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Clinical Profile of Patients with Chronic Cough, Assessment of Feno Values and Corticosteroid Responsiveness

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Abstract: ***Background: Cough is the most common symptom for which patients seek medical attention. Estimates of prevalence of cough vary, but as much as 12% of the general population report chronic coughing defined as cough lasting for more than 8 weeks. Evidence suggests that the common medical conditions associated with chronic cough are Cough Variant Asthma (CVA), Upper Airway Cough Syndrome (UACS), Non Asthmatic Eosinophilic Bronchitis (NAEB), Gastro Esophageal Reflex Cough (GERC). Materials and Methods: A retrospective observational study was conducted in the Respiratory Medicine OPD of SRMS Bareilly which included 100 patients with chronic cough, with normal radiology and normal spirometry. Relevant information related to clinical characteristics was extracted and Fractional Exhaled NO levels were obtained in patients using the portable FENO device. Based on the FENO values, the HIGH FENO group was given an ICS LABA trial of 8 weeks, and then reassessed by repeating FENO testing. Results: out of 100 patients, 58 were males, 42 were females. The mean FENO values were 47.98ppb for males and 59.00 ppb for females.61 patients fell in the HIGH FENO group with a mean FENO of 71.2 +/-44.15 while 39 people were included in the LOW FENO group with mean FENO value of 14.92+/-6.55. Higher FENO values were seen in patients with associated allergy and recurrent URTI symptoms. Chronic/ ex smokers (11%) showed a higher FENO value as compared to non smokers (65.91ppb versus 48.38ppb). In this study, there was a significant decrease in FENO value after ICS LABA trial in the HIGH FENO group (67%) Conclusion: Study showed that FENO values may be used to diagnose and phenotype patients with chronic cough, HIGH FENO group was the steroid responsive group, shown by the decreased FENO values after ICS trial.***

Keywords: Chronic cough, Clinical characteristics, Eosinophil, Fractional exhaled nitric oxide

1.Introduction

Cough is a vital protective reflex preventing aspiration and enhancing airway clearance. However, pathologically excessive and protracted cough is a common and disabling complaint, affecting perhaps 5–10% of the adult population.

Cough is the most common symptom for which patients seek medical attention. Estimates of the prevalence of cough vary, but as much as 12% of the general population report chronic coughing, defined as a cough lasting for more than 8 weeks.

While a wide range of diseases may be associated with chronic cough, it has become increasingly clear that the majority of adult patients presenting with chronic cough as the primary complaint have a common clinical presentation. They often complain of exquisite sensitivity to inhalation of environmental irritants such as perfumes, bleaches and cold air which result in sensations of tickling/irritation in the throat and an urge to cough; features suggestive of heightened sensitivity of the neuronal pathways mediating cough. In addition, there is a unique epidemiology with two-thirds of patients being female and the peak prevalence in the fifties and sixties. These observations have led to the concept of cough hypersensitivity syndrome as a diagnosis.

2.Materials and Methods

This was a retrospective observational study conducted in Respiratory Medicine OPD of SRMS Bareilly.

The inclusion criteria included cough as the predominant or sole symptom lasting more than 8 weeks, no overt abnormality of chest imaging, a normal lung function test and age ≥ 15 years old. We excluded the patients with obvious dyspnea or wheeze, concomitant severe systemic diseases, any or lacking independent ability of answering the questions. Relevant information was extracted and analyzed, including demographics, duration, characteristics, timing, seasonality, concomitant symptoms, smoking status, as well as exposure history. Concomitant symptoms consisted of rhinitis/sinusitis-related, reflux, as well as respiratory symptoms (wheezing, dyspnea, chest tightness, etc.

Fractional exhaled NO levels was obtained in patients using the portable FeNO device and then assessed.

3.Statistical Analysis

Suitable statistical methods were applied after data collection procedure and were analyzed using Microsoft Excel and SPSS version 23.

Quantitative data was expressed in mean and standard deviation. Qualitative data was expressed in proportion and percentages. Independent t-tests were applied to compare means of quantitative data and chi-square test was used to compare categorical data. P-value < 0.05 was considered to be significant. Graphs were formed using Excel software.

4.Results

Out of 100, 58 patients were males and 42 were females. The mean FENO values were 47.98ppb for males and 51.00ppb for females.

Table 1: Gender distribution of Subjects

Sex	Frequency	Mean FeNO (ppb)
F	42	51.00
M	58	47.98
Total	**100**	**49.25**

Demographically, out of 100 patients, 61 patients fell in the HIGH FENO group with a mean FENO of 71.2+/-44.15 while 39 people were included in the LOW FENO group with a mean FENO of 14.92+/-6.55.

