The exacerbation risk prediction by fractional exhaled nitric oxide in younger and elder children with bronchial asthma

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ABSTRACT The usefulness of the Fractional exhaled nitric oxide (FeNO) measurements for asthma exacerbation risk prediction in asthmatic children is controversial. Fifty-seven asthmatic children who were regularly treated and had previously been stable for at least 3 months were enrolled. The asthma excerbations risk prediction by the FeNO levels and age contribution on it were investigated. As analyzed all the patients, FeNO cut off value for the significant risk of asthma exacerbation was 36.9 ppb (risk odds was 5.1 [95% C.I., 1.8 to 15.0], chi square valve = 9.0, p = 0.0028). However, sensitivity and specificity were not adequate for predicting asthma exacerbation (Sensitivity, 77.8%; Specificity, 59.9%; Area under the curve [AUC], 0.674). These parameters were improved only when 6-10 year old children were assessed (FeNO threshold=39.9 ppb, risk odds=10.2 [3.1 to 33.1], chi square valve 14.8, p=0.0001); Sensitivity, 80.8%; Specificity, 71.8%; AUC, 0.758). High value of FeNO is a risk factor for the asthma exacerbation, and FeNO measurement may be more useful for asthma control in younger children than elder asthmatic children. doi:10.11482/KMJ-E40(1)41 *(Accepted on December 24, 2013)*

Key words: **Childhood bronchial asthma, Fractional exhaled nitric oxide, Prediction of asthma exacerbation, Airway hyperreactivity test, Inhaled corticosteroid**

INTRODUCTION

Childhood bronchial asthma is a disease associated with wheezing during exacerbation and characterized by repeated episodes of dyspnea. The dyspnea in most cases is improved spontaneously or by treatment, otherwise, it can be fatal in rare cases. The persistent airway inflammation and remodeling are involved in the airflow limitation [1)]. Meansurement of fractional exhaled nitric oxide (FeNO), which is considered to reflect the eosinophilic airway inflammation, is simple and noninvasive and it can be performed easily even in children [2, 3)]. Asthma worsening and FeNO level in childhood bronchial asthma are correlated [4－9)].

Four randomized controlled trials (RCTs) examined the usefulness of FeNO as a marker for childhood asthma control, however, these have shown different conclusions, an achievement of

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favorable levels of bronchial hyper-responsiveness and forced expiratory volume in 1 second (FEV1) without increase of the inhaled corticosteroid (ICS) doses[10], no change in respiratory symptoms with increased ICS doses[11, 12], or no change in either respiratory symptoms or ICS doses[13]. Though no one can tell who will catch a cold beforehand, is it true if the airway inflammation level is higher, will the worsening of the asthma condition be increased? It might be difficult to predict asthma exarcebation by FeNO levels. For children, the impact of age should be considered, because the patterns of exacerbation are different between younger and elder children.

In the present study, we retrospectively examined if the high FeNO level is a significant risk factor of asthma exacerbation, divided by the age range.

METHODS

Subjects and methods

Fifty seven children with bronchial asthma (38 boys and 19 girls, range 6.0 to 15.0 years, median 9.2 years) who regularly attended the Department of Pediatrics, Kawasaki Medical School Hospital between July 2008 and March 2012 were the subjects. Bronchial asthma had been diagnosed by confirming dyspnea accompanied by recurrent wheezing and treated according to the 2012 Japanese Guidelines for Treatment and Control of Childhood Bronchial Asthma[1] (Table 1). The association between a total of 161 FeNO measurements obtained from the patients with their asthma were well controlled at least 3 months and subsequent asthma exacerbation in 3 months was retrospectively examined. Asthma exacerbations were defined as apparent wheezing or dyspnea confirmed by the children themselves and/or members of their families, according to an asthma diary. The presence or absence of allergic rhinitis was confirmed by medical records and/or the comments of family members of children. Treatment steps (mild,2; moderate,3; severe,4) were defined by ICS dosage according to the Japanese guideline. An airway hyperreactivity test was performed to determine the bronchial hyperesponsiveness. This study was approved by the ethics committee of our institution (409-1), and written informed consent was obtained from the parents of all the participated children.

