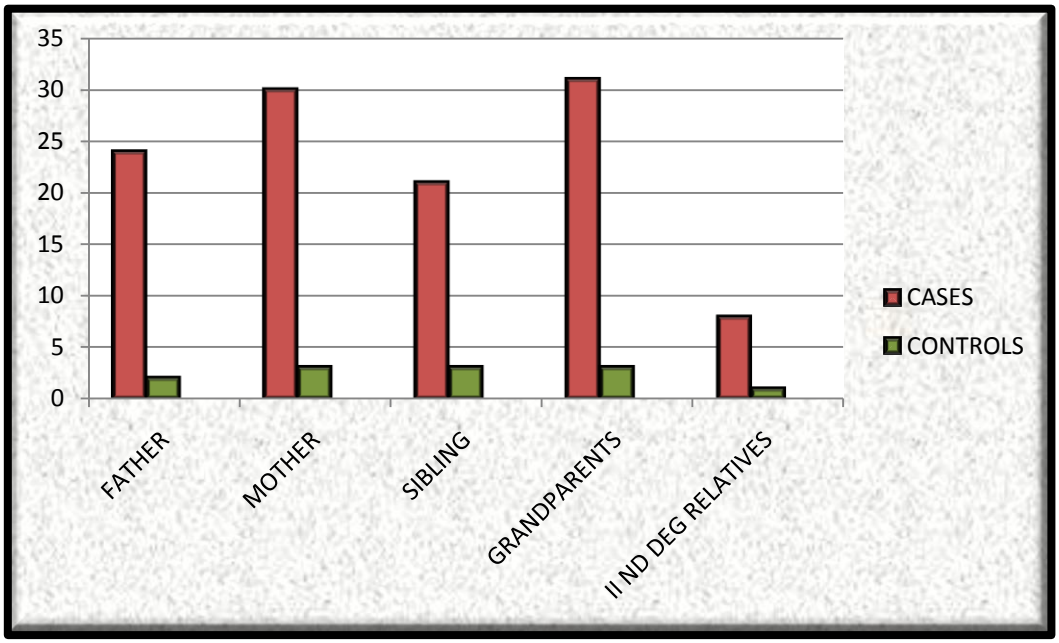


Figure5: Comparision of family H/O Asthma among asthmatics and controls

TABLE 5:

Family H/O atopy among asthmatics and nonasthmatics – Univariate analysis (n=250)

Family H/O Atopy	**Cases no (%)**	**Controls no(%)**	**OR (95%CI)**	**X^2**	**P value**
Father	12(4.8)	2(0.8)	6.25(1.38 - 28.23)	7.34	<0.006
Mother	13(5.8)	2(0.8)	6.8(1.51-30.4)	8.31	<0.003
Sibling	10(4)	2(0.8)	5.1(1.1-23.8)	5.46	<0.019
Grandparents	3(1.2)	0	-	-	-
Relatives (second degree)	2(0.8)	0	-	-	-
Total	40(16)	6(2.4)	7.7(3.2-18.6)	27.68	<0.000

- Family H/O atopy was noted in 16% of asthmatics compared to nonasthmatics(2.4%) and family H/O atopy was seen 8 times more commonly among asthmatics when compared to nonasthmatics. [OR (95%CI)= 7.7(3.2-18.6)]

- Both father and mother accounted 4.8% and 5.8% with maternal atopy having more influence than paternal atopy in inception of asthma.

- Atopy in sibling is observed in 4% of asthmatics compared to 0.8% in nonasthmatics with statistical significance[OR(95% CI)= 5.1(1.1-23.8)].

- Children born to atopic parents are 8 times at increased risk of developing asthma

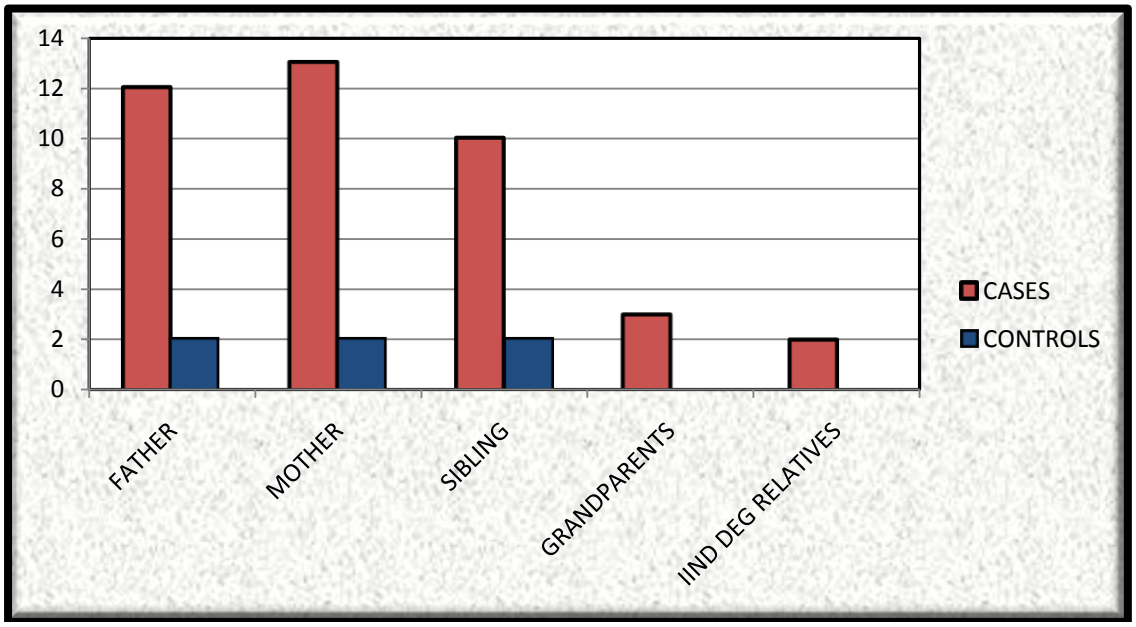


Figure 6: Comparision of family H/O atopy among asthmatics and controls

TABLE 6

Outdoor environmental factors which act as triggers in children with asthma and controls – Univariate analysis (n= 250)

Triggers	Cases no(%)	Controls no(%)	OR (95%CI)	X^2	P Value
Nearby factory	23(9.2)	10(4)	2.43 (1.13 - 5.22)	5.48	<0.019
Nearby traffic road	50(20)	17(6.8)	3.42 (1.91 - 6.13)	18.7	<0.000
Automobile exhaust and dust allergy	156(62.4)	4(1.6)	102.1 (36.7 - 83.2)	212.4	<0.000
cold air allergy	17(46.8)	1(0.4)	219 (30.26 - 1586)	149.3	<0.000

- Among the asthmatic children (62.4%) develop symptoms on exposure to automobile exhaust and dust with statistical significance. [OR(95% CI)= 102.1 (36.7 -283.2)].
- 46.8% children develop asthma symptoms on exposure to cold air with statistical significance [OR(95% CI)= 219 (30.26 - 1586)].
- 9.2% of asthmatic children were having factory nearby when compared to 4% among nonasthmatics. The asthmatic children are twice more likely to be living nearby factory, when compared to the nonasthmatics [OR(95% CI)= 2.43 (1.13 - 5.22)].

