



Is There A Relation Between Gender and Age of Onset of Asthma With Severity of Asthma? – A Study of 181 Cases

KEYWORDS

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ABSTRACT *Background: Severe asthma is associated with poor quality of life and increased morbidity and mortality. Identifying the risk factors, triggers and co-morbid conditions associated with severe asthma will help in further defining this phenotype and developing targeted interventions which can help in better control of severe asthma. There are not many studies between the association of severity of asthma with gender and age of onset of asthma.*

Aims and objectives: 1. To study association between gender and severe asthma.
2. To study association between late onset asthma and severe asthma.

Material and methods: This was a case control study done on 181 bronchial asthma patients, attending Respiratory Medicine department of A.J. Institute of Medical Sciences, Mangalore. Detailed history and clinical characteristics of all study subjects were noted & they were asked standard asthma related questionnaires. Patients with onset of asthma symptoms after the age of 20 years were categorized as adult onset asthmatics/ late onset asthmatics. These patients were further divided into two groups, those having onset of asthma symptoms during 20 to 40 years of age, and those with onset of asthma symptoms after 40 years of age. Remaining patients were grouped as early onset asthmatics. Severe asthma was defined as per GINA & American Thoracic Society recommendations. Data was compiled and statistical analysis was done using Chi-square test and P-value was calculated (P-value < 0.05 significant)

Results: Total number of patients included in the study was 181 between the age group of 15 to 80 years. Mean age was 40.19 years. Out of 181 patients, 113 (62.4%) were females and 68 (37.6%) were males. Out of 113 female patients, 67 (37%) had severe asthma and out of 68 male patients, 28 (15.5%) had severe asthma. Severe asthma was more common in females than in males which was statistically significant (p value <0.05). Out of total 181 patients, 114 (62.9%) patients were early onset asthmatics, of which 35 (19.3%) patients had severe asthma. 47 (26%) had onset of asthma symptoms during the age between 20 to 40 years, of which 42 (23.2%) had severe disease. 20 (11%) patients had onset of asthma symptoms after 40 years of age, out of which 18 (9.9%) had severe asthma. Severe asthma was more common in adult and late onset asthmatics than in early onset asthmatics. Prevalence of severe asthma increased with increasing age of onset of asthma symptoms. This was statistically significant.

Conclusions: 1. Severe asthma is more common in females as compared to males.

2. Severe asthma is more common in adult/ late onset asthmatics as compared to early onset asthmatics

Introduction:

Bronchial asthma is no longer considered as a single disease entity but a spectrum of diseases with various phenotypes with different underlying disease processes with different clinical presentation, severity and prognosis^{1, 2}. Recognizable clusters of demographic, clinical and / or pathophysiological characteristics are often called "Asthma phenotypes"¹.

Around 5- 10 % of asthma patients have severe asthma and this is recognized as a distinct asthma phenotype^{3, 4}. Severe asthma includes patients with 'refractory asthma' or 'treatment resistant asthma' in which patients with a confirmed diagnosis of asthma, whose symptoms or exacerbations remain poorly controlled despite high-dose inhaled corticosteroids plus a second controller medication such as long acting beta 2 agonist (and /or systemic corticosteroids) and management of comorbidities, or whose asthma control deteriorates when this treatment is stepped down and in whom response to treatment of comorbidities is incomplete¹.

Severe asthma is associated with poor quality of life and increased morbidity and mortality^{3, 5}. Identifying the risk factors, triggers and co-morbid conditions associated with severe asthma will help in further defining this phenotype and developing targeted interventions which can help in better control of severe asthma. Severe asthma during childhood is more common in males but after adolescence it is more in common females⁶⁻⁸

Late onset asthma or Adult onset asthma is defined when asthma symptoms appear first time in adulthood^{9, 10}. It is recognized as one of the phenotypes of asthma which is mostly non-atopic, more common in obese women and is associated with severe asthma⁵.