Table 2: Distribution of patients according to FeNO (High or Low)

FeNO	Frequency	Mean FeNO (ppb)
Low FeNO≤25	39	14.92±6.55
High FeNO≥25	61	71.2±44.15
Total	**100**	**49.25**

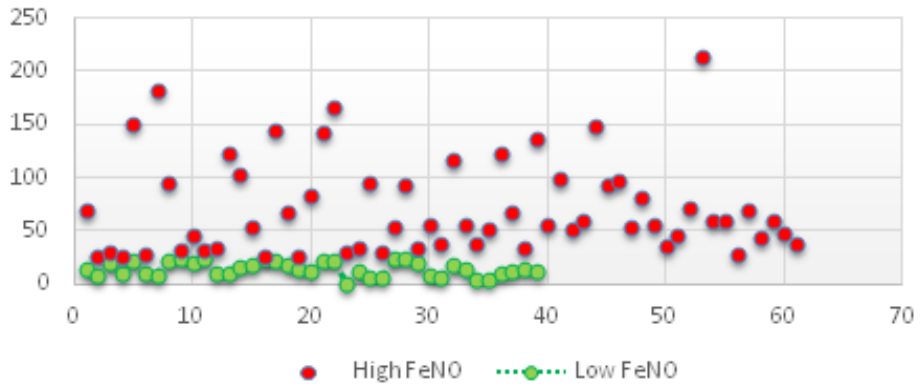

Figure 1: Distribution of patients according to FeNO (High or Low)

Overall, the highest FENO value (mean= 57.32) was seen in the age group of 30-39 years, while lowest FENO value were seen in the 60-69 years age group (mean= 24.83).

Table 3: Distribution of FENO as per age

Age	Frequency	Mean FeNO (ppb)
<20	5	50.40
20-29	34	46.44
30-39	19	57.32
40-49	19	55.74
50-59	10	41.00
60-69	6	24.83
70-80	7	55.29
Total	**100**	**49.25**

Among females, highest FENO values (mean=144, n=1) were seen in the age group of 59-68 years, while lowest FENO values (mean= 27, n =2) were seen in 39-48 years age group. The most common FENO value among females was 30 (n=6).

Among males, highest FENO levels (mean= 129.67, n=3) were seen in the age group of 29-38 years, while lowest FENO values (mean = 20, n= 1) were seen in the age group of <19 years. The most common FENO value among males was 52.33 (n= 6).

Current/ ex-smokers (11%) showed a higher FENO value as compared to non-smokers (65.91ppb vs 48.38ppb), showing a higher degree of airway inflammation in these subjects.

Table 4: Distribution of FeNO of Smokers (Yes/No)

SMOKER	Frequency	Mean FeNO
N	88	48.33
Y	11	65.91
Total	**100**	**49.25**

Among biomass fuel exposure, low FENO values were associated with patients who had a history of biomass fuel exposure (44.75ppb vs 49.64ppb).

Table 5: Distribution of FeNO of Biofuel Users (Yes/No)

BIOFUEL	Frequency	Mean FeNO
N	92	49.64
Y	8	44.75
Total	**100**	**49.25**

Based On the Symptomatology

- High mean FENO values were seen in patients with associated allergy (65.42 vs 45.46)
- Higher FENO values were also associated with productive cough (52.93 vs 38.20)
- The mean FENO was higher in patients presenting with seasonal variation of symptoms (57.68 vs 41.77)

Table 6: Distribution of subjects according to allergic symptoms

Symptoms	Response	Frequency n=100	Mean FeNO (ppb)
Cough	N	25	38.20
	Y	75	52.93
Cold	N	50	43.36
	Y	50	55.14
Sneezing	N	64	40.39
	Y	35	66.20
Breathlessness	N	29	48.38
	Y	71	49.61
Chest Pain	N	45	58.07
	Y	55	42.04
Fever	N	81	50.10
	Y	18	46.89
Expectoration	N	52	44.92
	Y	46	55.20
Associated Allergy	N	81	45.46
	Y	19	65.42
Recurrent Cold	N	50	42.28
	Y	50	56.22
Allergy to Dust	N	64	41.56
	Y	36	62.92
Seasonal variation	N	53	41.77
	Y	47	57.68

Based On Blood Eosinophils:

The mean FENO levels showed a positive association with blood eosinophils with highest FENO values seen in patients with maximum blood eosinophil counts (n=8, FENO=125), an important marker of inflammation.