- Asthma prevalence was also significantly associated with exposure to traffic in the area of residence[OR(95% CI)= 3.42 (1.91 - 6.13)]. The asthmatic children are thrice more likely to be living nearby traffic roads or streets compared to nonasthmatics.

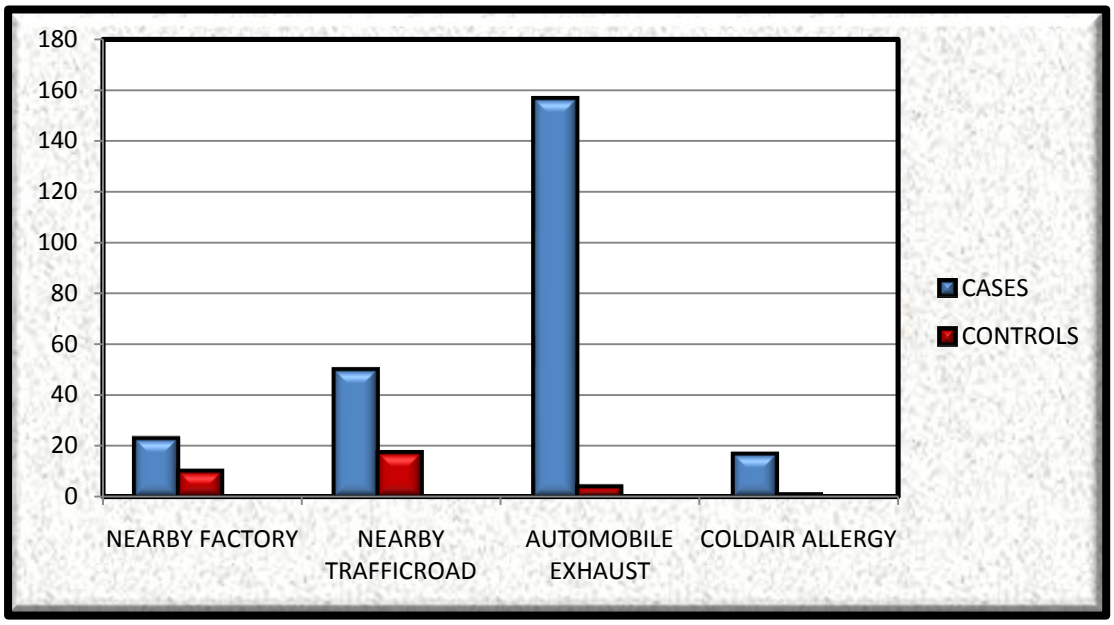


Figure 7: comparision of outdoor environmental factors in children with asthma and controls

TABLE 7:

Indoor environmental factors which act as triggers in children with asthma and controls – Univariate analysis (n=250)

Indoor factors	Cases no(%)	Controls no(%)	OR (95%CI)	X^2	P Value
Overcrowding	24(9.6)	16(6.4)	1.553 (0.80 - 3)	1.739	<0.187
Dusty home Environment	72(28.8)	35(14)	2.48(1.5-3.89)	16.28	<0.0000
Passive smoking	51(20.4)	12(4.8)	5.08 (2.63 - 9.79)	27.62	<0.000
Cooking					
Wood	**19(7.6)***	**1(0.4)**	**20.48 (2.72 -154.2)**	**16.88**	**<0.00003**
Cowdung	1(0.4)	8(3.2)	0.12 (0.01 -0.97)	-	-
Kerosene	52(20.8)	47(18.8)	1.13 (0.73 - 1.76)	0.31	<0.57
Gas	178(71.2)	194(77.6)	0.71 (0.47 - 1.06)	2.68	<1.101
Pets					
Dog	31(12.4)	12(4.8)	2.74 (1.33 - 5.63)	9.18	<0.002
Cat	**18(7.2)***	**2(0.8)**	**9.62(2.2 – 41.9)**	**13.33**	**<0.0002**
Fowl	5(2)	1(0.4)	5.08(0.58-43.8)	2.68	<0.1
Total	45(18%)	15(6%)	3.43(1.86-6.35)	13.05	<0.00003
Use of Mosquito coil	82(32.8)	15(6)	7.64 (4.26 - 13.72)	57.42	<0.000
Strong odours	14(5.6)	0		-	-
Moulds	32(12.8)	10 (4)	3.52 (1.69 - 7.33)	12.58	<0.0003
cockroaches	28(11.2)	6(2.4)	5.13(2.08-12.68)	15.27	<0.00009

*-significant

- Dusty home environment was observed in72(28.8%) of asthmatic children compared to 35(14%) of nonasthmatic children and was seen twice more commonly among asthmatics compared to nonasthmatics. [OR (95%CI) =2.48 (1.5-3.89)]

- Cooking with wood was noted in 19(7.6%) asthmatic children compared to 1(0.4%) nonasthmatic which was seen 20times more commonly in asthmatics compared to nonasthmatics. [OR(95%CI)= 20.48 (2.72 -154.2)]

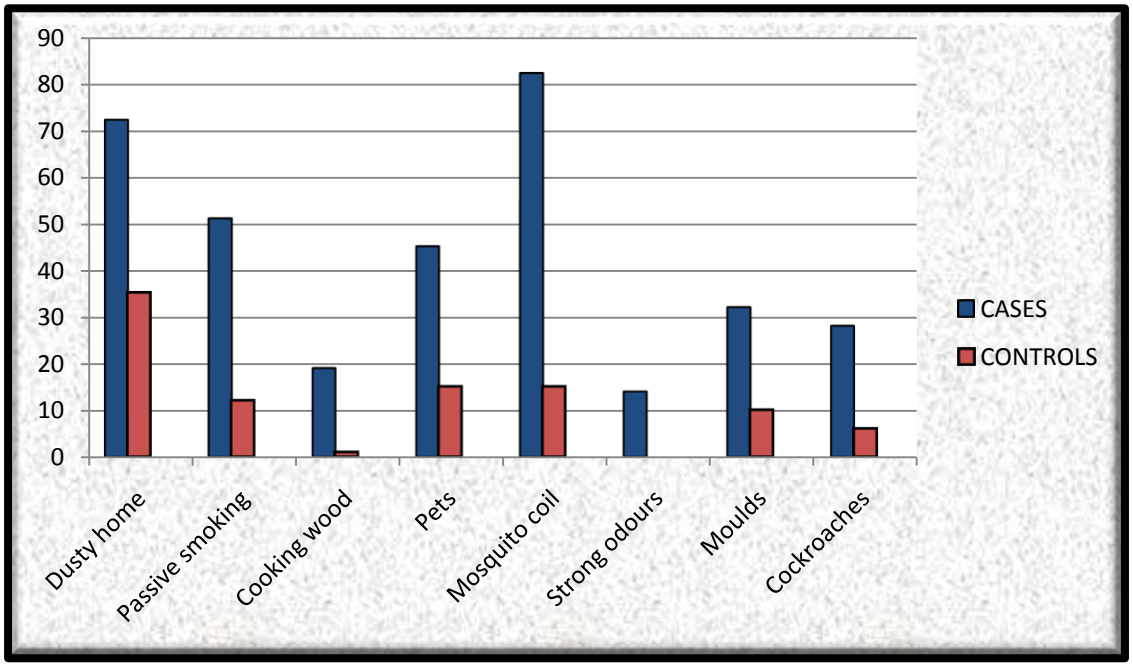


Figure 8: comparision of indoor environmental factors in children with asthma and controls

