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第6回日本職業アレルギー学会開催予告

1．会　　期：平成10年7月16日（木）～17日（金）

2．会　　場：名古屋国際センター

〒450-0001　名古屋市中村区那古野1丁目47番1号

TEL：052－581－5678　　FAX：052－581－5629

3．参 加 費：10,000円（懇親会費を含む）

4．演題申込み

（1）演題申し込み方法：

①抄録原稿送付をもって演題申し込みとします。

②演題受け付けには、発表者が学会員であることを要します。

（非会員の場合には、学会入会手続をお願いします）

（2）演題申し込み締め切り日：

平成10年5月6日（水）必着

（3）演題申し込み先；〒461-0047　名古屋市東区大幸南1-1-20

名古屋大学医学部環境皮膚科学講座内

第6回日本職業アレルギー学会事務局

事務局長　加藤佳美　宛

TEL：052－719－1983　　FAX：052－719－1984

5．講演抄録原稿

同封の講演集原稿作成要項にしたがって、指定の抄録用紙を使用し作成して下さい。

（原本にコピー2部を添えてご送付下さい）

6．特別企画

（1）会長講演　「職業アレルギー性皮膚炎の診断と予防」

早川　律子（名大・医・環境皮膚科）

（2）特別講演　「職業性ラテックスアレルギーの実態」

Ian Richard White (Guy's and St.Thomas Hospital)

（3）シンポジウム「アジアにおける職業アレルギー性皮膚疾患」

日　　本	東　禹彦（堺病院　皮膚科）
韓　　国	Hyung-Ok Kim (Kangnam St.Mary's Hospital)
シンガポール	David Koh (The National University of Singapol)
台　　湾	Chung-Hsing Chang (Kaohsiung Medical College)

7．懇 親 会

日　　時：平成10年7月16日（木）18：00～20：00

場　　所：ホテル　キャッスルプラザ

〒450-0002　名古屋市中村区名駅4-3-25

TEL 052－582－2121

会　　費：参加費に含まれる

8．スケジュール

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	13：00～14：00	評議員会
	14：00～16：40	一般演題
	16：40～16：50	休　憩
	16：50～17：30	特別講演
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	10：20～11：30	一般演題
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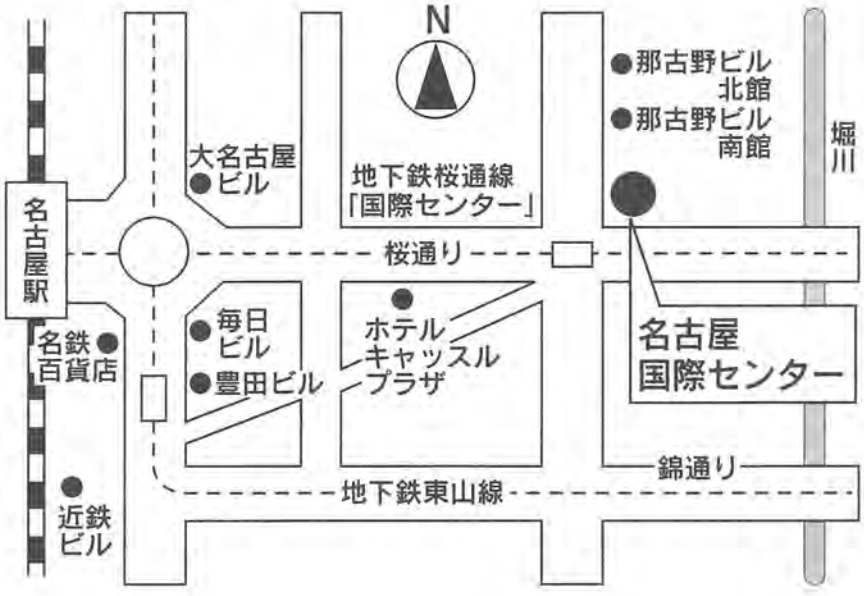
	13：30～16：00	シンポジウム

9．交通機関

（1）ＪＲ新幹線「名古屋駅」下車後　地下鉄　桜通線
今池方面乗車、次駅「国際センター」下車　徒歩２分
（またはＪＲ名古屋駅より徒歩７分）

（2）飛行機　名古屋空港よりリムジンバスにて「名古屋駅」下車後
地下鉄　桜通線　今池方面乗車次駅「国際センター」徒歩２分
（またはＪＲ名古屋駅より徒歩７分）



会長講演

化学物質に起因するアレルギー反応の予測

Prediction of allergy induced by chemicals

松下　敏夫

鹿児島大学医学部衛生学講座

Abstract

To prevent the outbreak of allergic diseases from chemicals being introduced to our human society, the development of effective preventive procedures to predict their health risk from those chemicals is necessary.

The author present about recent progress in various procedures to predict allergic potentiality, especially for allergic contact dermatitis, and discussed on the related preventive countermeasures.

Key words:chemical allergy, prediction, prevention

はじめに

近年の産業構造の変化や科学技術の急速な進歩に伴い，わが国でも，毎年，1,000種以上にも及ぶといわれる新規の化学物質が次々と登場し，生活の場にも導入されてきている．これらの化学物質の中には，DDTやPCBなどのように，その毒性によって，社会に極めて深刻な問題を惹起する物質も少なくない．感作性物質に関しても，同様である．従って，人類が，新たな化学物質を開発・使用するに当たっては，事前に，その適切なリスク・アセスメントを行い，予想されるリスク・ハザードに対して適切な管理を行うことが不可欠である．

アレルギーは，免疫学的には，抗原－抗体反応に起因する過敏反応による生体への傷害であるが，アレルギー疾患の発生は，疫学的には，感受性のある個体（感受性者：host）に対して，抗原となり得る物質（感作要因：agent)が，特定の環境要因（曝露条件下：environment)において作用し，抗原の関与及び誘因・交絡因子の引き金によって，発症すると考えることができる．これらの関係を，近年急増しているアレルギー性疾患の発症に関わる疫学的要因として整理すると，図1のごとく示すことができよう．

アレルギー発症の予測とその対策樹立のためには，これら諸要因の具体的な内容を明らかにし，それらの相互の係り合いを明確にすることが不可欠である．このうち，アレルギーの発症に係る感受性者の問題（遺伝素因など）につい

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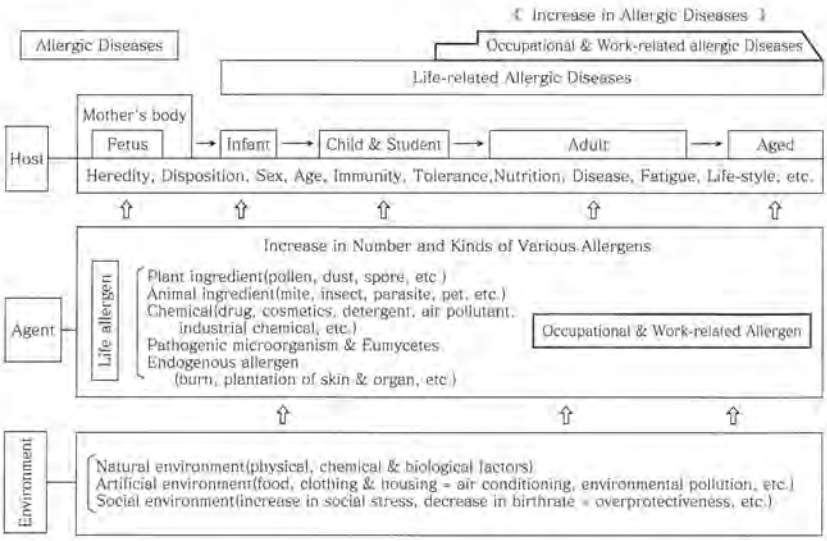

Fig.1 Epidemiological factors related to the outbreak of allergic diseases

ては，人の全遺伝子を明らかにするというヒトゲノム計画が進行中で，次々と新しい遺伝子が単離され，それらの性状が明らかにされつつある．また，アレルギーの予防に影響を与える人のライフスタイルや遺伝素因の重要性についての研究も，近年，急速な進歩が認められている[1,2]．

そこで，ここでは，予防医学の視点から，化学物質を例にして，主として抗原となり得る要因（agent）の問題，即ち，感作物質のリスク・アセスメントの問題と，アレルギー反応が惹起される曝露条件に係る問題について焦点を絞って述べることにしたい．

Ⅰ．抗原となり得る化学物質の問題

感作性物質に係る有害性の評価，即ち，リスク・アセスメントは，(1) 当該物質の感作能の有無とその程度を明らかにすること，(2) その物質の職場や社会における使用の範囲の広がりの状況を明らかにすることに大別できる．そこで，先ず，化学物質の感作能の有無とその程度を明らかにする問題について述べる．この際，アレルギー反応は，気道・鼻腔・皮膚など種々の場で認められるが，ここでは，皮膚におけるⅣ型アレルギー，即ち，アレルギー性接触皮膚炎（接触アレルギー）を中心にして考えてみたい．

接触アレルギーのリスク・アセスメントの方法に関しては，古くは1885年にJadassohnがアレルギー性接触皮膚炎の概念を確立して以来，モルモットを用いた接触アレルギーの実験モデルの開発[3]を始め，化学構造と生物活性の相関に関する研究を中心にして，多くの手法が開発され，推奨されてきている．

化学物質によるアレルギー反応では，化学物質の多くが低分子の化学物質であるため，haptenとして蛋白などcarrierと結合して抗原を生成し，アレルギー反応を惹起する．また，皮膚感作性物質は、皮膚の角質層を通過し，抗原提示細胞に取り込まれ，次いで，代謝を受けて反応性の高いハプテンとなる．あるいは，代謝の過程を迂回してハプテンとなることもある．従って，皮膚感作性の最も基本となる化学

的性質は，(1) 母物質あるいはその細胞で代謝された産物の，生体の高分子物質で最も抗原となり易い蛋白質との反応性の高低と，(2) 抗原－抗体反応の場への到達し易さ，即ち，皮膚の透過性の2つである．また，接触アレルゲンによる発症過程は，感作段階と誘発段階に分けられ，アレルゲンの性状のみならず，曝露量が，その発症に大きな影響を及ぼす．

健康のリスク・アセスメントの手法と評価

健康のリスク・アセスメントの基本的な手法としては，(1) 有害性の確認（ハザードの同定・確認），(2) 量－反応関係の評価，(3) 曝露評価（曝露経路・様式），(4) リスク判定（リスクの種類・大きさ）がある[4,5]．リスク・アセスメントの健康影響の評価法には，(1) 動物実験法，(2) 疫学的調査研究法，(3) ボランテイアを対象とした実験室内研究法，などがある．

これを，接触アレルギーの場合を例に，化学物質による感作性リスク・アセスメントの情報源として考えると，(1) ヒトへの感作物質の曝露成績（a.症例及び疫学的資料，b.ボランテイア対象の試験成績），(2) 感作能の動物実験成績，(3) 感作能のin vitro試験成績，(4) 感作能の化学構造－アレルギー作用関係からの理論的解析乃至推論，に大別することができる．このうち，症例及び疫学的成績については，化学物質が既に社会や職場に導入された後の検討であり，また，ボランテイアを対象とした試験成績は，倫理上，その適用には，おのずと限界がある．従って，アレルギー発症の事前の予知・予測の方法としては，(2)～(4)が中心とならざるを得ない．

アレルギーのリスクの予測・評価のためには，感作の成立及び誘発のメカニズムの解明が不可欠ではあるが，この場合，従来の動物を用いた試験法，in vivo試験法のみならず，最近は，サイトカイン・プロフィール解析の応用など，新たな手法の開発も種々試みられている．