Table 7: Distribution of FeNO in patients according to eosinophil count

Eosinophil count	Frequency	Mean FeNO (ppb)
0	6	37.67
1	10	23.20
2	14	23.00
3	9	44.11
4	11	42.73
5	12	67.42
6	13	79.15
8	3	125.00
22	1	60.00
30	1	43.00
N	20	48.10
Total	**100**	**49.25**

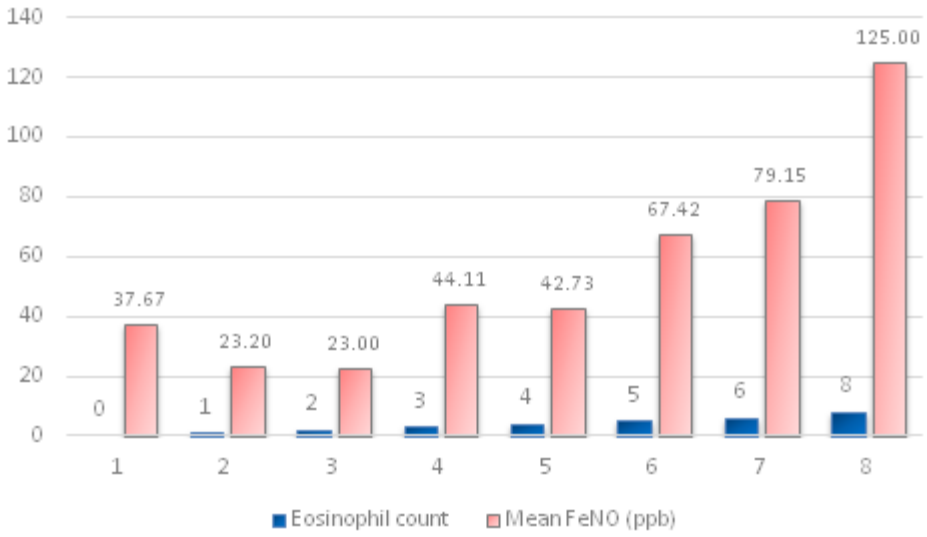

Figure 2: Effect of Eosinophil count on FeNO

5.Discussion

We have evaluated the demographic data, clinical features and blood eosinophils of 100 patients of chronic cough. Based on their FENO values the patients were divided into LOW FENO and HIGH FENO group.

In our study the mean FENO for females was more than for males (61.1+-56.73 vs45.3+-39.36) which was not in accordance to K W Tsang (exhaled nitric oxide the effects of age gender and body size).

The FENO values showed a positive association with blood eosinophils, an important marker of inflammation. Hence FENO levels can be used for the diagnostic utility of chronic cough as also shown in the study conducted by Zhonghua Jie He He Hu Xi Za Zhi (pub med-values of FENO in diagnosis and treatment of chronic cough).

The FENO levels also showed a positive co relation with associated allergies, and seasonal variation of symptoms.

Among smoking and biomass fuel exposure our study showed a positive association with smoking.

The patients (n=41) in the HIGH FENO group were given 8 weeks trial of ICS LABA. The mean value of FENO dropped for 84.8 to 560.31 post 8 weeks. This was in accordance with the study of EMAN SHEBI (assessment of the role of FENO as a predictor of airway inflammation).

Table 8: High FeNO after 8 weeks of intervention

High FeNO	Frequency	Mean±SD	p-value
Baseline FeNO	41	84.8±46.71	<0.001
FeNO after 8 weeks	41	60.31±32.27	

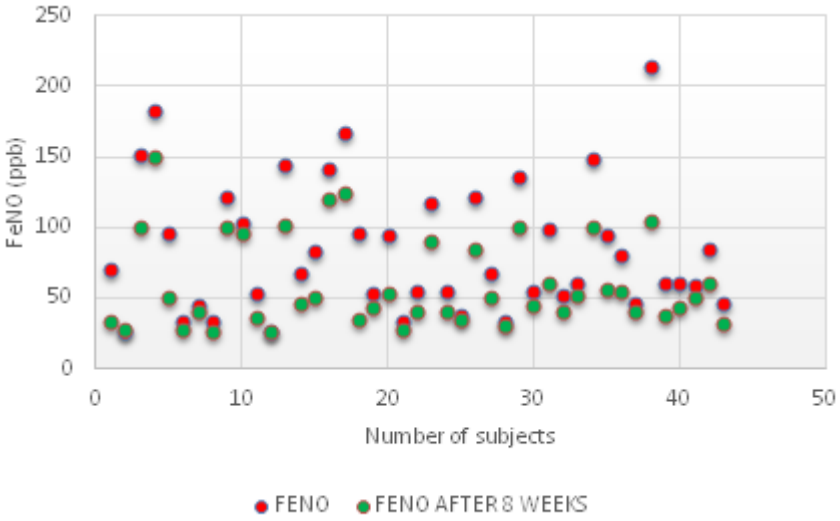

Figure 3: High FeNO after 8 weeks of intervention

Limitation of the study was the small sample size.

6.Conclusion

Our study showed that the patients with chronic cough.

1. Are mostly males, generally smokers or ex-smokers
2. Experience productive cough mostly
3. Are generally smokers or ex-smokers
4. Differential leucocyte counts demonstrate high eosinophil counts corresponding to high FENO values
5. Showed heterogeneity according to FENO level.

Since chest spirometry and Chest-xray of these patients are normal, FENO values may be used to diagnose and phenotype these patients and this may be of therapeutic relevance.

HIGH FENO group was the steroid responsive group shown by the decreased FENO values after an ICS LABA trial of 8 weeks.

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