- Passive smoking was observed in 51(20.4%) asthmatics compared to 12(4.8%) nonasthmatics with statistical significance. [OR (95% CI)= 5.08 (2.63 - 9.79)]
- Pet ownership was observed in 45(18%) asthmatic children compared to 15(6%) nonasthmatics with statistical significance [OR (95%CI)= 3.43(1.86-6.35)]. Among them especially cats [OR (95%CI)= 9.62(2.2 – 41.9)] remained significant.
- Use of mosquito coils[OR (95% CI)= 7.64 (4.2-13.7)],strong odour allergy and presence of moulds on the walls[OR (95% CI)=3.52 (1.69-7.33)] found to be strongly associated with increased risk for asthma.
- Presence of cockroaches were significantly associated with asthma. [OR (95% CI)= 5.13(2.08-12.68)].

TABLE 8

Perinatal and epidemiological factors among children with asthma and controls – univariate analysis (n =250)

Factors	Cases no(%)	Controls no(%)	OR (95%CI)	X^2	P Value
Residence					
Inner city (Urban)	170(68)	130(52)	1.96(1.3 - 2.82)	13.33	<0.0002
Birthwt <2.5kg	56(22.4)	30(12)	2.11 (1.30 - 3.43)	9.49	<0.002
Exclusive breastfeeds <6months	89(35.4)	27(10.8)	4.56(2.83 - 7.34)	43.15	<0.0000
Head bath	32(12.8)	0	-	-	-
SE status					
Upper	1(0.4)	0	-	-	-
Upper middle	13(5.2)	4(1.6)	3.37(1.08 – 10.49)	4.93	<0.02
Lower middle	222(88.8)*	235(94)	0.5(0.26 – 0.97)	4.3	<0.03
Upper lower	13(5.2)	11(4.4)	1.19(0.52 – 2.71)	0.17	<0.67
Lower lower	1(0.4)	0	-	-	-

- Among asthmatics, 170 (68%) children were from urban comparing to nonasthmatics who were about130(52%). Residing in urban areas was observed to be almost twice among asthmatics when compared to nonasthmatics. [OR (95%CI)=1.96(1.3 - 2.82)].
- Lowbirthweight was observed in 56(22.4) asthmatic children compared to 30(12%) nonasthmatic children with statistical significance[OR (95%CI)=2.11 (1.30 - 3.43)].

- Asthmatics were 4 times likely to be exclusively breastfed less than 6months when compared to non asthmatics. [OR (95%CI)=4.56 (2.83 - 7.34)]
- 13% of asthmatics found to develop asthma attacks after taking head bath.
- Among asthmatics 222(88.8%) children were from lower middle socioeconomic status with no statistical significance. [OR (95% CI)= 0.5(0.26 – 0.97)] . Among them 5.2% were from upper middle class but with significance. [OR(95%CI)= 3.37(1.08 – 10.49)].

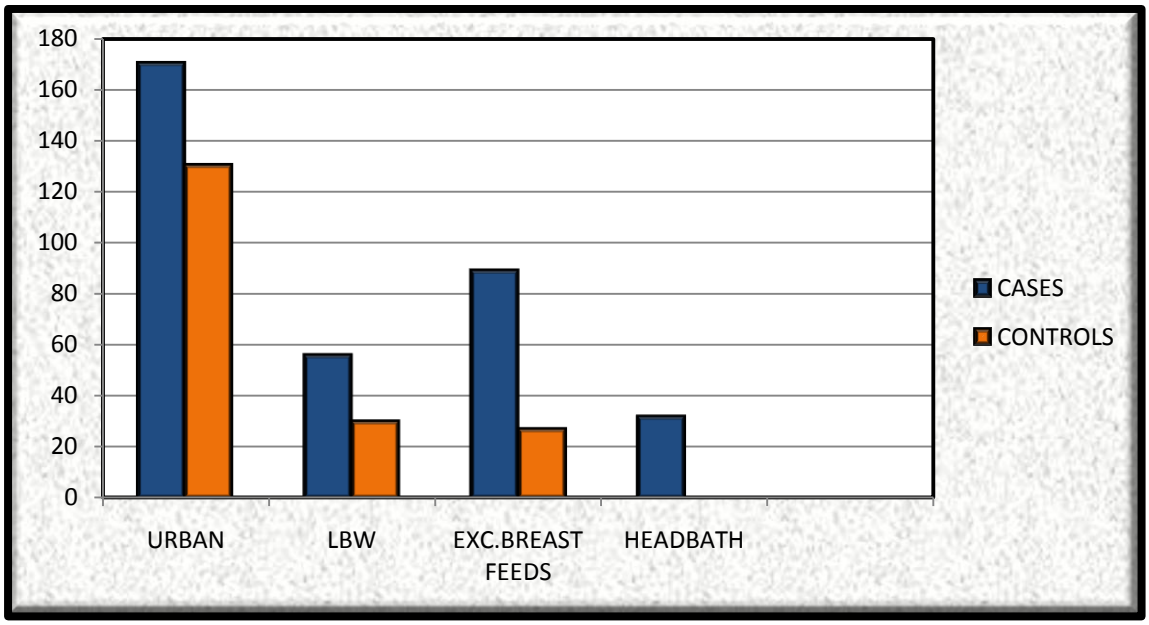


Figure 9: Perinatal and epidemiological factors among children with asthma and controls

Multivariate analysis

Multivariate binary logistic regression analysis after adjustment for confounding factors shows that personal atopy, family H/O asthma, cold air allergy and cooking with wood were independently associated with increased risk of developing asthma. The results are given in table 9.

TABLE 9:

Comparision of risk factors in children with asthma and controls– Multivariate analysis

S.NO	Factors	Adjusted OR(95%CI)	P value
1	**Personal atopy**	**17.8(7.9-39.8)**	**<0.0000**
2	Family H/O atopy	1.7(0.5-5.8)	<0.348
3	**Family H/O asthma**	**11.4(5.4-24)**	**<0.000**
4	**Cold air allergy**	**167.5(22.4-1248)**	**<0.000**
5	Automobile exhaust and dust allergy	2.2(0.92-3.1)	0.052
6	**Cooking with wood**	**3.2(1.03-10.47)**	**0.044**

Cytological profile of bronchoalveolar lavage fluid in atopic and non-atopic asthma

BAL cytology was done in 23 atopic asthmatic patients and 12 nonatopic asthmatic patients. The selected patients belonged to 4 to 12 years of age and comprised 20 males and 15 females.