接触アレルギーの予知法[6]

(1) in vivo試験法

接触アレルギーの試験法としては，モルモットを使用した方法が一般的である．これは，その感作処置法から，(1) 表皮塗布法（Buehler test (BT)[7,8],Open epicutaneous test[9]，など），(2) 皮内投与法（Draize法(DT)[10],完全フロイントアジュバント法[9,11]，など），(3) 両者併用法（Maximization test (GPMT)[12,13]，Split adjuvant technique (SAT)[14],Optimization method[15]，など）に分類され，汎く用いられている[16]．また，マウスを使用した試験法[17]としては，耳介肥厚試験（Ear Swelling test）[18]，Local lymph node assayなど，種々のものが試みられてきている．

動物を用いた皮膚感作試験法としては，古くは，モルモットを用いたDraize法[10]があるが，これは操作方法は簡単ではあるが，ヒトの反応性を予知するには，感度が劣ることが知られており，その改良法として，種々の方法が考案されている．

我々も，接触感作性に関する各種の試験法についての検討を行った[19]．因に，接触感作性を有すると思われる若干の農薬を試験物質として，DT，GPMT，BT，及びSATの5種類の試験法について比較検討を行ったところ，GPMTとSATが比較的鋭敏にヒトへの皮膚感作性を予知出来ることが分った（表1）．しかし，これらの方法にも，改善すべき問題点がある．例えば，GPMT法では，その評価法として，Kligmanの方法[20]に基づき，感作成立動物の発生率により，その感作能の強さ弱さを評価している．従って，感作の成立と誘発・発症の条件は，この評価基準には盛り込まれていない．そこで，GPMTを用いた場合の感作能の強弱を，これらの条件を加

Table 1 Comparison Of cutaneous allergenicity from chemicals predicted by some experimental techniques.

Substance	LDT	Challenge conc.(%)	GPMT	Buehler test	Split adju. technique
Captafol	III(30)	5	IV (77)[2.0]	I (0)[0.0]	III(60)[1.6]
		0.5	III(60)[1.7]	I (0)[0.0]	III(43)[1.3]
chlorothalonil	III(60)	5	V (83)[2.0]	I (3)[1.0]	V (97)[2.6]
		0.5	IV (77)[1.9]	I (0)[0.0]	IV (73)[1.8]
Fenitrothion	II (20)	5	III(60)[1.7]	I (7)[0.3]	I (7)[0.3]
		0.5	III(37)[0.9]	I (0)[0.3]	I (0)[0.1]
Maneb	II (20)	2	V (97)[2.6]	II(23)[0.6]	V (97)[2.7]
		0.2	V (83)[2.2]	I (3)[0.2]	IV (73)[1.8]
Thiram	II (10)	2	III(49)[1.1]	I (0)[0.0]	III(33)[1.1]
		0.2	II (27)[0.7]	I (0)[0.0]	II (13)[0.6]
Triazine	II (10)	1	III(33)[1.0]	I (3)[0.2]	III(43)[1.4]
		0.1	I (3)[0.2]	I (0)[0.0]	II (10)[0.4]

Notes: 1) Allergenicity rating shows grade, ranging from weak (grade I) to extreme (grade V), using a procedure developed by kligman (1965).
2) Allergencity was read at 2, 24 and 48 hours after removal of the 24 hrs closed patch, expect LDT (Landsteiner-Draize's test), and mean values were expressed in the table.
3) The numerals inside parentheses indicate the percentage for. gensitized animals.
4) [ ]: The intensity of reactions were evaluated according to the following sclae: no visible change = 0, slight or discrete erythema and swelling = 3.

Table 2 Evaluation of cutaneous allergenicity predicted by the guinea pig maximization test (scale for scoring).

(1)Induction:Intradermal conc.(%)		(4)Allergenicity rating(Kligman)	
100	 1	I (0-8%)	 2
10	 2	II (9-28)	 4
1	 3	III(29-64)	 6
0.1	 4	IV (65-80)	 8
0.01	 5	V (81-100)	10
0.001	 6		
(2)Induction:Topical conc.(%)		(5)Intensity of reaction	
100	 1		(Draize's score)
10	 2	0 -	 1
1	 3	1 -	 2
0.1	 4	2 -	 3
(3)Challenge:Topical conc.(%)		3 -	 4
100	 1	4 -	 5
10	 2		
1	 3	Total score	5-37
0.1	 6		
0.01	 9		
0.001	12		

Table 3 Score grading for evaluation of guinea pig maximization test.

Score	Grade
6-10	Weak
11-16	Mild
17-22	Moderate
23-29	Strong
30-37	Extreme

Note: Score gradings were calculated from summation of scores grading for concentrations of intradermal and topical induction and challenge, allergenicity ratings and Draize score.

味して評点化して評価することを試みた．即ち，2,4-DNCBなど4種類の試験物質を用い，まず 4種類の試験法で60％以上の陽性反応を示す試験法の数を評点化し，ついで，Kligmanの判定法による成績，Draize法の成績及び誘発濃度別の成績を総合して，評価判定基準を示そうとしたものである．検討の結果，評点化はかなりきれいに行い得ると判断されたが，この方法では，操作の手間と経費が掛かり過ぎるきらいがある（表 2,3）[19]．

さらに，これらの方法では，皮膚の炎症反応を肉眼的に判定するために，その判断に主観が入る危険性が大きい．そこで，我々は，このような点を改善するために，Laserdoppler flowmetry 法を導入し，炎症部位の血流の測定によって，皮膚炎症反応を定量的に評価する方法[21]を提唱している．

中村ら[22]は，Magnusson&Kligmanの方法を改良し，感作能の定量的な評価法を試み，当該物質の感作能の定量的な評価法として，(1) 陽性反応を惹起するための最小感作処置濃度と，(2) 最高感作処置濃度を適用した動物で，平均反応がほぼ1.0となる誘発濃度を採用することを提唱している．これは，若干

手間が掛かるという難点はあるものの，妥当な評価法と思われる．

マウスは，モルモットよりも一般に廉価であり，且つ，免疫学的な特性がかなり明らかにされている．従って，この種を用いた適切な接触アレルギー予知法の開発と現場への適用が期待されるところである．マウスを用いた感作試験法としては，従来，Asherson& Ptak が推奨した耳介肥厚試験[18]が使用されてきている．そこで，我々もこの方法について種々検討を行ってみた．しかし，この方法では，DNCBやpicryl chlorideのような強い感作能を示す物質の反応の予測は可能であるが，感作能が低い物質では，その反応性を予知することは困難であることが分かった．この手技を検討する場合，比較的鋭敏な反応が得られる動物種の選択や，ハプテンの曝露・感作処置（特にFCAなどの使用）と誘発条件の設定などが重要である．そこで我々は，これらの諸点を考慮して，一連の研究を行い，原法の改良を試みた．その結果，弱い感作能物質での予知に関してはなお困難ではあるが，中等度の感作能を有する物質の反応性までは，予測可能な方法を確立することができた（図 2）[23]．しかし，この研究はまだ未完成であり，今後，更にこの領域の研究が発展することを期待したい．

in vivoの試験法は，動物愛護の精神に反して，一般に多くの動物を用いる難点がある．従って，in vivoの試験法を用いる場合には，使用する動物数を極力少なくすると共に，その反応をより客観的且つ正確に評価できる動物種の選択など，その改善策の確立が期待される．

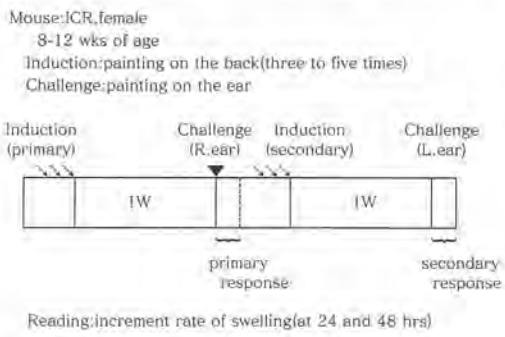

Fig.2 Outlines of our modified Asherson & Ptak's method (Aoyama & Matsushita)

（2）in vitro試験

in vitro試験法は，変異原性・発がん性のスクリーニングに汎用されているAmes-testのように，in vivo試験法に代わる有効な動物代替実験法として，その開発が時代の要請になってきている．こうした社会的な要望に応えて，接触アレルギーの領域でも，免疫・アレルギー学の新知見を導入した，感作性のin vitro予知法の開発が世界的にも注目されてきている．

ところで，ここでいうin vitro予知法には，二つの種類がある．一つは，動物をin vivoで感作し，感作動物のリンパ球を採取し，in vitroにおいて，種々の刺激に対するリンパ球の機能変動に関して検討し，感作性の予知を行うものである．現時点では，接触アレルギーのin vitro予知法は，主にこのタイプに属するものである．もう一つは，in vivoの過程を含まず，あらゆる操作をin vitroで実施する，完全なin vitro予知法である．しかし，後者の方法は，技術的にも種々の難問があり，今日までその研究は殆ど進展しておらず，実用化への道は，まだ遠いのが現状である．

そこで，ここでは，前者を中心に述べる．この予知法の代表的なものは，ハプテンによるリンパ球の幼若化試験がある．教室の李ら[24]は，DNCBでモルモットを感作し，in vitroでのDNCBに対するリンパ球の幼若化反応を検討した．そして，この方法によって，DNCBの感作性や量－反応関係，更に，関連物質であるDNBSとの交差感作反応の状況などが適切に評価出来ることが分かり，その有用性を明らかにした．

他方，サイトカインは，細胞の成長や分化，炎症，免疫などに関与する低分子蛋白からなるメデイエーターの総称であるが，その主たる働きにより，インターロイキン，インターフェロン，成長因子，キモカインなどの名称で分けられている．その種類は，現在100以上あるといわれ，その働きが分かるにつれて，その多機能性から，名称による明確な分類は難しくなってきている．

サイトカインは，炎症，免疫，細胞の分化・増殖などに関連する生物反応の発現に重要な役割を持つ物質として，主に各種抗体との関係についての研究が，近年，盛んに行われてきている．アレルギー性接触皮膚炎に関しても，その発症におけるサイトカインの役割，特にTh1細胞のサイトカインの動態が注目されてきている（図3）．我々は，サイトカイン産生の解析を，化学物質による接触アレルギーの評価に応用できないか明らかにするために，マウスのアレルギー性接触皮膚炎モデルを用い，種々検討を行った．まず，DNCBで感作したマウスを用い，そのリンパ球の in vitro IL-2産生を指標として，DNCBの感作性，及びDNBSとの交差反応を検討した結果，DNBSの感作性と，その量－反応関係との間のみならず，関連物質のDNCBとの交差反応の量－反応関係も認められた．また，in vitro IL-2 産生と，in vivoにおける耳介肥厚反応との間にも正の相関を認めてた[25,15]．

