Airway inflammation in asthmatic children

本村知華子

国立病院機構福岡病院小児科

（日小誌 2011;25:712-718）

はじめに

日韓交換講演者のお話を頂いたのは、2010年早春ではなかったがかと記憶しております。2011年10月第48回日本小児アレルギー学会が第16回アジア太平洋小児アレルギー呼吸器免疫学会（Asia Pacific Association of Pediatric Allergy, Respirology and Immunology: APAPARI）と福岡で合同開催されることはすでに決定しております。われわれは13年前内科医の夫の留学に伴ってカリフォルニアで2年間生活したものので、産子育てに終始し、自分自身には留学経験がなく、韓国語はもちろん英語での講演に自信ありませんでした。数年前からアメリカ胸郭疾患学会への参加をしていましたが、アジアにおける小児アレルギー医療という視点がないわたしに、小川会長は国際経験に乏しい若手アレルギー小児科医が韓国アレルギー小児科医と交流することの重要性を話され、計3回ソウルに行こうと依頼してくださいました。よってこのソウルへの旅が実現したのです。5月になりますと、KAPARDのDirectorでありますJin-Tack Kim先生からご連絡を頂き予定を打ち合わせました。

2010年10月23日Young-Yull Koh会長（Seoul National University Hospital）のもと、ソウルのSheraton Grand Walkerhill hotelでKAPARD学術集会は開催されました。この集会は秋季大会にあたり、2招待講演とシンポジウムで構成されていました（写真1）、もう一つの招待講演では紀太博仁先生（メイヨー医科大学内科学教授）が主にIL-33の新しい知見について話されました。
1. Airway inflammation in the pathogenesis of asthma

First, I’ll give a brief introduction on airway inflammation in the pathogenesis of asthma. As you can see, Asthma is a chronic inflammatory disorder of the airways. The chronic inflammation is associated with airway hyperresponsiveness that leads to recurrent episodes of coughing, shortness of breath, wheezing, chest tightness, and secretions. These episodes are usually associated with airflow obstruction within the lung that is often reversible with treatment. The presence of airway inflammation remains a consistent feature. In Fig. 1, I’ll show the pathogenesis of asthma from childhood to adolescent period. In childhood asthma, almost all of first exacerbation occurs till three year old. The clinical spectrum of asthma consists of three components, airway inflammation, airway responsiveness and airflow limitation. The airway inflammation in asthma is persistent even though symptoms are episodic. We can use the fraction of nitric oxide in exhaled air (FeNO) as a marker of eosinophilic airway inflammation. Airway responsiveness reflects the “sensitivity” of the airways. Airflow limitations are characteristic structural changes as airway remodeling. Spirometry is the method of measuring airflow limitation and reversibility for a diagnosis of asthma. I’ll introduce measurements of airway responsiveness to direct airway challenges such as inhaled agents for example, methacholine, acetylcholine or histamine. We usually measure airway responsiveness by acetylcholine provocation test for asthmatic children. The test results are usually expressed as the provocative concentration of acetylcholine causing a 20% decrease in FEV1.

2. The biology, measuring and characteristics of the fraction of nitric oxide in exhaled air (FeNO)

Now, I’d like to show you the biology of Nitric oxide (NO). NO is a reactive, free radical gas, and forms in the airways when L-arginine is oxidized to L-citrulline. This reaction is catalyzed by the NO-synthases (NOS), of which three distinct isoforms exist. Constitutive NOS, it consists of two forms; neuronal NOS and endothelial NOS. The expression of inducible NOS (iNOS) is increased in inflammatory states induced by proinflammatory cytokines and endotoxin. Corticosteroids inhibit induction of
iNOS in epithelial cells. In the presence of oxygen, NO will be mostly converted to the end-products nitrite (NO\(^2\)) and nitrate (NO\(^3\)). NO may increase as a result of acid-induced NO evolution from nitrite during acute asthma exacerbations. Nitrite is an important storage for NO. NO reacts quickly with super oxide (O\(^2^-\)) to form peroxynitrite (ONO\(^-\)). And NO reacts with cysteine to form S-nitrosothiols. Both of them may again release NO and act as carrier or storage for NO.