The mean values of the eosinophils, neutrophils, lymphocytes and macrophages in BAL fluid of both atopic and non atopic asthma were calculated along with standard error mean. The significance was confirmed by student t-test (p=<0.0000).

The results are given in table 10.

TABLE 10:

Cell type	No of cells		
	Atopic(n=23)	**Non-atopic(n=12)**	**Normal ref values[88]**
Eosinophil	12.48%	0.57%	1.0%
Neutrophil	5.2%	7.14%	4.8%
Lymphocyte	13.05%	3.41%	28.6%
Macrophages	30.5%	53.25%	81.2%

- The percentage of eosinophils(12.48%) was significantly increased in atopic asthma compared to nonatopic asthmatic subjects and to the normal reference values. (p=<0.000)
- The percentage of neutrophils(12.48%) was significantly increased in nonatopic asthma compared to nonatopic asthmatic subjects and to the normal reference values. (p=<0.000)
- The lymphocytes remained within normal values in both atopic and nonasthmatic children.

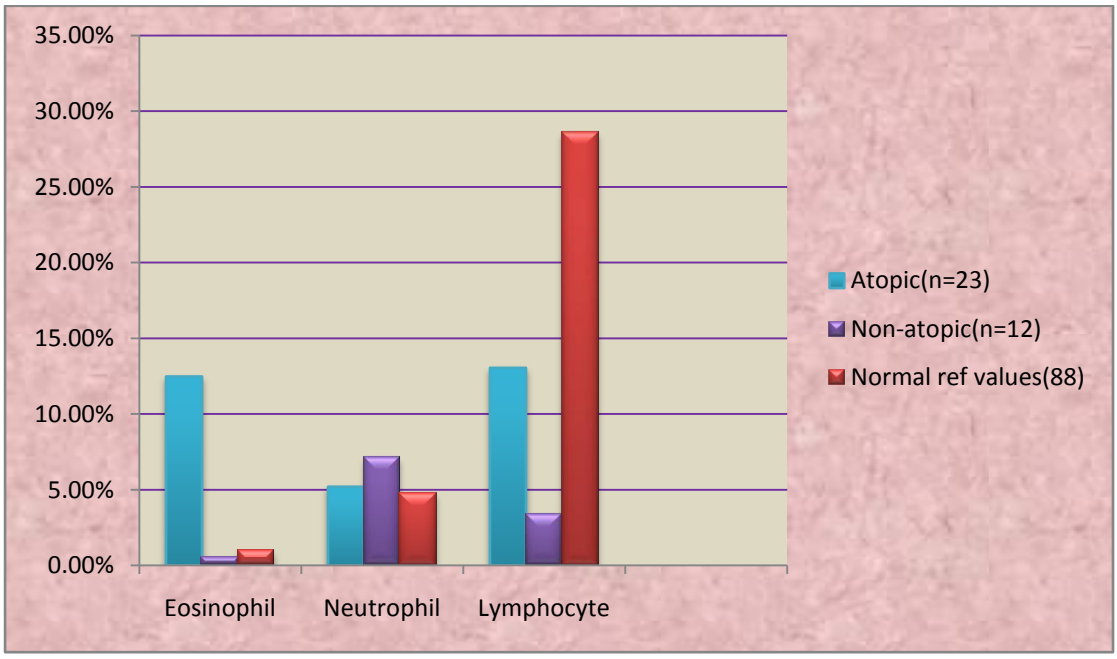


Figure 10 : Comparison of inflammatory cells in bal fluid in phenotypes of asthma with normal reference values

DISCUSSION

Asthma is a disease characterized by variability of airflow obstruction and episodic occurrence of symptoms in individual patients ('attacks'). It is also a disease which varies in prevalence and severity within populations, between countries, and over time.

The environment, in terms of chemical and biological air pollutants, is much more clearly related to the provocation of asthma attacks and to asthma severity than it is to the induction of the asthmatic state and the prevalence of asthma where the genes are related to the causation of asthma. Genetic factors influence susceptibility to the development of asthma regardless of the environment whereas environmental exposures may also influence to some degree the susceptibility to asthma in the absence of genetic predisposition [13].

In our study, 250 asthmatic children and 250 nonasthmatic children were taken as cases and controls respectively.

Among them 52% were males and 48% were females with nearly equal distribution with slight male preponderance where S. Hasan Arshad et al[21] and other studies [22,23,24,65] observed that asthma prevalence is higher in males than females. Though there was no gender difference observed in two earlier studies[25,26] these studies followed a different methodology and the former was carried out a longtime ago. The male predominance may be related to a greater degree of reduced

tone of airways in males compared to females[27] in early childhood. But one study has revealed the female preponderance[28].

Out of them 52.8% were found in the age group of 4-8yrs , where as 47.2% were found in 9-12yrs of age[29]. In our study, males dominate in the age group of 4-8yrs where as females start to dominate in 9-12yrs of age[28]. But this picture does not clearly depict the prevalence in age groups as the children less than 4 years were not included in this study.

In our study population around 69% of children started having their symptoms at 0-3yrs of age whereas 28.4% at 4-8years of age and very few after 8years(2.8%) as seen in DSY Lam et al [69] where some studies reveal that mean age of onset is 3 years and 8 years for males and females respectively[70].

GENETIC FACTORS

Personal atopy

In our study , among 250 asthmatic children, 109(43.6%) children had atopic manifestations, compared to 11(4.4%) children in non asthmatic children denoting that personal atopy has strong influence and asthmatic children were 20 times more likely to be having various atopic manifestations when compared to those children without asthma in univariate analysis where in multivariate analysis it was

found that asthmatic children with personal atopy were at 17 times more risk of getting asthma. S. Hasan Arshad et al [21] and also other studies [24,30,31,32] observed that personal atopy was seen 3 times more commonly among asthmatics than the nonasthmatics though it was much lower than the present study.

Among the atopic asthmatic children 65 children (26%) had allergic rhinitis which was significantly associated with the development of asthma and noted 7 times more in asthmatic children where Arnedo – pena et al [24] and other studies[32] observed it 4 times more in children with asthma.

33(13.2%) Children had eczema which also had significant association in the development of asthma and eczema was observed 24 times more in asthmatic children than the nonasthmatic children similar to A.vander Hust et al [31].

Food allergy was observed in 33 (13.2%) asthmatic children compared to 1(0.4%) non asthmatic children which was found to be significant factor in asthma. Among them the children were allergic to ice cream (4%), cool drinks (3.2%), sweets (3.2%), fruits(1.6%) and sea foods (1.2%) as observed in other studies[34,63], but one study observed that some susceptible individuals develop asthma on taking fruits[64].

No significance was found out for conjunctivitis and no clear relationship was made out for it as the participation is very low in this

study. So, it is very well observed that personal atopy plays major role in causation of asthma.