Aims and objectives:

1. To study association between gender and severe asthma.

2. To study association between late onset asthma and severe asthma.

Materials and Methods:

This was a case control study done on 181 bronchial asthma patients, attending Respiratory Medicine department of A.J. Institute of Medical Sciences, Mangalore. Bronchial asthma was diagnosed as per GINA guidelines. Both male and female patients between age group 15 to 80 years were included in the study. Current or past Smokers, patients with a previous history of pulmonary tuberculosis or active tuberculosis, those with chest wall deformities, co-existent neuromuscular disorders, and cardiovascular diseases were excluded from the study.

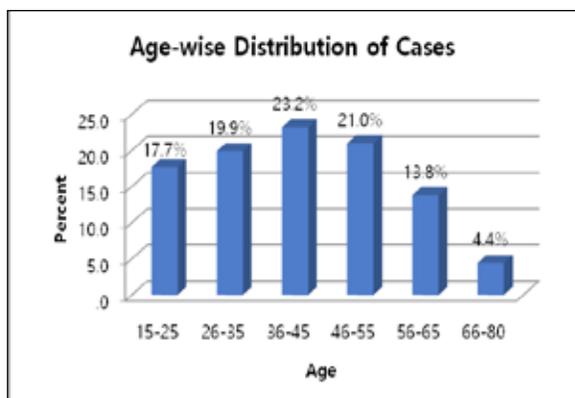
Detailed history and clinical characteristics of all study subjects were noted & they were asked standard asthma related questionnaires (peer reviewed). Patients with onset of asthma symptoms after the age of 20 years were categorized as adult onset asthmatics/ late onset asthmatics. These patients were further divided into two groups, those having onset of asthma symptoms during 20 to 40 years of age, and those with onset of asthma symptoms after 40 years of age. Remaining patients were grouped as early onset asthmatics.

Severe asthma was defined as per GINA & American Thoracic Society recommendations, depending on parameters like level of control of asthma, persistent symptoms despite optimum therapy, and use of high dose of inhaled steroids, frequent use of systemic corticosteroids, frequent exacerbations, frequent hospital admissions and Intensive Care Unit (ICU) admissions due to asthma^{1,5}.

Data was compiled and statistical analysis was done using Chi-square test and P-value was calculated (P-value < 0.05 significant)

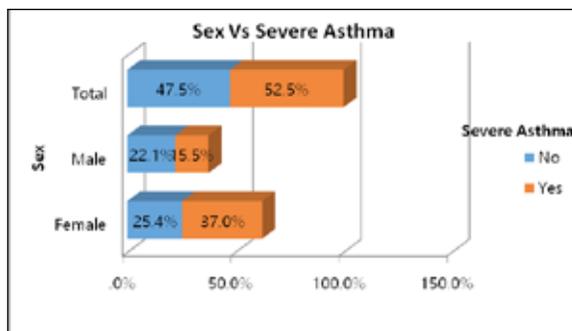
Results:

Total number of patients included in the study was 181 between the age group of 15 to 80 years. Mean age was 40.19years. Most of the patients belonged to the age between 26 to 55years of age.



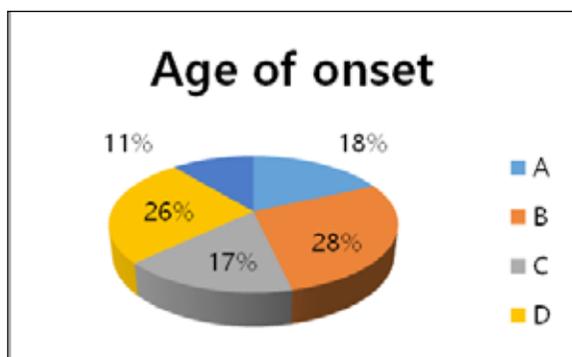
Graph showing age wise distribution of patients

Out of 181 patients, 113 (62.4%) were females and 68 (37.6%) were males. Out of 181 patients, 95 (52.5%) patients were having severe asthma. Out of 113 female patients, 67 (37%) had severe asthma and out of 68 male patients, 28 (15.5%) had severe asthma. Severe asthma was more common in females than in males which was statistically significant (p value <0.05).