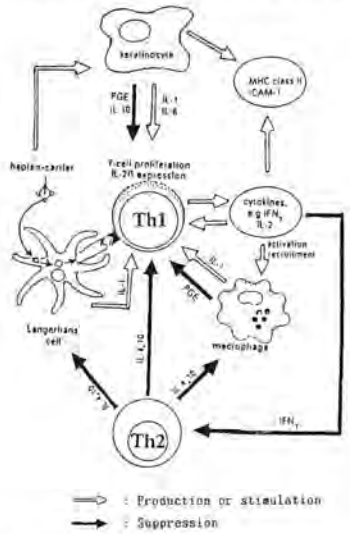

Fig.3 Interaction of various cytokines in contact allergy

さらに，サイトカイン産生のプロフイールについて，マウスのアレルギー性接触皮膚炎モデルを用いて，局所リンパ節及び炎症皮膚における数種のサイトカインmRNAの発現をRT-PCR法で検討した．その結果，接触感作マウスのリンパ節及びその炎症皮膚では，Th1細胞のサイトカインmRNAのみならず，Th2細胞のサイトカインのmRNAをも誘導することが明らかになった[27]．また，感作段階のリンパ節及び誘発段階の皮膚におけるこれらのサイトカイン，特に IL-2，IL-4,IL-12とIFN-γのmRNAの同時解析は，化学物質の接触感作能の評価に極めて有用な手法であるとの知見を得ている[28,29]．しかし，ここで用いた試験物質は，DNCBなど極めて強い感作能を有する物質であり，弱い感作能を持つ物質においてもこれが適用可能であるか否かについては，今後の検討課題である．また，一般に，in vitro試験法の問題点としては，試験物質の溶解性，細胞毒性などがその汎用を妨げており，in vivo反応との関連性を含めて，更に検討が必要である．

いずれにせよ，これらの方法が実用的に使用されるためには，それらが当該物質の感作能を正確に把握できる感度と特異性を有することが必要であるのはいうまでもないが，同時に，可及的に操作が簡便かつ廉価であり，然も比較的短時間で成績が得られることなどが期待される．

コンピューター・ネット・ワーク利用によるハザード予測

近年，インターネットに代表されるコンピュー

ター・ネットワークの発達は目覚ましく，化学物質のハザード情報のみならず，ハザード予測のエキスパートの利用，リスク管理のコンサルテイション，オン・ラインで更新される一次毒性情報へのアクセスも可能にしつつある．ハザードの情報の収集・検討に関しては、多くの研究所・政府機関などからの既存のハザード情報のデータ・ベースが，容易に収集・活用可能となってきている．また，人工知能を導入したハザード予測については，DEREK（deductive estimation of risk from existing knowledge）というエキスパート・システムがイギリスの民間と Leeds大学との共同研究機関で開発され，利用可能になっている[30-32]．

接触アレルギーの予測については，化学構造－活性相関を中心にして種々の研究が行われている[33-36]．これらの知見を元にして，DEREKのエキスパート・システムでは，ルーベンスの推論を採用して，その判断したルールを表示し，かなり具体的に皮膚への感作性を予測してくれることを示している[37,38]．しかし，このようなシステムでは，いうまでもなく，その基礎となる化学構造－活性関係に関する詳細な知見やデータの信憑性が問題となる．化学物質による呼吸器感作に関しては，接触感作抗原に比べて化学構造－作用の関係は余り確立していない．従って，この領域の基礎的な研究の蓄積も，今後大いに期待されるところである．

いずれにせよ，現在の人工知能は，多くのルール・ベースに基づく推論方法を採用しているため，現状では，なお限界はあるものの，今後，その基礎的研究の進展と人工知能の活用によって，その精度は向上するものと期待される．

周知のごとく，接触アレルギーに関しても，交差感作[39-41]や多価感作[42]，さらには光線過敏症[43]など種々の問題があり，これらの領域の問題解決には，今後，さらに多くの努力が必要と思われる．

Ⅱ．アレルギー反応が惹起される曝露条件に係る問題

現実の社会で認められる化学物質に起因するアレルギーは．ごく一部の感受性者に発症するように見受けられる．しかし，例えば，皮膚感作におけるDNCBのように，極めて強い感作性物質では，その接触・曝露の条件次第で，ほとんどすべての人に感作の成立と症状惹起が認められる．

そして，アレルギーにおいても、量－効果（反応）関係が存在することが明らかにされている[44,45]．この場合，アレルギーの量－反応関係は，生体に感作を成立させるのに要する抗原曝露量（濃度），即ち，感作処置・誘導の側面と，感作が成立した個体において発症に要する抗原曝露量（濃度），即ち，誘発・発症の二つの側面からみることができる．現実には，感作の成立濃度と，既に感作が成立した人でのアレルギー反応の発症濃度を決めることはなかなか困難ではあるが，感作成立は，その曝露濃度が高いほど成立しやすく，その発症は，感作成立濃度よりも、より低濃度で生じる．この領域の研究は，予防医学的な見地からは，極めて重要であると思われるにも拘らず，まだ極めて立ち遅れているのが現状であり，今後の研究の発展が大いに期待されるところである．

職業性アレルギーの発症予防と許容濃度

職業性アレルギーの発症を予防するためには，いうまでもなく，（1）感受性者への対策（健康管理），（2）抗原となり得る物質のリスク評価と人体への接触・侵入の防止対策（環境管理），（3）有害な作業工程や作業方法の改善などの労務対策（作業管理），（4）健康教育が必要である．しかし，これらの中で，とりわけ環境管理対策が重要である．

既に感作されている人では，その物質との曝露（接触）を避けるか，より感作性が弱い物質

に変更してやることが最も大切である．従って，気中の感作性物質の対策，すなわち気道アレルギーに関しては，許容濃度／限界値の設定と，その現場での活用が重要である．この際，感作性物質の許容濃度としては，既述のごとく，感作成立に要する曝露抗原の限界濃度と，感作された個体の発症抑制のための限界濃度の二つの側面がある．現実的には，大多数の作業者で通常の反応を示す人々を対象にした，後者のceiling valueを念頭においた環境対策が必要と思われる。

職場における感作性物質の取り扱いに関しては，許容濃度のリストの中に「感作性に注意すべき物質」としてのmarking，標示マークを付している国がある[46]．これらのうち，フランス・南アフリカでは，呼吸器系の感作性物質のみ標示しており，ドイツは，近年，許容濃度表の中で、感作性物質に関してはSマークを標示し，また，強い感作性を有する物質を別表として列挙している．この別表では，「呼吸器感作性物質」と「呼吸器感作も生ずる物質」を区別して示している．類似の方法をスウエーデンでも採用している．しかし，感作性物質として取り上げているこれらの物質は，国によって，かなり大きな差異が認められるのが現状である．この問題に関して，我々は，国際がん研究機関（IARC）の発がん性物質の分類の方法論を準用して，皮膚及び呼吸器感作性物質の分類・標示方法を試みている（表4）．今後，それらの適切な国際的標準化が，速やかに完成することが期待されるところである．

Table 4 Industrial chemicals to be marking as sensitizers on the list of occupational exposure limit.

〈Respiratory tract〉	
Group 1	
Beryllium compounds	Phthalic anhydride
Cobalt	Platinum salts
Diphenylmethane-4,4'-diisocyanate(MDI)	Toluene diisocyanates(TDI)
Glutaraldehyde	Trimellitic anhydride
Hexane-1,6-diisocyanate	
Group 2	
Chromium	Maleic anhydride
Ethanolamine	Nickel compound
Ethylenediamine	p-Phenylenediamine
Formaldehyde	Piperazine
Hexamethylene diisocyanate	Pyrethrum
Methylmethacrylate	Vanadium
〈Skin〉	
Group 1	
Chromium compounds	Mercury compounds
Cobalt salts	Nickel compounds
Formaldehyde	p-Phenylenediamine
Glutaraldehyde	
Group 2	
Aniline	Lindane
Antimony	Malathion
Arsenic compounds	Maleic anhydride
Benzofuran	Methyl methacrylate
Beryllium compound	Naphthalene
n-Butyl glycidyl ether	Pentachlorophenol
Copper	Phenothiazine
Dibenzoyl peroxide	Platinum compounds
Dibutyl phthalic acid	Polyvinyl chloride
Dichloropropane	Pyrethrum
Dichlorvos	Resorcinol
Diphenylmethane-4,4'-diisocyanate(MDI)	Thirum
Ethylenediamine	Toluene diisocyanate(TDI)
Ethylene glycol	Turpentine
Ethylene oxide	Vanadium
Hydrazine	Zinc
Hydroquinone	Zirconium
Iodine	

Group1 : The chemical is allergic to humans.
Group2 : The chemical is probably allergic to humans.

おわりに

以上，化学物質を例として，感作物質のリスク・アセスメントの問題と，アレルギー反応惹起に関わる環境対策に関する若干の問題について述べた．

WHOは，近年，業務に直接関係がなくても，就業によってその進行や増悪があり得る疾患を作業関連疾患（work-related disease）と呼び，これらに対する予防対策の重要性を強調している[47]．アレルギー疾患に関しても，単に，狭義の職業性アレルギー対策を進めるのみならず，就業に関わるすべてのアレルギー性疾患やアレルギー性疾患様の症状を示す作業者に対しても，同様の視点での対策が必要であろう．また，アレルゲンの反応性を修飾する交絡因子としては，ストレス，喫煙，大気汚染物質，その他，種々のものが明らかにされつつある．現実社会における適切な対応の面からも，今後，それらに関するより詳細な解明が期待されるところである．

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General situation on occupational immunologic diseases in China

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Occupational Immunologic Diseases(OID) are a group of the disorders in which immunologic mechanisms are involved. It includes obstructive airways disease (asthma), pulmonary granulomatous disease and interstitial fibrosis (extrinsic allergic alveolitis, chronic beryllium disease), contact dermatitis and others. In this paper, the author will present some investigations on the beryllium disease and occupational asthma in China.

BERYLLIUM DISEASE

Since Weber and Hardy firstly reported about acute and chronic beryllium disease, more than thousand cases have been registered only in Beryllium Case Registry at the Massachusetts until 1980s. Beryllium industry in China has been established in the mid-1950s and about 6,000 workers have been estimated to occupationally exposed to beryllium or its compounds in the smelting, metal processing, alloy, ceramic, fireproof material and trial production industries. Outbreak of acute beryllium disease had been reported in second half of 1950s due to the worse work conditions. Up to now, more than 130 case for acute beryllium disease and 81 cases with chronic beryllium disease, respectively have been diagnosed China.

It has been reported that the immune reaction especially cellular immunity plays an important role in the pathogenesis of chronic beryllium diseases. To further clarify by which immunologic mechanisms the disease is mediated, an experimental model of beryllium disease was successfully produced in guinea pigs by the endotracheal injection of beryllium oxides. Various immunologic parameters were then examined in this animal model[1]. We found that the numbers of total cells were significantly elevated in bronchoalveolar lavage fluid (BALF). An

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increase in polymorphonuclear cells was observed in the early phase whereas an increase in lymphocytes was observed in the late phase. Moreover, the lymphocytes from BALF showed more stronger proliferative response to beryllium in vitro compared with the lymphocytes obtained from peripheral blood. Furthermore, it was seen that IL-1 was significantly produced by beryllium-treated alveolar macrophages in vitro. These results thus proved that beryllium may enhance both specific and non-specific immune responses which in turn contributes to granulomatous formation in chronic beryllium disease.

Recently, the national diagnostic criteria of beryllium disease is issue in China. In clinic, acute beryllium disease generally occurs following the inhalation of high concentration of beryllium aerosols and can be easily diagnosed mainly on the basis of acute chemical bronchitis or pneumonitis. On the other hand, exposure history, objective and subjective findings in respiratory systems are important for the diagnosis of chronic beryllium disease. In X-ray radiography, more than 1-4 zones with a diffuse reticular, granular shadows are obligatory for identifying the cases. However, there are some difficulties for the diagnosis, if only relying on X-Ray images. We found that the in vitro technique such as leukocyte migration inhibition test (MIT) with beryllium antigen is useful for the differential diagnosis. In support for these, we have demonstrated that 70% cases showed positive MIT response among the suspected patients[2].