Out of 250 asthmatic children, 114(45.6%) Children had family history of asthma which was observed in 13 non asthmatic children only(5.2%) and the likelihood of developing asthma was 15 times more compared to nonasthmatics in univariate analysis where in multivariate analysis it was found to be of 11times risk whereas Augusto et al [33] and other studies[22,23,34,35,68] showed 3-5 times of risk. Among them even though father and mother contributed nearly equal, the risk of developing asthma was higher in children whose father had asthma which was similar to Karunasekara KA et al [26], and other studies [36,21] where other studies indicate maternal asthma being risk factor than the paternal asthma [22,23,33,37]. 21asthmatic children (8.4%) had history of sibling asthma whereas in non asthmatic children it was only 3 (1.2%) . In this study it was inferred that presence of asthma in sibling increases the risk 8 times more in getting asthma as noted in other studies [21,35,36,68]. It was independent of asthma in other family members.

Grandparents of 31 asthmatic children had asthma compared to 3 children in non asthmatic group which had a significant relationship in inception of asthma as observed in Bijanzedah et al (35). Asthma in second degree relatives was noted in 8(3.2%) asthmatic children whereas it was noted in 1(0.4%) nonasthmatic child. Though the

participation was low, it was found to be significantly related to the inception of asthma.

In our study family history of atopy was noted in 40(16%) of asthmatic children compared to non asthmatics where it was 6(2.4%) denoting a significant relationship that children born to atopic parents are 8 times at increased risk of developing asthma which was similar to MR sears et al[23] and other studies [32,34,36,38,65,68]. Among the parents father and mother accounted for 4.8% and 5.8% respectively with maternal atopy having more influence (8times) than the paternal one as noted in previous studies. History of atopy in sibling is also a significant risk factor having 5 times more risk of developing asthma than the nonasthmatic children as noted in some studies (KAW Karunasekera et al) [36].

Out of 250 asthmatic children 156 children (62.4%) had dust and automobile exhaust allergy comparing to 4 non asthmatic children (1.6%). It was found that dust, automobile exhaust allergy is a very significant risk factor for inception of asthma in univariate analysis like Von Mutius et al[15] and other studies[39,40,41]. But in multivariate analysis it was found to be insignificant [OR(95% CI)= 2.2(0.92-3.1)] like Sunil K Chabra et al [42] who noted that outdoor pollution especially SO2 particulates have no major role in asthma.

In our study cold air allergy was observed in 117 (46.8%) asthmatic children and 1(0.4 %) non asthmatic child . Though the previous studies have not discussed about the cold air and its contribution in enough, it was found to be significantly related to the increased risk of asthma in both univariate and multivariate analysis in our study . [OR(95% CI)= 167.5(22.4-1248**)**].

In our study it was observed that 23(9.2%) asthmatic children were residing near factory comparing to 10(4%) non asthmatic children. Though the participation was low it was significantly associated with the risk of asthma 2 times more than the nonasthmatics similar to other studies (C E Dunn et al[(15).]

Among the 250 asthmatics, 50(20%) children were found to reside near the traffic roads or streets comparing to the 17(6.8%) non asthmatic children. There was 3 times risk higher in the asthmatic group which was found in Liebhart et al [(22)] and other studies [(24,39,40,41).] Contrarily it was observed in some studies that nearby traffic road and pollution has no major role in asthma[(76,77).]

Indoor environmental factors

In our study overcrowding was observed in homes of 24(9.6%) asthmatic children and in 16(6.4%) non asthmatic children which was not significantly related to the asthma similar to Liebhart etal [(22)] which

also observed that overcrowding was significantly associated in adult asthma only .

In this study 72(28.8%) asthmatic children found to live in dusty home environment comparing with 35(14%) non asthmatic children. It was observed that dusty home environment increases risk 2 times more in getting asthma as previously noted in Etzel R A et al[14] and Karunasekara et al[10].

In our study, passive smoking was observed in 51 (20.4%) asthmatic children comparing to 12(4.8%) non asthmatic children which has got 5 times more risk of developing asthma as noted in other studies (Ramesh.J et al [34] and other studies [43,44,45,46,65,66]. Very few studies have contradicted the role of passive smoking like Liebhart et al [22] [OR (95% CI)- 0.99 (0.75 – 1.30)] and p value is 0 .917.

In our study cooking with wood was observed in homes of 19 (7.6%) asthmatic children compared to 1(0.4%) child in non asthmatic group. It is inferred that those who are cooking with wood in their houses are having 20 times more risk in getting asthma by univariate analysis, but in multivariate analysis the risk was 3 times more than the nonasthmatic children which was observed in other studies [36,47,48,65]. But cooking with cowdung, kerosene and gas was not significantly related to asthma where some studies reveal the risk of gas stoves [20,49,50]

In our study 45 (18%) asthmatic children had pets in their home or had the habits of playing with pets compared to 15(6%) non asthmatic children where they had 3 times more risk of precipitating asthma similar to other studies Etzer R et al[43]and other studies[65]. Among them presence of cats found to be more significant followed by the dogs. Arnedo-pena et al[24] had observed no relationship between cats and asthma. Several large studies have found either no association between asthma and pet ownership[51] or an inverse relationship, particularly with early dog ownership[52].

It was observed that in houses of 82(32.8%) asthmatic children they regularly use mosquito coils which was noted only in 15 (6%) non asthmatic children. It was found to be a significant risk factor in inception of asthma with 7 times more risk than the nonasthmatics similar to other studies[36,48].

Allergy to strong odours like perfumes and toilet cleaners was observed in 14 (5.6%) asthmatic children where as it was not noted in any non asthmatic children there by indicating the significant association in asthma as revealed by Azizi BH et al [48].

Out of 250 asthmatic children moulds were found in walls of houses of 32(12.8%) asthmatic children compared to the 10 (4%) non asthmatic children. It was observed that the presence of moulds on the

walls increases the risk 3 times more in getting asthma as in other studies[20,22,38,53,54, 55,65,66].

Among the 250 asthmatics cockroaches were found in houses of 28(11.2%) asthmatic children compared to the 6 (2.4%) non asthmatic children. It was observed that presence of cockroaches in homes increases the risk of inception of asthma by 5times which was observed in other studies also[38,66].

Among the 250 asthmatic children 170 were from urban comparing to the 130 non asthmatic children. Children coming from urban areas were at 2 times risk of developing asthma than nonasthmatic children similar to previous studies as observed in FJ Malveaux et al[71] where MH Weiringer et al[72] observed that living in urban areas is not a riskfactor for developing asthma..

In our study out of 250 asthmatics, 56(22.4%) children were born with low birth weight comparing to the 30(12%) non asthmatic children which found to be a significant risk factor with 2 times more risk in development of asthma as observed by other studies[67,73]. Perinatal factors like low birth weight influences the development of atopy in early life, increase the risk of developing lower respiratory tract infections, and may play a role in the development of asthma in later life. Very low birth weight may have reduced pulmonary function similar to those described in children at risk for transient or early

childhood wheezing. But some studies show that low birth weight had no significant role in developing asthma (MRsears et al) [23]

In this study out of 250 asthmatic children 89 (35.4%) children were exclusively breast fed for less than 6 months compared to 27 (10.8%) non asthmatic children. Hence there is an increased likelihood of developing asthma by 4 times in those children who were not exclusively breast fed for more than 6 month which was observed in many other studies like Arnedo-pena et al[24] and [56,57,58,59,60]. Human milk contains factors that provide specific immunity, nonspecific protective factors that inhibit the binding of bacterial pathogens and their toxins, and lipids that may disrupt enveloped viruses. Breast milk contains growth factors and cytokines that may play a role in modulating the development of asthma by enhancing infant lung development, preventing sensitization to environmental allergens and reducing susceptibility to respiratory infections[61]. The role of breastfeeding as a protective factor against asthma and atopic diseases however, continues to be controversial, with some studies showing a negative effect of breastfeeding (ToveyER et al[62]. Our results support a strong protective effect of breastfeeding against asthma in children.