FeNO measurement

FeNO levels were measured with the online method, using Nitric Oxide Analyzer NOA 280i (Sievers Instruments, Inc., Boulder, CO, USA). According to the guidelines recommended by the American Thoracic Society and European Respiratory Society, FeNO levels were measured in the resting-sitting position with conditions meeting respiratory resistance of 5-20 cm H_2O from maximal inspiratory level, respiratory flow of 0.05 L/sec ± 10%, and duration of at least 6 seconds[2]. At least 3

Table 1. Medication and treatment step of subjects

N	161
Treatment steps (/day)	
Step. 2	48 (30%)
LTRA	28
ICS 100 μg	13
ICS 100 μg + LTRA	7
Step. 3	54 (34%)
ICS 200 μg	11
ICS 200 μg + LTRA	17
SFC 50 μg	1
SFC 100 μg	19
SFC 100 μg + LTRA	2
BIS 0.5 mg + LTRA	4
Step. 4	59 (36%)
ICS 400 μg	7
ICS 400 μg + LTRA	2
SFC 200 μg	16
SFC 200 μg + LTRA	23
SFC 250 μg + LTRA	3
SFC 500 μg + LTRA	5
BIS 1 mg	1
BIS 1 mg + LTRA	2

Treatment Steps are based on JPGL 2012
LTRA: leukotriene receptor anatagonist
ICS: inhaled corticosteroid
SFC: salmeterol/fluticasone combination
BIS: budesonide inhalation suspension

measurements were conducted, and the mean within an error of 10% was used as the measurement result.

Airway hyperreactivity test

Bronchodilators are withdrawn 12 hours before the airway hyperreactivity test, and anti-inflammatory drugs, such as ICS, and histamine H_1 antagonists were withdrawn 24 hours before the test. Regarding the measurement procedure, FEV1 was first measured immediately before the test, and the value obtained was used as the reference FEV1. It should be confirmed that FEV1 measured after inhalation of physiological saline for 2 minutes was not decreased by 10% or more from the reference FEV1. Then, FEV1 was measured after inhalation of solutions containing various concentrations of acetylcholine for 2 minutes each, starting from the lowest concentration solution. The solution concentration at which the measured FEV1 was decreased by at least 20% was determined as PC_{20} from single logarithmic charts. Less than 8 mg/ml of PC_{20} was considered as positive bronchial hyperresponsiveness.

Statistical analysis

The Mann-Whitney U and χ^2 tests were used for comparisons of each factor between the 2 groups (with and without exacerbation), and the χ^2 test and correlation analysis were used for analyzing other factors affecting FeNO levels. Moreover, the FeNO cut-off level for the prediction of asthma exacerbation was calculated employing a receiver operating characteristic (ROC) curve. The criterion for a statistically significant difference was $p < 0.05$.

RESULTS

The mean (SD) FeNO was significantly higher in the children who had exacerbation within 3 months than those who did not (49.8 (24.1) vs. 37.0 (24.1) ppb, $p = 0.017$) (Table 2). Mean values of age, disease duration, ratio of male-to-female, the atopic status, concomitant allergic rhinitis, or severity at the time of measurement, or PC_{20} were not different between the groups (Table 2).

The ROC curve analysis revealed that the best FeNO cut-off level suggested the significant increasing risk of asthma exacerbation was 36.9 ppb. The sensitivity, specificity, and area under the curve (AUC) were 77.8%, 59.9%, and 0.674, respectively, however none were considered to be sufficiently high for clinical application (Fig. 1). The risk odds of asthma exacerbation was 5.1 (95%C.I., 1.8 to 15.0, chi square = 9.0, $p = 0.0028$).

A positive correlation was observed between age and FeNO levels ($p < 0.001$, $r = 0.326$) (Fig. 2). There was no significant correlation between the duration of asthma and FeNO levels ($p = 0.396$, $r = 0.068$). There was no significant difference in FeNO levels between children with and without allergic rhinitis (34.43 (23.86) vs. 42.24 (27.95) ppb, $p = 0.078$).