OCCUPATIONAL ASTHMA

With the development of modern scientific technology and industry, thousands of new chemicals have been appearing. Some of them may have sensitizing potential to human. Because of their wide application in both industrial and domestic uses, the prevalence of occupational allergic diseases has an increasing trend at present. More than 140 low molecular weight chemicals have been shown to cause occupational asthma[3]. Therefore, it is therefore necessary to clarify the mechanisms and clinical characteristics of chemical sensitizing agents in order to prevent and treat the diseases.

Bronchial asthma is a chronic airway inflammation in which various cells, especially mast cells and basophils, participate. Its basic pathological changes are acute bronchial constriction, edematous swelling of mucosa and submucosa, mucus hypersecretion, bronchial epithelial denudation, chronic mucus plug formation in the airway lumen, irreversible airway wall remodeling, airway hyperresponsiveness and airway obstruction. Cytokines are important signal transmitters among the inflammatory cells, and contribute to the pathogenesis in asthma. Th2 cells produce IL-4 and IL-5. The former is responsible of B cell stimulation and IgE production, whereas the latter is responsible for eosinophil activation and recruitment. Both cytokines are considered to cause important

immediate-type hypersensitivity reactions. On contrary to Th2 cells, Th1 cells produce IL-2 and IFN-γ which inhibit IgE production by antagonizing IL-4. Th1 cells are considered to mediate delayed-type hypersensitivity reactions[4].

Chemical allergy

Occupational chemical sensitizing agents are divided into organic chemicals, inorganic chemicals and pharmaceutical products. The characteristics of their sensitizing action are: (1) low molecular weight (usually less than 5kD), most of them are too small to serve as antigens by themselves. These chemicals could trigger immediate hypersensitivity responses by combining with tissue proteins or by altering tissue proteins to create new antigenic determinants. (2) Many organic chemicals have strong activity. There are some active groups such as -C=3DN, -N=3DN and others in their structure. These active groups are thought to be responsible for the sensitizing ability[5]. (3) Among the same kind of chemical sensitizing agents, cross sensitizing reactions often occur. (4) Most of chemical sensitizing agents have irritant and corrosive action to mucosa, but some of them have only irritant action. Long term exposure to low concentration of the chemicals can induce chronic irritant inflammation in airway, whereas inhalation of high concentration can induce acute bronchitis, pneumonia or pulmonary edema. Both acute and chronic injuries in the airway may trigger the occurrence of asthma and airway hyperresponsiveness. It is likely to be responsible for the direct epithelial injuries, inflammatory mediator release, neuropeptide release at nerve endings[6].

Some representatives of the chemical sensitizing agents such as phthalic anhydride (PA), toluene diisocyanate(TDI) and platinum salts (Pt) were studied.

(1) Experimental study[7-10]

Guinea pigs were sensitized by the peritoneal injection of PA, TDI, Pt-BSA conjugate in combination with complete Freund's adjuvant, respectively. Three to 8 weeks later, most of the animals experienced the asthma attack (88%) after challenged by inhaling the same sensitizer. Using dynamic ventilation lung imaging with Tc-99m-DTPA, the central accumulation of radioactivity was developed in asthmatic animals. Bronchial spasm and obstruction were found following antigen challenge. Histologically, characteristic findings for allergic asthma were found. For example, eosinophil infiltration was seen in the bronchial wall of the sensitized animals with asthma. Plug with epithelium, mucus and eosinophils were formed in bronchial lumen.

Moreover, we have performed the passive transfer test using the sera from sensitized animals. We demonstrated that severe asthma could be provoked in the recipients by inhaling challenge. In PCA test, blue speck reactions were observed, further confirming the production of specific IgG and IgE antibody. Asthma was also provoked in the offsprings following

maternal sensitization. In severe cases, pups died following the inhalation of the antigens.

Chemical mediator and specific antibody levels were determined in the sera of sensitized guinea pigs. A significant increase in serum PGF2a was found in most animals after challenge with the antigen. It increased 7.6 times, ranged 2 to 25 times. The levels of S-IgG in TDI and Pt sensitized animals were significantly elevated. It progressively increased with prolonging or intensifying the immunity. With s-IgG inhibition test, it was found that the antibody was hapten specific. The author may be concluded that allergic mechanisms is responsible for chemical asthma in one aspect.

(2) A study for etiologic diagnosis[11]

Evaluating whether the occupation is responsible for the attack of asthma is very important to the management and prognosis of the disease. We evaluated occupational etiology in 43 patients who was suspected to has chemicals (TDI, ethylenediamine, clophony and PA)-induced asthma. All cases were collected by medical history, physical examination and laboratory tests such as antigen bronchial provocation test(A-BPT), skin test (ST), S-IgE, S-IgG4 and others. The results indicated that the positive rate of A-BPT is 67.4%. Nuclear ventilation imaging was observed while A-BPT was performed. The imaging showed a central accumulation of radioactivity after challenge. Its extent is consistent with clinical symptoms, signs and FEV1 decrease. The positive rates for ST, S-IgE, IgG4 were 53%,54.5% and 59%, respectively. The corresponding rates between ST, S-IgE, S-IgG4 and A-BPT were 71%, 69.4% and 73.4%, respectively. The corresponding rate between S-IgE and S-IgG4 was 78.3%.

Therefore, the authors considered that: (i) Typical occupational history is an important evidence in evaluating the etiology for occupational asthma. (ii) A-BPT can evaluate whether the suspected allergen could induce the airway reactions and which type of immune reactions could be produced. A-BPT is also useful for establishing the relationship between occupational environment and airway obstruction. Then, it is more direct and reliable than other tests used in etiologic evaluation of occupational asthma. (iii) Some immunological indices may be helpful in etiologic diagnosis.

Other kinds of occupational asthma

Silk-induced asthma: The sericulture industry has a long history in China. The allergic asthma may caused by different production of silkworm such as larva urine, moth scales, chrysalid powder, cocoon and sericin itself. The prevalence rate of asthma in sericulture and weaving workers in China have not been exactly counted. In a survey conducted in in silk manufacture factory, 33 cases with asthma (total prevalence rate is 1.8%) were observed among 2,174 workers. The cases occurred mainly in selective cocoon and reel-off workshops. The prevalence for

both workshops was 4.6%. Clinical statistical analyses have shown that silk-related asthma account for 6% in outpatients suffered from asthma[12-13].

Silk-induced asthma is associated with hypersensitivity mechanism. Among the silk asthma patients, the positive rate of specific IgE and skin test to cocoon extracts were 84% and 100%, respectively. As for S-IgG4, the positive rates for larva urine, moth scales, and moth urine and cocoon silk were 55.6%, 43.3%, 35.6%, 24.4%, respectively, in sericulture workers. IgG4 level in sericulture workers was also significantly higher than that in control subjects .This results indicated that the above materials are major allergic agents for silk asthma[14].

Grain dust-induced asthma: Grain dust is considered to be a complex mixture of grain particles, fiber of fringe, mold and spore, insect fragments, pollen, avian and rodent proteins, chemicals such as pesticide as well as inorganic silicon particles and so on. A survey in 12,612 grain mill workers has shown that the prevalence of occupational asthma was 2.29%, while the prevalence of chronic bronchitis was 4.56%. The major allergens were fungus, mites and grain particles. Among these, twenty-one species of pure fungus and 5 species of mites have been separated. Most of fungus were Homoderdrum, Penicillium Sp, Asperfillum Sp, Mucor, Rhizopus nigricans, Alternaria Sp and others. Using different antigens, skin test was performed among 723 grain workers. It was demonstrating that the positive rates for grain, mites, and fungi were 34.2%, 30.5% and 12.9%, respectively. The positive rate of serum specific IgE against grain dust was 67.7%. The positive bronchial provocation test was observed in 47.5% of grain workers with positive skin test. Compared with control group, serum S-IgE, S-IgG4 and IL-4 levels were significantly elevated , but IFN-? decreased significantly in 32 patients with Rhizopus Nigricans asthma. These results indicate that Rhizopus nigricans asthma may belong to type I allergic disease[15].

DIAGNOSTIC CRITERIA FOR OCCUPATIONAL ASTHMA

A diagnostic criteria for occupational asthma has been widely used in our country[16]. The basic principles for current criteria are as follows. Firstly, the clinical findings of bronchial asthma are essential. This includes paroxysmal or reversible dyspnea, asthma attack and diffuse, pulmonary wheezing. Second, occupational exposure history and no pre-existing asthma prior to employment are obligatory. The asthmatic symptoms occur with a distinct relationship to work exposure. The asthma attack only at work and relives during vacation or weekend. Antigen specific bronchial provocation test, skin test, specific IgE, IgG, IgG4 would be important in differential and etiologic diagnoses.

The present criteria is only limited to some chemicals. Diisocyantes such as TDI, MDI, NDI HDI, acid anhydrides such as PA, TMA, TCPA, amines such as ethylenediamine, triethylene tetramine;

platinum complex salts and sisal hemp are currently recognized as occupational asthmogenic agents in the criteria. Other occupational causative agents should be approved by the corresponding national organization and gradually listed up.

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職場が関係した木材アレルギー性鼻炎の8症例

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われわれは、職場にて特異的にアレルギー性鼻炎症状を呈した26例（男性20例、女性6例、平均年齢36歳）を経験し、その内、木材が原因と考えられたのは8例（男性6例、女性2例、平均年齢31歳）であった。アトピー性疾患の家族歴は5例（アレルギー性鼻炎4例、薬剤アレルギー1例）に、既往歴は2例（喘息1例、蕁麻疹1例）に認められた。木材粉塵の抗原検索は全例皮内テストで行なわれ、米スギ7例、ラワン5例、米ツガ4例、米マツ3例、米ウメ3例、米サクラ2例に陽性を示した。この8例が受けた治療法は、抗ヒスタミン剤内服、インタール点鼻、下甲介粘膜切除術などであった。

はじめに

職場で発症する気道アレルギーは、初期にはアレルギー性鼻炎で始まり、後に、より重篤な喘息へと発展することはbakers asthmaでよく知られている[1]。それ故、職業性アレルギーを鼻炎のうちにわれわれ耳鼻咽喉科医が発見し、適切な指導を行なうことは、患者の予後にとって極めて重要なことと思われる。そして、このような対策を講じるためには、当然のことながら耳鼻咽喉科医が職業性アレルギー性鼻炎の実態を熟知しておくことが必要である。そこで今回われわれは、職業性アレルギー性鼻炎の中でも最も多く見られる木材アレルギー性鼻炎症例について[2]、当教室アレルギー専門外来で経験した8症例について臨床的検討を行なったので報告する。なお、これらの一部は本邦にて過去に報告を見なかった抗原例であった。

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症　例

当教室アレルギー専門外来開設(1976年)以来、職場にて特異的にアレルギー性鼻炎症状を呈し、職業性アレルギー性鼻炎が疑われたのは26例（男性20例、女性6例、平均年齢36歳）で、その内、抗原物質が特定できたのは17例(65.4%)であった。これらの中で、木材が原因と考えられたのは8例（男性6例、女性2例）で、詳細は表1に示したごとくである。受診年齢は16～48歳で平均31歳と働き盛りであった。罹病期間は2～16年で平均5年であった。アトピー性疾患の家族歴は5例(62.5%)に認められ、その内容はアレルギー性鼻炎4例、薬剤アレルギー1例であった。既往歴は1例に喘息、