Among the 250 asthmatic children most of the children (222 - 88.8%) were from lower middle class according to modified Kuppusamy scale but with no significance. But 13 asthmatic children were from upper

middle class having 3times more risk of getting asthma. Studies like Arnedo pena etal[24] and other studies [34,65,67] showed asthma is prevalent in lower socioeconomic status. Some studies reveal that asthma is prevalent in higher socio economic states (Harshan arshad etal) [21] where some other studies reveal that social economic status has got no role in asthma (MRsears et al) [23]

Out of 250 asthmatic children 32 (12.8%) children develop asthma attacks after taking head bath. Eventhough there are no detailed studies regarding role of headbath , it was found to be having significant association with asthma. However, many studies have not addressed this issue and hence there is a need for further studies to look into this aspect.

In our study, the factors personal atopy, family H/O asthma, cold air allergy, cooking with wood were found to be independently related to the risk of developing asthma.

BAL Cytology

In our study BAL cytology was taken from 35 children. Among them 23children belonged to atopic asthma category and 12 children to non atopic asthma category. The asthmatic children with persistent symptoms who were on bronchodilator therapy, but not yet started on inhaled steroids were subjected for bronchoalveolar lavage.

Fibreoptic bronchoscopy was found to be a very safe procedure. None of our patients developed any complications during or after the procedure. No abnormality was found in the airways.

In atopic asthma the mean eosinophil count (12.48%) was found to be significantly increased comparing to the normal reference values[88]. But in non atopic children the mean neutrophil count (7.1%) was increased significantly. In both of the phenotypes of asthma lymphocytes were found to be within normal limits.

In our study it is clearly observed that the atopic asthmatic children being predominantly eosinophilic and the nonatopic asthmatic children being neutrophilic according to the cytology.

Previous studies showed noneosinophilic patients were less likely to be atopic and less hyperresponsive[75] as seen in our study and have noted neutrophilic inflammation in some patients with severe asthma[74,76,77,79] and in small numbers of patients studied during asthma exacerbations[78]. Intense neutrophilic inflammation has also been demonstrated in patients ventilated for acute severe asthma[80]. In our study both eosinophilic and neutrophilic groups did not show much difference in their severity.

Most children with asthma can be treated successfully with low-to-moderate doses of inhaled corticosteroid and long-acting β-2 agonist.

Those that fail to respond are a heterogeneous group. Reasons for persistent difficult asthma include persistent eosinophilic inflammation, non-eosinophilic inflammation, airway reactivity without residual inflammation and persistent airflow limitation. In some previous studies, they proposed a protocol to determine an individualized treatment plan[81]; (i.e) cyclosporin for persistent eosinophilic inflammation, azithromycin for persistent neutrophilic inflammation[82] and continuous subcutaneous terbutaline if there is airway reactivity without residual inflammation.[81] Further studies are needed in this view especially in a case of poorly controlled asthma. In previous studies done in adults , it is noted that patients having higher eosinophil count in BAL respond very well to corticosteroid therapy rather than conventional bronchodilators[83].

But in our study both these categories were responding well to inhaled steroids during the followup in contrast to the abovementioned studies. It is necessary to followup them to look for the exacerbations. Nowadays, studies on inflammatory biomarkers (interleukins) of BAL fluid are being conducted to address the severity, response to treatment and prognosis[89]. The previous studies have not addressed in detail in this view and hence further studies are needed to enlighten this subject.

SUMMARY

- 68.8% of the asthmatic children started having their symptoms at their 0-3 yrs of age and around 3% started after 9 yrs of age.
- Some form of personal atopy is noted in 43.6% of asthmatic children compared to nonasthmatics(4.4%). Children with personal atopy were 15 times more likely to develop asthma. Allergic rhinitis accounted for 20% with statistical significance. Eczema accounted for 8% with statistical significance. Food allergy is strongly associated with 37 times increased risk of asthma.
- Among the asthmatics, 45.6% had family history of asthma and the likelihood of having family members with asthma is 11 times more compared to the nonasthmatics. Paternal asthma accounted for has more influence in development of asthma than the maternal asthma. 12.4% of asthmatic children had history of asthma in grandparents whereas it is only 1.2% in nonasthmatics with statistical significance. Presence of asthma in sibling is 8.4% in asthmatics with 1.2% in nonasthmatics with statistical significance.
- 62.4% of asthmatic children develop symptoms on exposure to automobile exhaust and dust comparing with 1.6% of nonasthmatics with high statistical significance. 46.8% children

develop asthma symptoms on exposure to cold air when compared to 0.4% of nonasthmatics who develop other symptoms.

- Passive smoking and presence of cockroaches in homes were found to be having 5 times increased risk of asthma. Cooking with wood, presence of pets, especially cats remained significant. Use of mosquito coils, strong odour allergy and presence of moulds on the walls found to be strongly associated with increased risk for asthma. Residing in urban areas and low birth weight (<2.5kg) is significantly associated with 2 times increased risk of asthma.
- Exclusive breastfeeding for less than months were found to be significantly associated with asthma with 4 times increased risk.
- 13% of asthmatics found to develop asthma attacks after taking head bath
- Among asthmatics 222(88.8%) children were from lower middle socioeconomic status but without significance. 5.2% were from upper middle class but with significance.
- In BAL fluid, in atopic asthma eosinophils (12.48%) were increased significantly with neutrophils and lymphocytes within normal limits. In nonatopic asthma neutrophils(7.14%) increased significantly while eosinophils(0.57%) and lymphocytes (3.41%) remained within normal limits.

CONCLUSION

- This study reinforces that asthma has multifactorial aetiology. Our results confirm the hypothesis that the mechanism underlying this phenomenon is complex, without a single factor that could be identified as the principal cause. Ultimately it is inferred that asthma is due to interaction between the genetic and environmental factors.
- The role of risk factors in our study correlate well with the previous literatures.
- In our study, the following factors are independently related to the risk of developing asthma.
    - Personal atopy
    - Family H/O asthma
    - Cold air allergy
    - Cooking with wood
- Measures to reduce exposure to environmental allergens and irritants and to eliminate barriers to access to health care are likely to have a major positive impact.
- Both atopic(eosinophilic) and nonatopic(neutrophilic) asthmatic patients respond well to inhalational corticosteroids. But followup is necessary in neutrophilic variety.