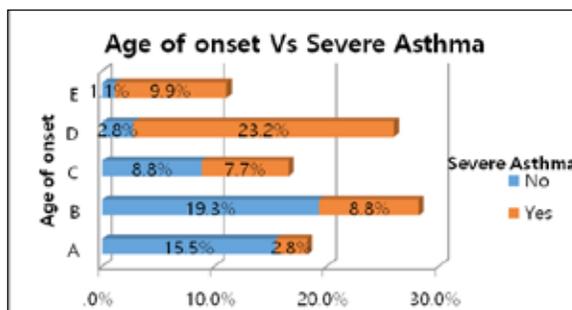


Graph showing comparison of prevalence of severe asthma among male and female patients.

Out of total 181 patients, 114 (62.9%) patients were early onset asthmatics, of which 35 (19.3%) patients had severe asthma. 47 (26%) had onset of asthma symptoms during the age between 20 to 40 years, of which 42 (23.2%) had severe disease. 20 (11%) patients had onset of asthma symptoms after 40 years of age, out of which 18 (9.9%) had severe asthma. Severe asthma was more common in adult and late onset asthmatics than in early onset asthmatics. Prevalence of severe asthma increased with increasing age of onset of asthma symptoms. This was statistically significant.



Pie diagram showing distribution of patients as per age of onset of asthma symptoms



Graph showing comparison of prevalence of severe asthma in early onset and adult or late onset asthmatics.

Discussion:

In our study most of the patients belonged to the age group of 26 to 55 years. Our study had more female patients (62.4 %) than male patients (37.6%). Studies have shown that the prevalence of asthma is higher in males than in females before adolescence as opposed to after adolescence where asthma is more common in women⁶⁻⁸.

Most of our patients were adults with female preponderance. In 1977, Wormald had reported incidence to be three times higher in males before 10 years of age which changed to 1.5 to 1.6 times higher in females in 3rd & 4th decade of life¹¹. Marco et al¹² did a cross sectional analysis of data of European Community Respiratory Health Survey in 2000, including 18000 subjects from 16 countries. All countries showed similar results with incidence of asthma 0.56 times lower in females at age of 5-10 years but 5.91 times higher in females after adolescence. An analysis of more than 260,000 asthmatic patients done by Osman et al from the General Practice Research Database also suggested reversal of sex ratio after adolescence¹³.

Role of female sex hormones progesterone and oestrogen has been linked to the more prevalence of asthma in adult females^{14, 15}. Progesterone increases secretion of IL-4 and oestrogen increases total IgE levels¹⁶. Testosterone in males is known to be protective against asthma. Risk of asthma decreases with the use of oral contraceptive pills and increases with Hormonal replacement therapy^{17, 18}.

The TRAILS (The Tracking Adolescents Individual Lives Survey) study done by Vink.N.M et al attributed this change in male to female ratio after adolescence to both increased incidence as well as decreased remission of asthma in females compared with males¹⁹.

In our study females had more incidence of severe asthma as compared to males, which is consistent with the findings that in adults, severe asthma is more common in women. All of our patients were above 15 years of age. Studies have shown that asthma related hospitalizations, emergency department visits, exacerbations, use of systemic steroids and asthma related mortality (all consistent with severity of asthma) were higher in females than in males after adolescence^{20,21}.

Schatz M et al²² showed that adult females with asthma had more outpatients and emergency department visits and used more oral corticosteroid than males. In a study done by Chen Y et al²³ the ratio of females versus males for hospitalization due to asthma were 2.8 in adults.

Patients hospitalized for asthma more than age 15 years are up to 3 times more likely to be females and those hospitalized for exacerbation at less than 15 years of age are up to 2 times more likely to be males²⁴. The differences in asthma prevalence before and after adolescence may be the likely reason for the differences in severity. Other factors considered are altered perception of airflow obstruction, female sex hormones, and gender specific differences in environmental exposure, comorbidities like obesity and those falling into adult onset asthma phenotype⁵.

In our study, severe asthma was more prevalent in adult/late onset asthmatics as compared in early onset asthmatics. Our study also showed that the prevalence of severe asthma increased in the study subjects with increasing age of onset of asthma symptoms. These results were consistent with earlier studies. In a study done by Ronmark E et al on outcome and severity of adult onset asthma, half of the patients had moderate to severe asthma²⁵. In a study by Marijke Amelink et al¹⁰, patients with adult onset asthma reported high symptoms scores, poor quality of life, need for high intensity treatment, low lung function and high exacerbation rate.