表1　職場が関与した木材アレルギー性鼻炎症例

症例	年令	性	職業	原因抗原
1	29	M	大工	米杉、ラワン
2	31	M	大工	米杉、米栂、米桜
3	48	M	製材業	米杉
4	44	M	建築業	米杉、ラワン、米松、米栂
5	34	F	木工業	米杉
6	22	F	木材会社事務	ラワン、米松、米栂
7	29	M	内装業	米杉、ラワン、米松、米栂、米梅
8	16	M	学生（自宅が製材所）	米杉、ラワン、米梅

表2　本邦に於ける木材粉塵によるアレルギー性疾患の報告例

抗原	業種	疾患	報告者	報告年
米杉	木工業者	喘息、鼻ア	関	1926
ねずこ	木工業者	喘息	関	1926
りょうぶ	細工業者	喘息	勝谷ら	1966
ほう	木工業者	喘息	和田ら	1966
ラワン	木工業者	喘息、鼻ア	青木	1968
くわ	家具製造業	喘息	中村	1969
かりん	家具製造業	喘息、鼻ア	高橋ら	1975
したん	家具製造業	喘息	高橋ら	1975
しらかば	割箸業者	喘息	高本	1979
まこも	彫刻業者	喘息	岡本	1979
日本桧	彫刻業者	喘息、鼻ア	宇佐神	1980
甘草	甘草粉末製造業	喘息	宇佐神	1980
日本松	木工業者	喘息、鼻ア	宇佐神	1980
米松	建築業	喘息	高本	1981
ナーラ	製材業者	喘息	栃木ら	1982
けやき	細工業者	喘息	勝谷	1982
台湾桧	彫刻業者	喘息	宇佐神	1984
つげ	細工業者	喘息	田原	1985
日本杉	木工業者	喘息	栃木ら	1993
米栂	建築業	鼻ア	内藤ら	1997
米梅	内装業	鼻ア	内藤ら	1997
米桜	建築業	鼻ア	内藤ら	1997

1例に蕁麻疹が認められた。

職種は、建築業3例、製材業1例、木工業1例、内装業1例、木材会社事務員1例、製材業に直接関与していないが生活環境が製材作業場に近接している学生が1例であった。木材粉塵の抗原検索は全例皮内テストで行なわれ、米スギ7例、ラワン5例、米ツガ4例、米マツ3例、米ウメ3例、米サクラ2例に陽性を示した。重複抗原（重複例あり）は、ハウスダスト5例、カンジダ4例、ワタ3例、キヌ2例、スギ花粉2例、ブタクサ花粉2例、ソバ粉2例、アルテルナリア1例、アカマツ花粉1例であった。

この8例が受けた治療法は、抗ヒスタミン剤内服4例、ヒスタグロビン注射1例、インタール点鼻1例、MSアンチゲン注射1例、下甲介粘膜切除術1例であった。

考　察

戦後、日本の経済復興は著しいものがあるが、その産業の発展に伴い、職場で曝露される抗原

の種類も増加し、多様化をもたらした。特に、近年の建築ブームにより木材の需要が拡大し、国内産の材木より、安価な輸入材の占める割合が格段に増大してきた。この結果、日本の山林に植林された多くのスギやヒノキが放置されることになり、現在の日本のアレルギー性鼻炎（スギ花粉症）の爆発的な流行に繋がったとも言われている[3][4]。その一方で、建築業者、製材業者は輸入材の取り扱いが増え、その粉塵に曝露される機会が多くなってきた。

宇佐神[5]は本邦での職業性アレルギー性鼻炎の抗原は42種類にも及ぶとしている。その中でも、木材によるものが最も多く、特に輸入材によるものが目立っている。また、日本人の食生活の欧米化に伴い、小麦粉の需要が著明に増加し、職業性アレルギー性鼻炎の抗原として小麦粉は木材に次いで2番目に多くみられる[2][6]。小麦粉アレルギーは先に触れたように、欧米ではbakers asthmaとして既に有名であり、鼻炎が先行し、後に、より重篤な気道アレルギーである喘息に移行することが知られている[1]。それ故、著者らは高濃度の抗原に持続的に曝露される環境下にある職業性アレルギーの場合、鼻炎のうちに正しく診断し、早期に適切な対処をすることが、われわれ耳鼻咽喉科医に与えられた重大な使命と考える[7]。

そこで今回、われわれは職業性アレルギー性鼻炎の中でも最も多いとされる木材アレルギー性鼻炎の自験例8症例の臨床的な検討を行なった。その結果をまとめてみると、職業性木材アレルギー性鼻炎は木材粉塵曝露下で作業を続けてきたアトピー素因を有する働き盛りの年代、それも職業の特異性からか男性に多く見られた。抗原は従来の報告[2]のように米スギ、ラワンなどの輸入材の粉塵が最も多かった。職業性木材気道アレルギーの抗原として過去に本邦で報告されたものを中村[6]や宇佐神[5]のまとめたものに追加して表2に示した。今回われわれの報告例では新たに米ツガ、米ウメ、米サクラの3種類が追加されたが、何れも輸入材であった。

自験例の重複抗原は、われわれが以前報告したように[8]ハウスダストやカンジダが多く、Blaineyら[9]やJimenez-Diazら[10]の指摘するように、粉塵職場でのダニや真菌は重複感作抗原として重要であることが再確認できた。

職業性木材気道アレルギーの治療としては、転職か職場内配置転換など吸入抗原の回避が理想的であるが、経済的、社会的事情から容易ではないことが多い。幸い自験例では一般的なアレルギー性鼻炎に対する治療で症状軽快し、職業を継続することが可能であったが、前述のごとく、今後の経過には十分注意が必要である。本邦での木材アレルギーの抗原特異的減感作療法の有効性は、高本[11]が日本スギ材の症例に施行し、有効であったと報告している。しかし、自験例のように多種類の木材に重複感作されている場合や、またハウスダストや真菌の重複感作を受けていることが多いこと、症例が働き盛りの年齢が多く頻回の定期通院が困難であることなどから、実際には抗原特異的減感作療法の施行は困難なことが多いと想定される。それだけに、抗原診断を正確に行ない、抗原回避など生活上の助言に万全を期すべきであろう。

結　語

当教室アレルギー外来を受診した木材アレルギー性鼻炎8症例について臨床統計的検討を行ない、以下の成績を得た。

1．8例（男性6例、女性2例）の平均年齢は31歳と働き盛りで、罹病期間は平均5年であった。アトピー性疾患の家族歴は5例に、既往歴は2例に認められた。

2．職種は、建築業3例、製材業1例、木工業1例、内装業1例、木材会社事務員1例、生活環境が製材作業場に近接している学生が1例であった。

3．木材粉塵の抗原は米スギ7例、ラワン5例、米ツガ4例、米マツ3例、米ウメ3例、米サ

クラ２例に陽性を示し、アンダーラインのものは本邦では過去に報告されていなかった。

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Eight cases of allergic rhinitis to timber dust in the occupational areas.

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We experienced 26 nasal allergy patients(20 men and 6 women, with the mean age of 36 years) complaining of their symptoms in only the occupational areas and 8 patients(6 men and 2 women, with the mean age of 31 years) of the 26 were sensitized with timber dust. They had 5 atopic family histories(4 nasal allergy and 1 drug allergy) and 2 atopic past histories(1 asthma and 1 urcicaria). Their skin reactions to timber dusts of western red cedar in 7 patients, lauan in 5, American hemlock in 4, American pine in 3, American apricot in 3 and American cherry in 2 were positive. They were treated with peroral ingestion of H_1 blocker, topical use of DSCG, turbinotomy, etc.

Japanese cedar pollen-specific IgE antibody carriage among an adult population in Gunma prefecture

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ABSTRACT

Japanese cedar pollinosis is increasing among the general population in Japan. The positivity rate of sensitization to the Japanese cedar pollen antigen is very high in the young adult population. This study was conducted to elucidate the yearly increase of the positivity rate of Japanese cedar pollen-specific IgE (JCP-IgE) among the general population in Gunma prefecture and to clarify the relationship between JCP-IgE and age-, sex- and region-related differences. Serum samples of 3,089 volunteers were obtained from the general population including a proportion of allergic individuals living in Gunma prefecture. JCP-IgE in the subjects was measured by fluorescence-ELISA. The positivity rate of JCP-IgE in the population was 33.1% (1,022 of 3,089). The positivity rates of males and females were 35.3% and 31.2%, respectively. Numerical differences were found in the JCP-IgE positivity rate between the present study (46.2%, 1994) and our previous study conducted in 1989 (31.5%) for the 18 to 39 age group, although pollen scattering in 1989 and 1994 was equally low. The highest antibody carriages and levels were predominantly found in young adults (18-29) and decreased slightly with age. In the 18 to 29 and 30 to 40 age groups, the positivity rate of JCP-IgE was slightly higher in females than in males. However, it was lower in females than in males in subjects over 40 years of age groups. Significant differences were found in the 50 to 59 and the over 60 years of age groups. The positivity rate in the rural young subjects was slightly higher than those in the urban young subjects. As a control study, the changes in mite-

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specific IgE (mite-IgE) positivity were observed. The rate of mite-IgE carriages changed between slightely 1989 and 1994.

Abbreviations used: fluorescence-ELISA, fluorescence-enzyme linked immunosorbent assay; RFU, relative fluorescence units; JCP, Japanese cedar pollen; JCP-IgE, JCP specific IgE; mite-IgE, mite specific IgE.

INTRODUCTION

During the past 10 years, Japanese cedar pollen-sensitive subjects have increased in the Japanese population, especially in young adults. The positivity rate of JCP-IgE in young adults has been reported to be more than 30%[1,2], and subjective symptoms have been noted in about 35% of antibody-positive subjects. Gunma prefecture is surrounded by mountains on 3 sides and many Japanese cedar trees are afforested. Therefore, a large amount of Japanese cedar pollen is scattered from the beginning of February until the middle of April, although the degree of pollen scattering is markedly influenced by the temperature of the preceding summer[3]. Previously, we reported the positivity rate of JCP-IgE and mite-IgE in the general population including a proportion of allergic individuals in Maebashi city, the capital of Gunma prefecture. The highest levels of JCP- IgE were found in young adults (18-29)[4,5] and the positivity rate of JCP-IgE among them was 31.5% in 1989. Recently, we observed yearly changes in the degree of pollen scattering and in the rate of JCP-IgE positivity within freshmen in our University from 1987 to 1995[6]. The positivity rates of JCP-IgE are mainly associated with the degree of JCP stimulation. In addition, the percentages of JCP-IgE carriers significantly increased during the examined 9 years, but the percentages of mite-IgE carriers in the same population changed only slightly during these years.

Many studies in adults with allergen specific-IgE have shown that specific IgE levels and skin reactivity are influenced by age, sex, race and environmental or occupational exposure[7-11]. We also described that the rate of specific IgE antibody carriage to mite and JCP gradually decreased with age and then decreased markedly in subjects aged 70 years and over. Moreover, there were slight sex-related changes in IgE production[4,5,12].

The present study was undertaken to investigate the rate of JCP-IgE antibody carriage in a large number of people and to elucidate the yearly increase of the positivity rate of JCP-IgE among the general population including a proportion of allergic subjects in Gunma prefecture. Furthermore, we attempted to clarify the relationship between JCP-IgE and age-, sex- and region-related differences in the population.

MATERIALS AND METHODS

Antigen: JCP-extract was prepared from *Criptomeria japonica* pollen by the method of Yasueda et al.[13]. The precipitate

fraction obtained from the pollen by 80% saturation with ammonium sulfate was dissolved in and then dialyzed against cold deionized water overnight. It was subsequently lyophilized for storage. Mite powder prepared from *Dermatophagoides farinae* was donated by Torii Yakuhin Co., Ltd (Japan). Prior to use, both extract powders were dissolved in 0.05 M carbonate buffer, pH 9.6 at a final protein concentration of 25 μg/ml.