LIMITATIONS

The major limitation of our study is that it is a hospital based study and the results can not be extrapolated into the community. In analysis of family history, among both the cases and controls a small population was not able to recall which might have led to bias. In the area of BAL cytology the population available for investigation was small and many of the parents were not aware of the duration of the treatment with corticosteroids which might have altered the cytology although most of the observations were in the direction expected from previous literatures. It is difficult to avoid these problems when one studies a small population. We believe our observations to be useful in spite of this problem.

RECOMMENDATIONS

Since it is difficult to modify the genetic propensity on asthma, reducing exposure to indoor allergens, especially in genetically susceptible children, can reduce the development of allergic sensitization and this may prevent childhood asthma and decrease the frequency and severity of asthma attacks.

Several potential indoor and outdoor risk factors for asthma, the avoidance of which may reduce or delay the development of asthma and may improve asthmatic children's respiratory health in susceptible individuals.

In a country like India, the economic burden due to asthma can be efficiently reduced by asthma education programmes emphasizing on early avoidance of triggers to parents of the affected child.

Our study adds that among environmental causes, exposure to automobile exhaust and cold air play a significant role in this region emphasizing the above factors in asthma education make many poor children away from recurrent attacks of asthma.

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ANNEXURE – I
DATA ENTRY FORM

1	Patient Name		
2	Age		
3	Sex	M	F
4	Reg. No.	Birth wt -	
5	Address		
6	Socio economic status (Modified Kuppusamy scale)		
7	Breast fed or not?	Yes	No
	If yes, duration of exclusive breast feeding		
8	Age of onset		
9	Personal atopy	Yes	No
	If yes 1.eczema,2.allergic rhinitis,3. food allergy, 4.conjunctivitis)		
	If food allergy present –type of food-		
10	Father asthmatic or not	Yes	No
11	Mother asthmatic or not	Yes	No
12	Siblings asthmatic or not	Yes	No
13	Grandparents asthmatic or not	Yes	No
14	Maternal uncle asthmatic or not	Yes	No
15	Maternal aunty asthmatic or not	Yes	No
16	Paternal uncle asthmatic or not	Yes	No
17	Paternal aunty asthmatic or not	Yes	No

18	Father atopic or not	Yes	No
19	Mother atopic or not	Yes	No
20	Sibling atopic or not	Yes	No
21	Grandparents atopic or not	Yes	No
22	Maternal uncle atopic or not	Yes	No
23	Paternal aunty atopic or not	Yes	No
24	Maternal aunty atopic or not	Yes	No
25	Paternal uncle atopic or not	Yes	No

OUTDOOR FACTORS

26	Near by factory if any (within 2 kilometres)	Yes	No
27	Residing on heavy traffic roads or streets	Yes	No
28	Allergic to cold air	Yes	No
29	Allergic to automobile exhaust and dust	Yes	No

INDOOR FACTORS

30	Number of rooms		
31	Family size		
32	Type of fuel used for cooking	1.gas 2.kerosene 3.wood 4.cowdung	
33	Any family members smoking inside house/ Neighbour smoking in the presence of child	Yes	No
34	Pets in house (dogs, cats, fowls)	Yes	No
35	Dusty home environment	yes	no
36	Using mosquito coils or not	Yes	No

37	Allergic to strong odours (perfumes, cleaning agent)	Yes	No
38	Presence of moulds on walls	Yes	No
39	Cockroaches in house	Yes	No

INVESTIGATIONS:

41	Bronchoscopy done If yes, Macroscopic findings -	Yes	No
42	BAL done - If yes Cytology findings -	Yes	No

Annexure – II

Patient information sheet

Role of hereditary propensity,environmental factors and possible phenotypic association in physician diagnosed asthma

Investigators Name: Dr. P.Ganesapandian

(To be read to caretakers in the presence of a witness)

Your child is suffering from bronchial asthma. Hereditary and environmental factorsplay important role in the development of asthma. To know how far these factors play role in the development of asthma, the questionnaire is formed. By analysing the factorial association in detail the common factors can be identified and it may be possible to reduce the severity of asthma by getting rid of it.

At present asthma is treated on the basis of severity of asthma. Some recent studies show that asthma can be reclassified based on the bronchoalveolar cytology and induced sputum cytotology which may be useful in the treatment of asthma.

How is the study being done ?

The doctor will ask you questions and examine the child to make sure that it is safe for him/her to enter the trial. If your child is suffering from asthma, you (parent/care taker) will have to answer the questions and the answers will be entered in the proforma.

Selected children will be subjected for bronchoalveolar lavage technique by the pulmonologist after local anaesthesia with proper oxygen saturation monitoring. The specimen obtained will be sent for cytological examination.

Can I refuse to join the study ?

You may refuse to participate or withdraw from this study at any time. In both cases your child will be treated in the usual manner in the hospital.

Is there a benefit or harm ?

- BAL technique may cause pain and bronchospasm in some children.
- It may be possible to reduce the severity of asthma and to improve the lifestyle of the child by treating the child using the results obtained in the study

Confidentiality

The data collected from the study will be used for the purpose of the study only. The results for the study are to be published in medical journals. Personal information of the children participating in the study will be kept confidential. There will not be any disclosure about your childs information without your attention.

Subject Rights

I understand that if I wish further information regarding my childs rights as a research subject, I may contact the hospital where the study is taking place.

Section II

Informed consent form

- I understand that my child is suffering from asthma and it is essential to answer the questionnaire and to collect bronchoalveolar lavage fluid for cytological examination from my child as told by the treating physician.

- I confirm that I have been told about this study in my mother tongue (Tamil) and have had the opportunity to ask questions. I confirm that I have told about the risks and potential benefits for my child's participation in the study. I agree to give my consent for the participation of my child in this study.

- I understand that my consent for my child's participation in the study is voluntary and I can withdraw my child from participation in the study at any time, without giving any reason, without my child's medical care being affected.

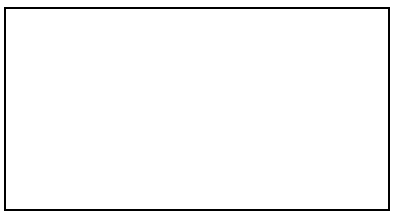
- I agree not to restrict the use of any data or results that arise from this study.

Name of the child : _____

Name of the Parent/Guardian : _____

Signature of the Parent/Guardian : _____
Date: ___/___/___

Thumb print of illiterate Parent/Guardian



Name of the witness : _____

Signature of the witness : _____
Date: ___/___/___

Name of the Investigator/Medical Officer : _____

Signature of the Investigator/Medical Officer : _____
Date: ___/___/___

தகவல் தாள்

ஆஸ்துமா நோய் உருவாவதில் மரபு மற்றும் சுற்றுப்புறச்சூழல் காரணிகளின் பங்கு மற்றும் இந்நோயின் வகைகளைப் பற்றிய ஆய்வு.