Severe Asthma Research Program (SARP), by cluster analysis of asthma patients, have recognized many phenotypes of severe asthma and adult onset asthma is recognized as one of them and most severe asthma phenotype also consisted majority of adult onset asthmatics⁵.

Adult or late onset asthma is considered when asthma symptoms start for the first time during adulthood⁵. Estimated incidence of adult onset asthma appears to be 4.6 cases per 1000 person years in females and 3.6 in males²⁶.

It is now recognized as distinct asthma phenotype with defining features like it is often non-atopic, lack of family history, persistent eosinophilic inflammation, associated with severe disease and faster decline in lung function, more common in females and associated with obesity⁵. These features indicate different underlying pathophysiological mechanisms compared with early onset asthmatics.

Some of the factors and triggers which appears to be associated with development of adult onset asthma are female sex hormones, workplace triggers (occupational asthma), environmental pollution including tobacco smoke, upper airway disease, aspirin intake, respiratory infections and stressful life events²⁷.

Specific phenotype driven treatment for adult onset asthmatics include Omalizumab for severe allergic asthma, mepolizumab, lebrikizumab for patients with persistent Eosinophilia, bronchial thermoplasty in non-eosinophilic asthma and bariatric surgery for obese adult onset asthmatics²⁷.

Indoor air pollution is an important cause for asthma²⁸. Smoke generated during domestic fuel is an important cause for asthma. In India most of the house hold work is done by females. Males rarely do any household work. Moreover females spend more time indoors compared to males. Hence we postulate that greater exposure to indoor pollution in females may be one of the important factors for increased incidence of asthma, severe asthma and late onset asthma being more common in females compared to males. Hence improving the indoor air quality may reduce the incidence and severity of asthma in females.

Conclusions:

1. Severe asthma is more common in females as compared to males.
2. Severe asthma is more common in adult/ late onset asthmatics as compared to early onset asthmatics.

References:

1. Global Initiative for Asthma. Global Strategy for Asthma Management And Prevention. Available at www.ginasthma.org 2014.
2. P Campo et al. Phenotypes and endotypes of Uncontrolled Severe Asthma: new Treatments. *J Investig Allergol Clin Immunol* 2013; Vol.23(2): 76-88.
3. Moore WC, Bleecker ER, Curran-Everett D, Erzurum SC, Ameredes BT, Bacharier L, Calhoun WJ, Castro M, Chung KF, Clark MP, Dweik RA, Fitzpatrick AM, Gaston B, Hew M, Hussain I, Jarjour NN, Israel E, Levy BD, Murphy JR, Peters SP, Teague WG, Meyers DA, Busse WW, Wenzel SE. Characterization of the severe asthma phenotype by the National Heart, Lung, and Blood Institute's Severe Asthma Research Program. *J Allergy Clin Immunol*. 2007;119(2):405-13.
4. Sally Wenzel. Severe Asthma in Adults. *Am J Respir Crit Care Med* 2005.172:149-160.
5. Moore WC, Meyers DA, Wenzel SE, et al. Identification of asthma phenotypes using cluster analysis in the Severe Asthma Research Program. *Am J Respir Crit Care Med* 2010; 181: 315-323.