The protein concentration of each antigen was measured using the "BIO-RAD" dye binding assay with bovine serum albumin as the standard.

Sera: In 1994, 3,089 serum samples were obtained from a general population of volunteers including a proportion of allergic individuals living in 4 areas, Central, West, East and North, of Gunma prefecture. Central area is urban including Maebashi, the capital of Gunma prefecture, and the other areas are in and around a farm area. The age range was 18-86 years, and profiles of the study population are given in Table 1. All serum samples added with 0.05% NaN_3 were kept in a refrigerator until use.

Measurement of an allergen specific IgE antibody: Serum levels of specific IgE antibody were measured by fluorescence enzyme immunoassay (fluorescence-ELISA) according to the method described by Nakazawa et al.[4]. Prior to measurement, all serum samples were diluted to 1:4. Each well of a black microplate was coated with 100 μl of the antigen solution. Each 100 μl of the diluted sera was tested using β-D-galactosidase conjugated anti-human IgE antibody (goat serum) as the second antibody and 4-methylumbelliferyl-β-D-galactoside as an enzyme substrate. The hydrolyzed probe, 4-methylumbelliferone released from the substrate at the final reaction step, was measured with a MicroFLUOR reader (Dynatech Product, USA). Results were expressed in relative fluorescence units (RFUs). The RFU values increased linearly in proportion to the amount of 4-methylumbelliferone present.

Criterion for specific IgE positivity: The RFU values of a criteria for specific IgE positivity were set as follows: 1) RFU values obtained from all tested sera were

Table1 : Profiles of the study population

(A) Population in the study area, sex balance of study population

Study Area	Number of test sera		
	Total	Male	Female
Central	1126	574	552
West	1369	513	856
East	263	163	100
North	331	192	139
Total	3089	1442	1647

(B) Population in each age group

Age	Total	Male	Female
18-29	724	259	465
30-39	652	496	156
40-49	830	332	498
50-59	431	166	265
60-	452	189	263
Total	3089	1442	1647

plotted on a histogram using a personal computer program, 2) The antigen specific-IgE negative population (the first peak showing low RFU values on the histogram) in the tested sera was determined, and then the mean value and standard deviation (SD) of the negative population were calculated statistically, and 3) Positivity for antigen specific IgE antibody was defined as any value above the cut-off limit of the "mean RFU value of the negative population + 3 SD". 4) RFU values for JCP-IgE of the 3,089 subjects were measured, and the criterion for positivity was determined according to the 1) - 3) procedures. A subject indicating an RFU value ≧ 45 to the JCP-antigen was defined as a JCP-carrier.

Materials: Polystyrene black microplates were purchased from Dynatech Product (USA). β-D-galactosidase-conjugated anti-human IgE antibody was obtained from MBL Co.Ltd. (Nagoya, Japan). 4-methylumbelliferyl-β-D-galactoside was obtained from Sigma Co. Ltd. All other chemicals used were of special grade and purchased from Wako Pure Chemicals Co. Ltd (Tokyo).

RESULTS

The positivity rate of JCP-IgE carriage in the population was found to be 33.1% (1,022 of 3,089). The rate of JCP-IgE carriage in males and females were 35.3% (509 of 1,442) and 31.2% (513 of 1,647), respectively. As a control study, the rate of mite-IgE carriage was determined by the method previously described[12]. Mite-IgE carriage in the same population was 18.9% (585 of 3,089), and those in males and females were 23.7% (342 of 1,442) and 14.8% (243 of 1,647), respectively.

Comparison of the positivity rates in the present study (1994) with the rates from 1989 was conducted in the 18-39 age group whose specific IgE was produced intensely. As shown in Fig.1, the positivity rates in 1989 and 1994 were 31.4% and 44.8% , respectively. The positivity rates for males and females were 32.7% and 30.4% in 1989, and 41.9% and 48.4% in 1994, respectively. There was a significant difference in the positive percentages between 1989 and 1994 ($P < 0.01$ by 2×2 X^2 test),although pollen scattering in 1989 and 1994 was equally low. These results indicate that the proportion of JCP-carriages significantly increased from 1989 to 1994. On the other hand, the proportion of mite-carriages changed only slightly in this time period.

The relationship between positivity percentages for JCP-IgE and aging in 1989 and 1994 are shown in Fig 2. The highest antibody carriages in both 1989 and 1994 were predominantly found in young adults (18-29), followed by the 30-39 age group, and then gradually decreased proportionally with age. The positivity percentages obtained from 1994 were higher than those from 1989 in the 18-29, 30-39, and 40-49 age groups, while the positivity rates in the 50-59 and over 60 age groups changed only slightly in this time.

Fig.1 Positive percentage of JCP-specific IgE in the 18-39 age group between 1989 and 1994, compared with those of mite-specific IgE.

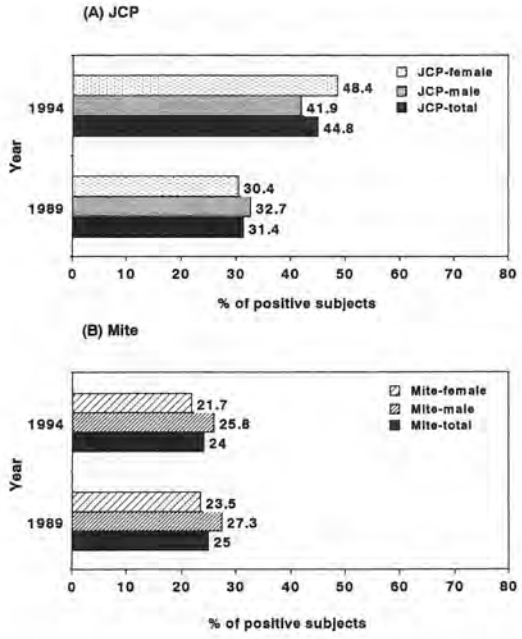
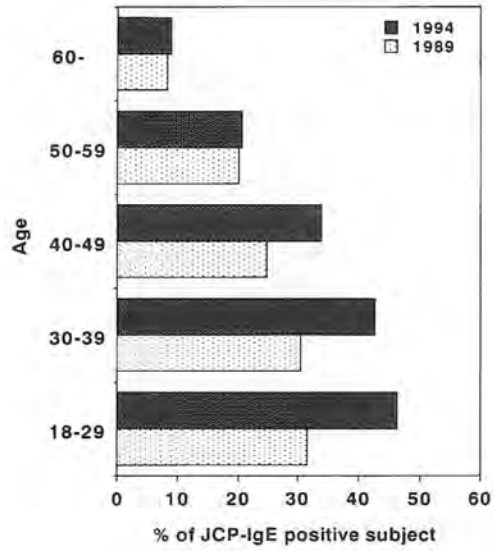


Fig. 2 Comparative studies of positivity rates for JCP-specific IgE antibodies between 1989 and 1994 with aging.



The sex-related positivity rates in each age group are shown in Fig. 3. In the 18-29, and 30-39 age groups, there appeared to be slightly higher rates of JCP-IgE positivity among women compared to men. In the 40-49 age group, the positivity percentage of men was slightly higher than that of women. In the 50-59 and over 60 age groups, the positivity rates of men were significantly higher than those of women ($P < 0.01$ by 2×2 X^2 test). On the other hand, a higher rate of mite-IgE positivity among men than women was found in the 18-59 age groups ($P < 0.01$ by 2×2 X^2 test).

Fig. 3 Relationship between the positivity rate of JCP-specific IgE, sex and age, compared with those of mite-specific IgE.

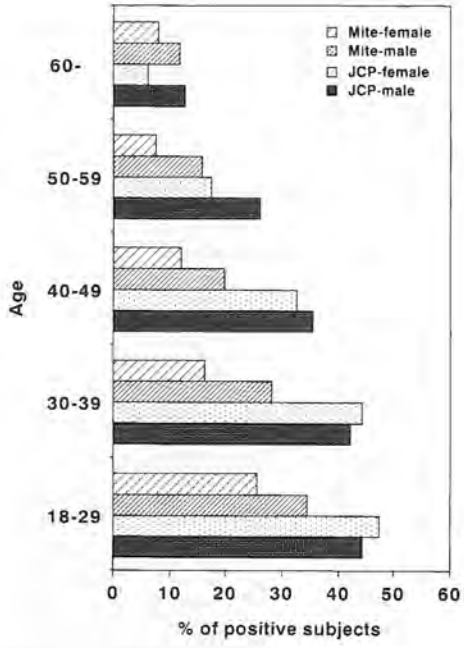


Fig. 4 shows the relationship between JCP-IgE levels and age. The highest antibody levels were predominantly found in young adults (18-29). The mean JCP-IgE levels with aging among the JCP-IgE carriers (RFU >45) was analyzed. The mean RFU values in each group in the 18 to 49 age group were similar (18-29; 371±253, 30-39; 356±247, 40-49; 381±238), while the mean value in the 50-59 age group was fairly low (317±228). In the over 60 age group, the mean value dropped to 231±182. The mean RFU value in each age group was not significantly related to the sex, although the mean value of men was slightly higher than that of women in each age group. JCP-IgE carriers having RFU values ≧500 are present in similar ratios as JCP-IgE carriers, among the 18-29, 30-39, 40-49 and 50-59 age groups. These percentage showed a significant fall in subjects over 60 years of age.

Gunma prefecture can be divided into 4 areas based on climate and life pattern. The Central area is located in an urban area and the West, East and North are located in and around farming areas. The positivity rate of JCP-IgE carriage in the 18-39 age group that produced a high level of specific IgE was examined among the 4 areas (Central, West, East and North). As shown in Fig. 5, there were only slight differences in the JCP-IgE positivities of these 4 areas; the positivity rates in the East and West were slightly higher than those in the Central and North areas. These results coincided with the data from Japanese cedar pollen scattering during the pollen season which described in "Studies on Japanese cedar pollinosis in Gunma Prefecture"[5],eg, pollen scattering in the East and West areas was more than that of the Central area, and the fewest pollen scattering was found in the North area.

Fig. 4 Relationship between JCP-specific IgE levels and age.

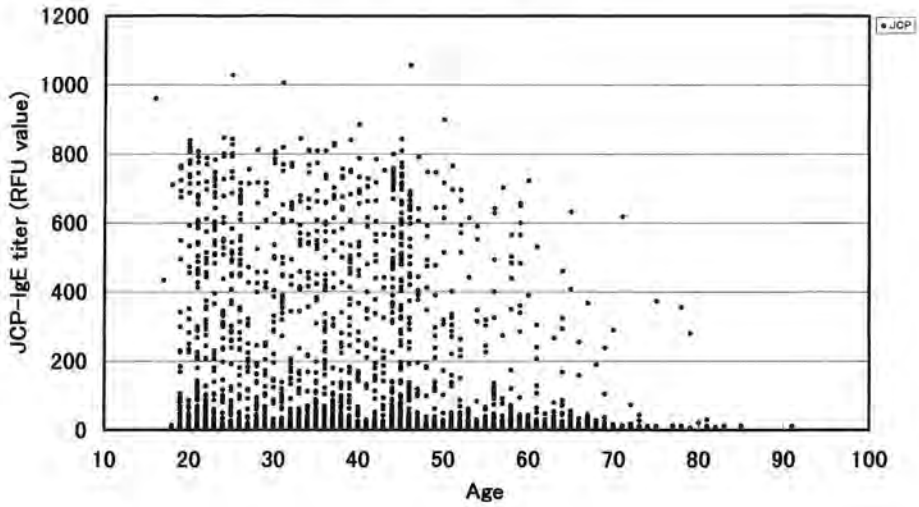
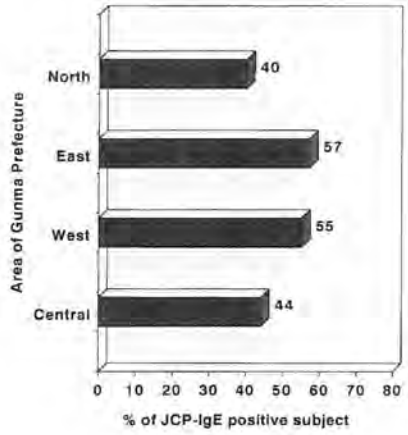


Fig. 5 Positive percentages of young adults (18-39) for JCP-specific IgE in the West, Central, East and North areas in Gunma prefecture.