ஆய்வாளர்கள்

1. மரு. பி.கணேசபாண்டியன் - முதன்மை ஆய்வாளர்
2. மரு. குணசிங் M.D.D.Ch., - மேற்பார்வையாளர்
3. மரு. விஜயசேகரன் M.D.D.Ch.Ph.D.,- மேற்பார்வையாளர்

ஆஸ்துமா நோய் குழந்தைகளை வெகுவாக பாதிக்கும் சுவாசப்பாதை நோயாகும். இந்நோய் உருவாவதில் மரபுக் காரணிகளும், சுற்றுப்புறச்சூழல் காரணிகளும் பெரும் பங்கு வகிக்கின்றன. ஆனால் ஆஸதுமாநோயில் அவற்றின் பங்கு எந்த அளவிற்கு உள்ளது என்பது கேள்விக் குறியாக உள்ளது. இக்காரணிகளின் பங்கை கண்டறிவதை மூலம் இந்நோயைத் தூண்டும் காரணிகளைக் குறைத்து நோயின் தீவிரத்தைக் குறைக்க வாய்ப்புள்ளது.

தற்பொழுது ஆஸ்துமா அதன் தீவிரத்தைக் கொண்டு வகைப்படுத்தப்பட்டு அதன்படி சிகிச்சையளிக்கப்பட்டு வருகிறது. ஆனால் சமீபத்திய ஆய்வுகளின்படி ஆஸ்துமாவால் பாதிக்கப்பட்ட குழந்தைகளின் மூச்சுக்குழாய் மற்றும் காற்றுப்பைகளில் இருந்து எடுக்கப்பட்ட சளித்திரவத்திலுள்ள செல்களின் எண்ணிக்கையைக் கொண்டு வேறு மாதிரியாக வகைப்படுத்தப்பட்டுள்ளது. இதனை மையமாகக் கொண்டு சிகிச்சை இளித்தால் ஆஸ்துமாவின் தீவிரத்தை கட்டுப்படுத்த இயலலாம்.

ஆய்வின் நோக்கம்

- ஆஸ்துமா நோய் உருவாவதில் மரபுக்காரணிகளும், சுற்றுப்புறச்சூழல் காரணிகளும் எந்த அளவிற்கு பங்கு வகிக்கின்றன என்பதை கண்டறிதல்.
- (Bronchoscope) கருவி மூலம் மூச்சுக்குழாயிலிருந்து எடுக்கும் திரவத்திலுள்ள செல்களின் வகைகளையும், எண்ணிக்கையையும் கண்டறிதல்.

ஆராய்ச்சி நடவடிக்கைகள

அரசு குழந்தைகள் நல மருத்துவமனை மற்றும் ஆராய்ச்சி நிலையத்தில் உள்ள ஆஸ்துமா நோய் பகுதியில் வரும் 4 முதல் 12வது வயது வரை உள்ள குழந்தைகள் இந்த ஆய்வுக்காக தேர்ந்தெடுக்கப்படுகிறார்கள். இக்குழந்தைகளின் பெற்றோரிடத்தில் இந்த ஆய்வு தொடர்பான கேள்விகள் டாக்டரால் கேட்கப்பட்டு, அதற்கான படிவத்தில் குறித்துக்கொள்ளப்படும்.

தேர்ந்தெடுக்கப்பட்ட குறிப்பிட்ட குழந்தைகளுக்கு கருவி மூலம் மூச்சுக்குழாயில் உள்ள சளித்திரவம் எடுக்கப்பட்டு பரிசோதனைக்கூடத்திற்கு அனுப்பப்படும்.

அபாயம் மற்றும் நன்மைகள்

- கருவி மூலம் மூச்சுக்குழாய் வழியே சளி எடுக்கும் முறையில் ஒரு சிலருக்கு வலி மற்றும் மூச்சுத்திணறல் ஏற்படலாம்.
- சாத்தியமாகும் நன்மைகள் யாதெனில், இவ்வாய்வில் கிடைக்கும் தகவல்கள் மூலம், ஆஸ்துமாவின் தீவிரத்தை எளிதில் கட்டுப்படுத்த வாய்ப்புள்ளது.

தகவலளிக்கப்பட்ட ஒப்புதல் படிவம

- எனது குழந்தைக்கு ஆஸ்துமா நோய் உள்ளது என்று மருத்துவரால் தெரிவிக்கப்பட்டது. இதற்காக மருத்துவர் கேட்கும் கேள்விகளுக்கு பதில் அளிப்பதும், Bronchoscope கருவி மூலம் மூச்சுக்குழாயிலுள்ள சளித்திரவத்தை எடுத்து பரிசோதனை செய்தல் அவசியம் என்றும் தெரிவிக்கப்பட்டது.
- இந்த ஆய்வு பற்றி எனக்கு விளக்கமாக எனது தாய் மொழியில் சொல்லப்பட்டது. இந்த ஆய்வில் பங்கெடுத்து கொள்வதால் எனது குழந்தைக்கு ஏற்படக்கூடிய அபாயங்கள் மற்றும் நன்மைகள் பற்றி எனக்கு விளக்கப்பட்டது. இந்த ஆய்வில் எனது குழந்தையை பங்கெடுத்துக்கொள்ள முழுமனதுடன் சம்மதிக்கிறேன். கேள்விகள் கேட்பதறகு எனக்கு வாய்ப்பு அளிக்கபட்டது.

- இந்த ஆய்வில் பங்கேற்பது தன்னிச்சையானது. எந்த நேரத்திலும் என் குழந்தை பங்கேற்பதை எந்த விளக்கமும் தராமல் நிறுத்தி கொள்ளலாம் மற்றும் இதனால் என் குழந்தைக்கு கிடைக்கவேண்டிய மருத்துவ சிகிச்சைக்கு எந்த இடையூறும் ஏற்படாது என்று எனக்கு தெரிவிக்கப்பட்டது.
- இந்த தொடராய்வில் செய்யப்படுகின்ற செய்முறைகளினால் ஏற்படும் பக்க விளைவுகளுக்கு மருத்துவ உதவி செய்யப்படும். எந்தவித நஷ்டஈடும் தரப்படமாட்டது என்பதையும் அறிந்து கொண்டேன்.

குழந்தையின் பெயர் ----------

குழந்தையின் பெற்றோர் / கண்காளிப்பாளர் பெயர்----------

குழந்தையின் பெற்றோர் / கண்காணிப்பாளர் கையெழுத்து ----------

தேதி ----------

(எழுதப்படிக்கத் தெரியாத பெற்றோர் / கண்காணிப்பாளர் கை கட்டைவிரல் ரேகை)

சாட்சியின் பெயர் ----------

சாட்சியின் கையெழுத்து ----------

(தேதி ----------)

ஆய்வாளர் / ஆய்வு மருத்துவர் பெயர் ----------

ஆய்வாளர் / ஆய்வு மருத்துவர் கையெழுத்து----------

(தேதி ----------)

III. ABBREVIATIONS

BAL	-	Bronchoalveolar Lavage
FEV_1	-	Forced expiratory volume in one second
FVC	-	Forced vital capacity
GINA	-	Global initiative for asthma
IAP	-	Indian academy of paediatrics
ICS	-	Inhaled corticosteroids
LABA	-	Long acting beta agonist
LTRA	-	Leukotriene Receptor Antagonist
LTC4,D4,E4	-	Leukotriene C4,D4,E4
PAF	-	Platelet activating factor
PEF	-	Peak expiratory flow