Because there was a significant correlation

Table 2. Comparison of the characteristics between the 6-15 years old children with and without exacerbations in 3 months

	With exacerbation (n = 18)	Without exacerbation (n = 143)	P value
Age, years, mean (SD)	8.83 (2.00)	9.79 (2.36)	0.095
Disease duration, year, mean (SD)	4.26 (2.29)	4.48 (2.29)	0.925
Sex (M/F)	13/5	87/56	0.445
Atopic/non-atopic	17/1	132/11	0.740
Allergic rhinitis, yes (%)	9 (50)	77 (53)	0.758
Treatment step, Step 2/3/4	7/7/4	41/47/56	0.408
FeNO (ppb)	49.8 (24.1)	37.1 (24.1)	0.017

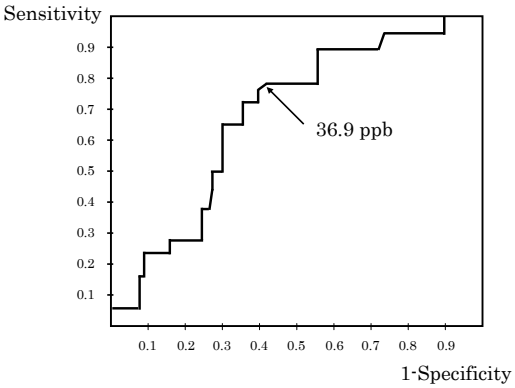

Fig. 1. ROC curve of FeNO for asthma exacerbation risk in 6-15 year old patients.
The best FeNO cut-off value was 36.9 ppb (Sensitivity, 77.8%; Specificity, 59.9%; AUC, 0.674; Risk Odds 5.1 [1.8 to 15.0, chi square=9.0, p=0.0026]).

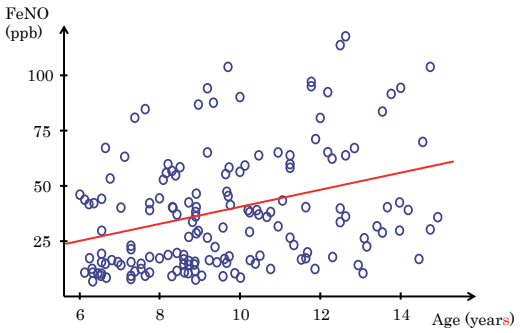

Fig. 2. Correlations between age and FeNO in asthmatic children.
There was a significant correlation between age and FeNO in asthmatic children ($p < 0.001$, $r = 0.326$).

Table 3. Comparison of the characteristics between the 6-10 years old children with and without exacerbation in 3 months

	With exacerbation (n = 15)	Without exacerbation (n = 85)	P value
Age, years, mean (SD)	8.14 (1.11)	8.16 (1.16)	0.915
Disease duration, year, mean (SD)	4.09 (2.48)	4.46 (1.90)	0.592
Sex (M/F)	11/4	57/28	0.631
Atopic/non-atopic	14/1	74/11	0.491
Allergic rhinitis, yes (%)	8 (53)	43 (51)	0.845
Treatment step, Step 2/3/4	5/6/4	29/30/26	0.903
FeNO (ppb)	49.9 (27.7)	30.0 (22.6)	< 0.001

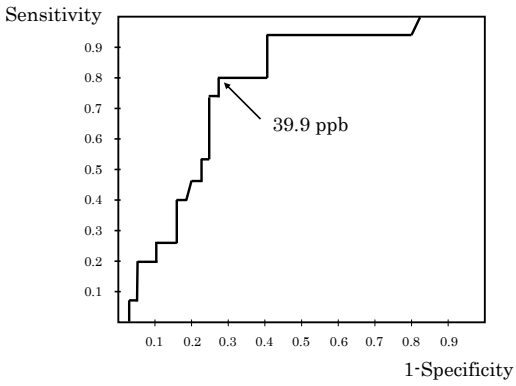

Fig. 3. ROC curve of FeNO for predicting asthma exacerbation in patients 6-10 years old.
The best FeNO cut-off value was 39.9 ppb (Sensitivity, 80.0%; Specificity, 71.8%; AUC, 0.758; Risk Odds 10.17 [3.1 to 33.1, chi square=14.8, p=0.0001]).