DISCUSSION

Recently, the number of JCP-sensitive patients has increased markedly in the Japanese population, especially in young people. The positivity rate of JCP-IgE in young adults has shown a yearly increase. We have reported that the percentages of JCP-IgE carriers varied from about 30% to 50% with the intensity of pollen stimulation from 1987 to 1995 and tended to increase yearly[6]. The percentages of JCP-IgE carriers in freshmen in our college (18-19 age group) significantly increased during 9 years examined; that is, pollen scattering in 1989 and 1994 was equally low, while the JCP-IgE positivity rates in those years were 32.5% and 46%, respectively although the percentages of mite-IgE carriers in the same populations changed only slightly during the same 9 years. The present study also showed that the proportion of JCP-IgE carriers significantly increased from 1989 to 1994 in a large number of people in the 18-39 age group whose specific IgE production was vigorous. The positivity rates in 1989 and 1994 were 31.4% and 44.5%, respectively. However, these findings were found definitely in the 18 to 29, 30 to 39, and 40 to 49-age groups and the positivity rate of people over 50 years of age changed only slightly in this time period. These results suggest that the increase of JCP-IgE positivity rate occurred in the younger groups which were sensitive to antigen stimulation.

Some reports confirmed that antigen-specific IgE carriages in healthy populations fell in proportion to increased age. In 1984, Freidhoff found that skin test positivity to 6 inhalant allergens and total serum IgE levels tended to decrease between 20 and 60 years of age[16]. Ishizaki reported that anti-JCP IgE decreased markedly among the residents of a heavily cultivated area aged 50 years or older[17]. We previously showed similar results regarding the relationship between JCP-IgE and mite-IgE with aging[4,5]. In addition, we also found that JCP-IgE levels were inversely proportional to aging in a large population in Gunma prefecture. The highest mean JCP-IgE levels were recognized in the young adult population (18-29), and the IgE levels decreased in proportion to age, while a few JCP-IgE carriages at over 60 years of age showed fairly high JCP-IgE levels. The mechanism which causes IgE production to decrease with age is still unclear. However, Kishimoto and Ishizaka suggested the existence of IgE class-specific regulatory T

cells and a decrease in the absolute number of blood lymphocytes, and alterations in T cell subsets in the elderly[18]. Some studies also suggest that changes of B cell tolerance, the existence of IgE-specific suppressor factors, and concomitant IgG antibodies contribute to the reduction of IgE production with aging [19-21].

In the 18-49 age group, the proportion of specific IgE carriage in females tended to be slightly higher than that in males. However, significant differences were found in both sexes in the over 50 years of age group; the positivity rate in males was higher than that of females. The results confirmed previous results that the sensitivity of IgE production to mite antigen was stronger in males than in females[12]. Tang et al. also described that boys had higher positivity rates of positive mite -IgE than girls, with an overall male to female ratio of 1.5 : 1[22]. A few studies on other allergens described the relationship between IgE production and sex[15,22]. However, we could not find definite evidence to explain the relationship between JCP-IgE positivity rates of both sexes and aging. Further studies are needed to provide an objective information on the influence of sex on the JCP specific-IgE production.

A lot of Japanese cedar trees are planted in Gunma prefecture, therefore, high pollen scattering is observed during every pollen season. There were only slight differences in the JCP-IgE positivities of these 4 areas; the positivity rates in the East and West were slightly high compared with those in Central and North areas. These results coincided with the data from Japanese cedar pollen scattering during the pollen season described in "Studies on Japanese cedar pollinosis in Gunma Prefecture"[15]. In our previous paper, we described that the JCP-specific IgE production is closely associated with pollen scattering similar to the data of other pollinosis such as ragweed pollen and timothy pollen etc[6]. The results obtained from regional analyse also confirmed that specific IgE production against naturally occurring allergen stimulation is mainly due to the intensity of allergen stimulation.

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ハンカチーフ縫製従業者にみられた職業性喘息の1例

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はじめに

近時、産業の発達に伴い職種も多様化し、職場で扱われる物質も多種類となり、職場でこれら物質の微細粉塵に感作されて発症する職業性アレルギー性疾患が注目され、種々の職業性喘息が報告されるに至っている。

筆者は約36年間実地医家として地域医療に携わっているうちに、真珠養殖従業者に発症したホヤ喘息の発見を契機として、職業性喘息に関心を持つようになり、これまで19種類を見出し報告した。

今回、ハンカチーフ縫製従業者に綿布に起因すると考えられる職業性喘息を見出し、若干のアレルギー学的検索と治療を行ったので報告する。

症　例

患者：47歳　女性

職業：ハンカチーフ縫製従業者

家族歴：特記すべき疾患なし

既往歴：特記すべき疾患なし

主　訴：喘鳴を伴う発作性呼吸困難

現病歴：平成5年10月にハンカチーフ縫製業に従事し、約3年経ってから喘息症状を訴えるようになり、次第に増悪するので平成8年10月6日に当院受診した。

作業内容は、民家の8畳の部屋にミシンを5台置いて、5名の婦人が綿布を材料としたハンカチーフ縫製を行っていて、作業量は1日500枚ということであった。室内には換気装置や吸塵装置もなく綿布の微細粉塵が舞っているという。

次に縫製作業と喘息発作との関係では、休業すると喘息発作は寛解し、就業すると喘息発作が起こるといい、窓を閉じて行う冬期に増悪すると訴えた。

来院時現症：咳嗽、喘鳴を訴え、胸部に乾性ラ音を聴取した以外、理学的に身体各部に異常所見は認められなかった。

一般検査成績：表1に示したごとく、末梢血好酸球8.5％、血清IgE値1476IU/mlと上昇を示した以外には、胸部X線像に異常所見なく、心電図正常範囲、血清蛋白分画、肝機能検査、血清電解質などはいずれも正常値であった。

アレルギー学的検査成績

1　皮内反応

本症例における皮内反応は表2のごとく綿布エキス1,000倍稀釈液で陽性を示し、他のアレルゲンエキスではカンジダエキス10,000倍稀釈液で陽性を示した以外は陰性であった。

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2　綿布エキスによる閾値検査

綿布エキス1,000倍より倍数稀釈液を作り、各濃度について皮内反応を実施したところ表3のごとく10万倍であった。

3　IgE RAST

表4に示すごとく綿布でscore 3を示した以外はキヌ、ハウスダスト、ダニ、眞菌類はいずれもscore 0であった。

職場におけるピークフロー値の変動

患者にピークフローメーターを職場に持って行かせて、就業前後を測定させたところ、就業20分でピークフロー値35％の減少と認めたので、本喘息は即時型の職業性喘息と診断された。

表1　一般血液検査成績

血液検査		血清電解質	
赤血球数	486×10⁴/μl	Na	136mEq/l
血色素量	14.3g/dl	K	4.6mEq/l
白血球数	8500/μl	Cl	103mEq/l
ヘマトクリット	42.2%	Ca	4.2mEq/l
白血球百分率（%）		血清蛋白分画（%）	
好中球	64.5	アルブミン	60.3
好酸球	8.5	α_1-グロブリン	4.2
好塩基球	0.7	α_2-グロブリン	8.0
単球	6.0	β-グロブリン	8.4
リンパ球	21.3	γ-グロブリン	19.1
生化学検査		免疫グロブリン	
血清総蛋白	7.2g/dl	IgG	1428mg／dl
総ビリルビン	0.4mg/dl	IgM	1206mg／dl
総コレステロール	182mg/dl	IgA	254mg／dl
GOT	15IU	IgE	1476IU／ml
GPT	10IU	その他	
ALP	96K-A-U	RA	(−)
LDH	280IU	CRP	(−)
γ-GTP	16IU	ASO	16u／ml
TTT	2.8M-U	赤沈	8mm／hr
ZTT	5.7K-U	心電図	異常なし
		胸部X線像	異常なし

表2　皮内反応

抗原	希釈倍数	発赤	膨疹
綿布	1,000×	32×30	14×13
キヌ	1,000×	7×6	3×2
ナイロン	1,000×	4×3	0
ハウスダスト	1,000×	16×16	8×7
アルテルナリア	1,000×	12×12	6×6
ペニシリウム	10,000×	10×9	4×4
クラドスポリウム	10,000×	9×7	4×4
アスペルギルス	10,000×	11×9	5×4
カンジダ	10,000×	22×20	10×9

特異的減感作療法の治療成績

以上の検査成績により本喘息が綿布に起因する職業性喘息と判明したのであるが、抗原の回避のための吸塵装置の設置は零細工場のため実施できず、職場の配置転換や転職も困難であり、患者も現職場での作業継続を希望するので、綿布エキスによる特異的減感作療法を実施した。

図1に示すように綿布エキス10,000倍0.1mlより週1回漸増方式により実施したところ、当初は対症剤、インタール吸入を併用していたのであるが、2ヶ月後より症状が軽快し、3ヶ月で喘息発作は寛解し、対症剤、インタール吸入を中止しても喘息発作は起こらなくなり、現在注射間隔を延ばして維持療法を行いながら、作業継続しているところである。

考　察

職業性喘息は、特殊な職業に従事するものにみられる気管支喘息であり、臨床症状に一般喘

表3　綿布エキスによる閾値検査

希釈倍数	発赤	膨疹
10,000×	26×23	11×10
100,000×	21×20	9×8
1,000,000×	16×14	6×4

表4　IgE RAST

抗原	Score
綿布	3
キヌ	0
ハウスダスト1	0
ハウスダスト2	0
コナヒョウダニ	0
ヤケヒョウダニ	0
カンジダ	0
ペニシウム	0
クラドスポリウム	0
アスペルギルス	0
アルテルナリア	0

息と異なる点はないが、発病に職業が関係し、発作出現が職業ないし職場に関係があるという特徴をもっている。筆者が今回経験した気管支喘息は問診によりハンカチーフ縫製作業と喘息発作との間に密接な関係があることが判明し、アレルギー学的検索により抗原が綿布であることが確認されたので、ハンカチーフ縫製従業者の綿布に起因する職業性喘息と診断された。

職業性喘息は発症までに一定の感作期間があり、職場で連日濃厚な抗原に曝露された結果感作されて発症すると考えられており、一般喘息に比して体質的にも遺伝性が弱い人にも発症すると考えられている。したがって、喘息の発症にも複雑な諸因子の介入が少く、抗原が単一の場合が多く、アレルギーの型としては1型の外因性喘息が多いために、特異的減感作療法が奏効するものと考えられている。

本喘息患者は抗原からの回避が困難であったので、綿布エキスによる特異的減感作療法を行ったのであるが、著効を奏したのは重複抗原がなく、1型の喘息であったためであると考えられる。