6. Osman M. Therapeutic implications of sex differences in asthma and atopy. *Arch Dis Child* 2003;88:587-90.
7. Almqvist C, Worm M, Leynaert B, working group of GA2LEN WP 2.5 'Gender'. Impact of gender on asthma in childhood and adolescence: a GA2LEN review. *Allergy* 2008;63:47-57.
8. Chen W, Mempel M, Schober W, Behrendt H, Ring J. Gender difference, sex hormones, and immediate type hypersensitivity reactions. *Allergy* 2008;63:1418-27.
9. Jon G Ayres. Late Onset Asthma. *BMJ* 1990 June; 300: 1602.
10. Amelink M et al. Severe adult-onset asthma: A distinct phenotype. *J Allergy Clin Immunol* 2013;132:336-41.
11. Wormald PJ. Age-sex incidence in symptomatic allergies: an excess of females in child-bearing years. *J Hyg (Lond)* 1977;79:39-42.
12. de Marco R, Locatelli F, Sunyer J, Burney P. Differences in incidence of reported asthma related to age in men and women. A retrospective analysis of the data of the European Respiratory Health Survey. *Am J Respir Crit Care Med*. 2000;162:68-74. [PubMed]
13. Osman M, Hansell AL, Simpson CR, Hollowell J, Helms PJ. Gender-specific presentations for asthma, allergic rhinitis and eczema in primary care. *Prim Care Respir J*. 2007;16:28-35. [PubMed]
14. Salam MT, Wenten M, Gilliland FD. Endogenous and exogenous sex steroid hormones and asthma and wheeze in young women. *J Allergy Clin Immunol* 2006 May;117(5):1001-7.
15. van den Berge M, Heijink HJ, van Oosterhout AJ, Postma DS. The role of female sex hormones in the development and severity of allergic and non-allergic asthma. *Clin Exp Allergy*. 2009 Oct;39(10):1477-81. doi: 10.1111/j.1365-2222.2009.03354.x
16. Hamano N et al. Effect of female hormones on the production of IL-4 and IL-13 from peripheral blood mononuclear cells. *Acta Otolaryngol Suppl*. 1998;537:27-31.
17. Jenkins MA et al. Parity and decreased use of oral contraceptives as predictors of asthma in young women. *Clin Exp Allergy*. 2006 May;36(5):609-13.
18. Tan KS, McFarlane LC, Lipworth BJ. Modulation of airway reactivity and peak flow variability in asthmatics receiving the oral contraceptive pill. *Am J Respir Crit Care Med*. 1997 Apr;155(4):1273-7.
19. Vink NM et al. Gender differences in asthma development and remission during transition through puberty: the TRacking Adolescents' Individual Lives Survey (TRAILS) study. *J Allergy Clin Immunol*. 2010 Sep;126(3):498-504.e1-6. doi: 10.1016/j.jaci.2010.06.018
20. Harju T, Keistinen T, Tuuponen T, Kivelä SL. *Hospital admissions of asthmatics by age and sex*. *Allergy*. 1996 Oct; 51(10):693-6.
21. Prescott E, Lange P, Vestbo J. Effect of gender on hospital admissions for asthma and prevalence of self-reported asthma: a prospective study based on a sample of the general population. Copenhagen City Heart Study Group. *Thorax* 1997;52:287-289 doi:10.1136/thx.52.3.287
22. Schatz M, Camargo CA. The relationship of sex to asthma prevalence, health care utilization, and medications in a large managed care organization. *Annals of Allergy, Asthma & Immunology*. 2003 Dec; 91(6): 553-558.
23. Chen Y et al. Sex difference in hospitalization due to asthma in relation to age. *J Clin Epidemiol*. 2003 Feb;56(2):180-7
24. Kynyk JA, Mastrorade JG, McCallister JW. Asthma, the sex difference. *Curr Opin Pulm Med*. 2011 Jan;17(1):6-11. doi: 10.1097/MCP.0b013e3283410038.
25. Ronmark E et al. Outcome and severity of adult onset asthma-Report from the obstructive lung disease in northern Sweden studies (OLIN). *Respiratory Medicine* (2007) 101, 2370-2377.
26. Eagan TM et al. The incidence of adult asthma: a review. *Int J Tuberc Lung Dis*. 2005 Jun;9(6):603-12.
27. Selma B, de Nijs, Lisette N, Venekamp and Elisabeth H. Bel. Adult onset asthma: is it really different? *Eur Respir Rev* 2013; 22: 127, 44-52. Doi: 10.1183/09059180.00007112.
28. Indoor air pollution and asthma. Results from a panel study. B D Ostro, M J Lipssett, J K Mann, M B Wiener, and J Selner. DOI: <http://dx.doi.org/10.1164/ajrccm.149.6.8004290>