between FeNO levels and age, the usefulness of FeNO for increasing risk of exacerbation was re-examined by limiting the subjects to children between 6.0 and 10.0 years of age (a total of 100 measurements) (Table 3). The FeNO levels were significantly higher in the children had exacerbation than those did not (49.9 (27.7) vs. 30.0 (22.6)ppb, $p < 0.017$). No significant differences were observed in any other factors. The ROC curve analysis revealed the best FeNO cut-off level for the asthma exacerbation risk to be 39.9 ppb. The sensitivity, specificity, and AUC were 80.8%, 71.8%, and 0.758, respectively, all of them were favorable (Fig. 3). The risk odds of asthma exacerbation was 10.2 (3.1 to 33.1, chi square = 14.8, $p = 0.0001$).

DISCUSSION

In this study, we found that high FeNO more than 36.9 ppb was a significant risk of asthma exacerbation in the following 3 months in children with stable bronchial asthma up to 5 times and this tendency was prevalent in the younger children (6 to 10 years of age than 11 years or more). However, the sensitivity and specificity were not sufficiently high (77.8% and 59.9%, respectively). Because we found that FeNO levels correlated with age ($p < 0.001$, $r = 0.326$), the analysis was repeated by limiting the subjects to children between 6.0 and 10.0 years of age. The results suggested that higher FeNO was a more significant risk factor (10.2 times) for asthma exacerbation in 3 months in younger children. The sensitivity and specificity of the recalculated cut-off level (39.9ppb) were favorable at 80.0% and 71.8%, respectively. The patient age ranges were broad, from 6 to 18 years in two previous RCTs conducted by Marielle *et al*.[9] or Fritsch *et al*. [10], from 12 to 18 years in an RCT conducted by Szifer *et al*.[11], and from 6 to 12 years in an RCT conducted by Jongste *et al*.[12], only in the latter RCT had different FeNO cut-off levels set: 20 ppb for the patients less than 10 years of age versus 25 ppb for those aged 10 years and older. FeNO levels were reported to be higher in older children[14]. Our study had shown similar results which was understandable.

Although FeNO can be a risk factor of asthma exacerbation in children before puberty, it might not be the same for pubertal patients. A similar indication was reported in a study that the airway hyperreactivity test could predict the course of asthma in children from 5 up to almost 11 years of age, but that it was difficult to predict the disease course in those between 12 and 16 years of age[15]. The exact reason is not clear, however, we speculate that older children may possess more extensive reasons for asthma exacerbation.

The first discrepancy of the study was that we did not find FeNO level differences between the children with and without allergic rhinitis ($p=0.07$). FeNO is elevated by not only bronchial asthma, but also viral infections[16–18], allergic rhinitis[19], and so on. Generally, bronchial asthma and allergy rhinitis are comorbid in about 80% each other[20, 21], our subject asthma children had allergy rhinitis in only approximately 50%. This might affect the FeNO levels and threshold also. No difference in FeNO levels between asthmatic patients with and without hay fever was reported[22]. The effect of allergic rhinitis on FeNO level is still controversial. The second inconclusive area was that the study was not performed in a prospective manner. We should have planned a prospective study, but we were not aware the adequate subject number and follow up periods. Therefore, we are now planning a prospective comparative study which set cut-off value in 39.9 according to this study results.

In conclusion, our results suggest that FeNO measurement may be useful for the consideration of predicting asthma exacerbation risk and the increase of risk is more significant in pre-pubertal children. Additionally, we may have to pay attention to worsening of asthma symptoms when child with asthma has high FeNO level.

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