I'll show you Single breath online exhaled NO Measurement. For the high nasal NO levels relative to the lower respiratory tract. We need slowly exhalating orally against a resistance for single breath online exhaled NO measurement the exploratory pressure is maintained between 5 and 20 cm H\(_2\)O to ensure velum closure. Here you can see single breath on-line method by Sievers, NOA280, chemiluminescence analyzer. An expiratory flow rate of 50 ml/s and a 2-s plateau duration should be used for children. Repeated exhalations are performed until three NO plateau values agree at the 10% level.

3. The effect of age in relationship between FeNO and airway hyperresponsiveness (AHR) in asthmatic children and adolescents

I'm going to look at what is the effect of age on relationship between FeNO and airway hyperresponsiveness in asthmatic children and adolescents. I'll show you these figures from Dr. Van den Toorn's report\(^1\). Adolescents in Clinical Remission of atopic asthma have elevated exhaled Nitric Oxide levels and bronchial hyperresponsiveness. The remission group have lower bronchial responsiveness than the asthma group. But both of the asthma and remission groups have high FeNO levels. In other words, there is persistent airway inflammation during clinical remission of atopic asthma. I'll introduce Dr. Strunk's report\(^2\) “mild to moderate asthma affects lung growth in children and adolescents.” in 2006 from CAMP study. These are boys FEV\(_1\) and FVC velocity. At 14 years old, boy's lung growth is at its peak. The right side shows girls FEV\(_1\) and FVC velocity. At 12 year-old, girl's lung growth is at its peak. Girl's peak is lower than boy's one. Here, you can see airway responsiveness increased with age, with boys having a greater increase after the age of 11 years than girls. Airway responsiveness is more severe in the postpubertal female with asthma than in males.

Now, I'd like to show you data from our recent study, "Effect of Age on Relationship Between Exhaled Nitric Oxide and Airway Hyperresponsiveness in Asthmatic Children\(^3\)". The objective is to determine the effects of age on the relationship between FeNO and AHR in asthmatic children.

Methods: Airway hyperresponsiveness (AHR) was examined in 267 asthmatic patients (age range, 5 to 20 years). A challenge test was performed using acetylcholine chloride (Ach). We determined the provocative concentration of Ach producing a 20% decrease in FEV\(_1\) from baseline (PC\(_{20}\)), FeNO was examined using the recommended online method before the Ach challenge test. The two groups children and adolescents exhibited similar disease onsets, gender, prevalence of received inhaled corticosteroids (ICS), numbers of nonatopic cases and total serum IgE values. Among adolescents, the duration of disease was longer than that among the children (9.7 years vs 6.2 years). Lung function and the AHR (PC\(_{20}\)) was not significantly different between the two groups FeNO value was also significantly higher among the adolescents than among the children (54 ppb vs. 36 ppb).

Now, I'd like to show you the relationship between AHR (PC\(_{20}\)) and FeNO among children (A) and adolescents (B). Among the children, decreasing AHR (PC\(_{20}\)) was associated with higher FeNO (Fig. 2-A). In contrast, among the adolescents, decreasing AHR (PC\(_{20}\)) was associated with higher FeNO weakly (Fig. 2-B). What does Fig. 3 tell us about the relationship between AHR (PC\(_{20}\)) and baseline lung function in terms of FEV\(_1\) percentage of predicted among children and adolescents? Among the children, the AHR (PC\(_{20}\)) was not associated with the FEV\(_1\) percentage of predicted (Fig. 3-A). Fig. 3-B shows, among the adolescents, the AHR (PC\(_{20}\)) was significantly related with the FEV\(_1\). I'd like to draw
your attention to the difference between children and adolescents. First, in children with asthma, AHR is associated with airway inflammation. AHR in children with asthma may consist of variable components mainly reflecting airway inflammation. Second, in adolescents with asthma, AHR is associated with airway structural changes and weakly with airway inflammation. AHR in adolescents with asthma may consist of chronic components mainly reflecting airway remodeling.

4. How to use FeNO for diagnosis and treatment in childhood asthma

Finally, I’ll focus on how we can use FeNO for diagnosis and treatment in childhood asthma.

This slide shows possible applications of FeNO measurements in pediatric asthma.

- Screening for asthma in epidemiological studies
- Diagnosis of eosinophilic airway inflammation
- Predicting response to steroids
- Evaluation of response to steroids (inhaled or systemic), LTRA. Other
Children with asthma,
AHR ↔ airway inflammation.

Adolescents with asthma,
AHR ↔ airway structural changes
↔ airway inflammation.

Consider growth stage of asthmatic children
Their each own optimal index
for their asthma control.

Children → FeNO
Adolescents → spirometry and FeNO

Fig. 4 Summary

- Selection of treatment modalities additional to ICS (e.g. LABA or LTRA)
- Predicting asthma exacerbations
- Predicting asthma relapse after clinical remission
- Adherence check
- Dose titration of ICS

FeNO is useful tool for diagnosis, management of asthmatic children.

Summary (Fig. 4)

What can we summarize from these studies?
These results tend to show that it is necessary to consider growth stage of asthmatic children. Choice their each own optimal index (for example, FeNO for children, spirometry and FeNO for adolescents) for their asthma control.

文献

日韓招待講演を終えて

講演前日にソウルに到着したのですが、夕食会に招待頂き、2010年度の日韓交換講演者であるSooyoung Lee先生をはじめ、KAPARDの先生方、敬具先生のご夫婦とご一緒しました。韓国焼肉はおいしく、初対面ながら日本語、英語、韓国語が飛び交い楽しい時間でした。韓国の食文化、植物の分布は隣国だけあって日本と類似しており、食物アレルギー、花粉症など共通点が多く見られます。おでん、ラーメン、うどんなど食品名が日本と同じであることを知りました。KAPARDの先生方のプライベートや子育てについても聴きしました。みなさんの留学経験を持ち、お子さんはほとんどアメリカ合衆国で大学生活を送っているそうです。女医の場合、家庭ではヘルパーさんが家事、子育てを助けてくれ、勤務を
写真 2 昼食会

写真 3 会場風景

続けることが当たり前のようです。

翌日に昼食を日本料理店で御一緒しました（写真2）。右から座長を務めて頂いた Sang-II Lee 先生、紀太先生、筆者、Young-Yull Koh 会長、韓国児科学会会長、Ha-Baik Lee 先生です。講演後は若手の先生から積極的に質問をして頂きました（写真3）。懇親会では、Ha-Baik Lee 先生のもと呼気中 NO と運動誘発喘息をテーマに研究しておられる Hey-Sung Baek 先生に質問して頂きました。Hey-Sung Baek 先生は11月に シンガポールで行われた APCAACI, APAPARI 合同大会で再会し、こちらからも質問し有意義でした。また数年前に当科に研修
に来られていた Tae Won Song 先生とお話でき楽
しい時間を過ごしました。
途中ソウル市中に買い物に連れて行ってもらいま
した。ソウル市は中央を漢江（ハンガン）が流れて
おり、南岸は豊かな地域。北岸は庶民的地域になっ
ているそうです。初めての韓国訪問で 3 日間という
短い期間でしたが、文化的には韓国は日本とアメリ
カの中間にある国との印象を受けました。今回の旅
で隣の国、韓国を深く知りたいという興味が生まれ、
また訪れたい国となりました。

おわりに

日韓交換講演という重要な国際交流の機会を与え
てくださいました日本小児アレルギー学会理事長の
近藤直美先生、第 48 回会長の小田鷹博先生に深謝い
たします。今回、若手小児アレルギー医が日本国内
だけでなくアジアだけでなく世界へとグローバルな視
点を早くから持つことの重要性を実感しました。こ
のような国際的プログラムを続けていく、若手アレ
ルギー小児科医が国内外で交流活躍されることを希
望します。まずは来年福岡で開催される
APAPARI に参加し、韓国をはじめアジアからの参
加者と顔を合わせてディスカッションをしましょ
う。皆様の参加をお待ちしています。