衣料品に関連する職業性喘息は、中村により1966年に洋裁学校勤務の女性で、しばしば絹を扱い喘息発作をみた症例[1]、および寝具店員で蒲団のまわた、蒲団カバーの絹に接触して感作されて喘息発作をみるに至った症例[2]が報告されているが、筆者も手袋製造者にみられたキヌ喘息[3]、洋服仕立職人にみられた羊毛喘息[4]、衣料品販売従業者の羊毛・綿喘息[5]、縫製工場従業者の綿喘息[6]を報告した。

綿を抗原とする衣料品に関連する職業性喘息は筆者の報告以外にはみられないようであり、最近経験したハンカチーフ縫製従業者にみられた職業性喘息も興味ある症例と考え報告した。

おわりに

衣料品を縫製する人や、扱う人は全国に多数存在すると思われる。その中でアレルギー素因を持った人たちは、そこで扱われている絹、羊毛、綿などの材料の粉塵に連日感作されて職業性アレルギー性疾患を発症することが予測されるので注意を喚起したい。

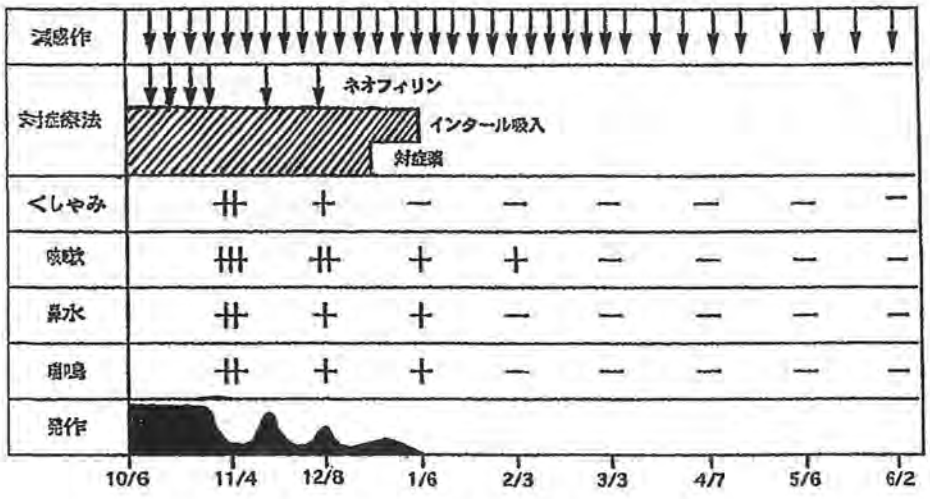

図1　綿布エキスによる特異的減感作療法の経過

本論文の要旨は第5回日本職業アレルギー学会において発表した。

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A case report of occupational asthma caused by cotton in a handkerchief sewing factory.

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Takamoto Clinic

Many types of occupational asthma uncovered in the primary care institution have been reported.In this report a patient engaged in a handkerchief sewing factory who suffered from asthma with cotton as antigen was found by some allergological investigations and treatment.

The patient was a 47 year old female. She has engaged in a handkerchief sewing factory since 1993.She developed asthma about three years afterward.It was asssumed that her attack of asthma could be caused by cotton which was material of handkerchief.On allergological tests,her serum level of IgE was indicated to have raisen to 1476 IU/ml and IgE RAST to cotton was found to be positive.The intracutaneous allergic reaction was demonstrated to be positive in respect of cotton extract with the threshold value of 100,000 times. Peak Flow Volume(PEF) was indicated to decrease remarkably 20 minutes after working. The patient reacted well to the specific desensitization treatment.

The case is reported here as it is assumed that a patient who was engaged in a handkerchief sewing factory had been sentitized with cotton.

Two cases of occupational latex allergy

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Abstract

Case 1 : A 25-year-old female dental assistant having no past history of allergies developed hand dermatitis after using latex gloves for a couple of months. Immediately after giving birth to a stillborn baby, she suffered erythema and swelling around her eyes, her blood pressure dropped and throat edema appeared after a rubber balloon was inserted into her uterus. Finally, she went into dyspnea. She recovered after an intravenous drip of a steroid. In scratch testing, ammoniated latex sheet extract solution showed wheal and flare at 5min, 10min, 20min, 30min and 50min after placing samples. Banana showed wheal and flare 20min after placing samples.
Case 2 :A 23-year-old female dental assistant developed hand dermatitis when she used rubber gloves. She showed positive reactions to the rubber gloves and to ammoniated latex sheet in 48h-closed patch testing and a urticarial reaction in scratch testing with an extract solution of ammoniated latex sheet.

Key word : latex, contact allergy, contact urticaria

Introduction

Latex allergy has become a big problem for health care personnel[1]. In previous papers, many patients with latex allergy were reported having atopic diathesis. Latex allergy is a troublesome symptom having cross-reactions to many fruits such as bananas, avocados, chestnuts, etc. Furthermore, anaphylaxis due to latex is life-threatening[2]. Recently, several cases of latex allergy have been reported in Japan[3]. In this paper, we are reporting on two cases of occupational latex allergy. One case was a dental assistant with anaphylaxis due to a rubber balloon. The other case was a dental assistant with hand dermatitis due to rubber gloves who also, showed a contact urticarial reaction and delayed type hypersensitivity to latex.

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Case 1

A 25-year-old female dental assistant having no past history of allergies developed hand dermatitis after using latex gloves for a couple of months. She took a leave from her work during pregnancy, and her hand dermatitis improved . Unfortunately, her baby was stillborn. After delivery her obstetrician inserted a rubber balloon into her uterus. Immediately after the operation, her hand dermatitis redeveloped, she suffered swelling around her eyes, her blood pressure dropped, and throat edema appeared. Finally, she fell into dyspnea. She recovered after an intravenous drip of a steroid.

Laboratory findings at her first examination in our clinic were as follows : white blood cell count was 3800/μl, eosinophil count was 312/μl and IgE RIST was 139 IU/ml. Specific IgE (Pharmacia CAP-RAST, Pharmacia & Upjohn, Tokyo, Japan) of latex was 3.80U/ml (class 3), specific IgE (Alastat, SRL, Inc., Tokyo, Japan) of a chestnut was 0.93U/ml (class 1), specific IgE (Pharmacia CAP-RAST) of a banana and an avocado were negative, and specific IgE (SHIONOGI CAP-RAST, Osaka, Japan) of the flesh and pollen of a chestnut were negative.

Case 2

A 23-year-old female dental assistant with no particular past history of allergies worked at a dental office over a 2 year period. She developed hand dermatitis after she used Professional (Baxter Limited, Tokyo, Japan) gloves for about one month. She felt a strong itching sensation on her hands and repeatedly scratched them. She developed many vesicles on her hands. Although she tried using different rubber gloves and applied Rinderon VG (containing 0.12% betamethason valerate and 0.1% gentamicin sulfate : Shionogi & co., Ltd., Osaka, Japan) ointment and Dermovate (containing 0.05% clobetasol propionate : Nippon glaxo p.l.c., Tokyo, Japan) ointment, her hand dermatitis continued.

Skin testing

1. Test methods and readings

(1) Scratch testing

The ammoniated latex sheet was kindly provided by Pacific Dunlop Japan k. k. (Tokyo, Japan). We incubated 0.2g ammoniated latex sheet in 1ml sterile distilled water. After 30 minutes, the ammoniated latex sheet was removed. Then, the solution was stored in a sterile bottle and used for scratch testing. Using a prick-lancetter(1 mm spiss)(Ewo Care AB, Bredaryd, Sweden) with shoulders to prevent deeper penetration, we carried out scratch testing on both cases with the latex sheet extract solution. Readings were made at 20min and 50min after placing the samples.

(2) Patch testing

Using Finn Chamber (Epitest Ltd Oy, Tuusula, Finland) and Scanpor tape (Norgesplaster A/S, Norway), we carried

out 48h-closed patch testing on case 2 with the rubber gloves she used, ammoniated latex sheet , 21 related allergens of rubber gloves and vulcanizing agents. Readings were made at 1 and 24 hours after removal according to ICDRG recommendations.

(3) "Use" testing with 1 finger of a latex glove

We conducted 5 minutes of "use" testing with 1 finger of White Latex Surgical Gloves (Smith & Nephewperry, Tokyo, Japan) on case 1. After dipping the patient's hand into water, we inserted one of her fingers into one finger of the latex glove, and then scrubbed it. Readings were made at 5min and 20min after putting on the latex glove.

(4) "Use" testing with a low-latex glove

"Use" testing with a low-latex latex dental gloves (Sumitomo rubber industries, Ltd., Kobe, Japan) was also conducted on case 1. After dipping the patient's hand into water, one low-latex glove was put on her hand and then scrubbed. Reading was made 20min after putting on the low-latex glove.

2. Results

Case 1 : The results of the scratch testing and "use" testing are shown in Table 1. The ammoniated latex sheet extract solution showed wheal and flare at 5min, 10min, 20min, 30min and 50min after placing the samples. Flesh of a banana showed wheal and flare at 20min after placing the sample. White Latex Surgical Gloves showed erythema, wheal and itching at 5min and slight erythema at 20 min after putting on the glove. Low-latex latex dental gloves reacted negatively.

Case 2 :The results of scratch testing and patch testing are shown in Table 2. The ammoniated latex sheet extract solution showed wheal and flare at 20min and 50min by scratch testing. Professional gloves and ammoniated latex sheet showed positive reactions at both 48h and 72h readings of the 48h-closed patch testing. Related allergens of rubber gloves and vulcanizing agents were all negative.

Discussion

Previous reports have defined a high risk group for latex allergy, including health care personnel, patients with spina bifiida undergoing frequent operations, atopic patients, and other people exposed to latex[2]. Case 1 showed hand dermatitis, and also anaphylaxis. In scratch testing, she showed a strong positive reaction to the ammoniated latex sheet extract solution.

Turjanmaa et al[4] reported specific IgE of latex was positive in 60~65% of patients with immediate type latex allergy and was negative in cases of weak latex allergy. Specific IgE of Latex was positive in case 1.

Previous papers reported the cross-reactivity between latex and fruits such as bananas, avocados etc[5,6]. Scratch testing with the flesh of a banana was positive, while specific IgE of banana was negative. After developing hand dermatitis due to

latex gloves, she reported an itching sensation when she ate a banana. We suspected that the positive reaction to the banana was a cross-reaction to latex.

We gave her plastic gloves and low-latex gloves that were negative by the "use" testing and asked her which gloves were more convenient. She answered that low-latex gloves were more convenient than plastic gloves. She said that she could not work as a dental assistant if she had to wear plastic gloves because they were so thick that she lost sensitivity in her fingertips. Now, she is able to continue her work as a dental assistant using low-latex gloves.

Case 2 did not consent to serological tests for latex-specific IgE and latex glove "use" tests. Therefore we conducted only scratch and patch testing of gloves and latex sheet.

Although previous reporters mention cross-reactivity between latex and banana and case 1 also experienced an itching sensation when she ate banana, case 2 did not have any problem when she ate this fruit.

We conducted control patch testing with ammoniated latex sheet on 59 patients with hand dermatitis. There was one positive reaction in the control patch testing with ammoniated latex sheet. This case had a previous history of contact dermatitis due to rubber gloves. In addition, we conducted control scratch testing on 3 dermatologists. All three dermatologists were negative. We decided that the positive reactions of case 2 from scratch and patch testings were allergic reactions.

We considered that latex contact urticaria developed initially, then her skin barrier was broken by scratching, and latex antigen penetrated into the living layers of the epidermis. Thus, delayed hypersensitivity to latex was induced.

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Table 1. Results of scratch and "use" testing of case 1

1. Results of scratch testing

Material	5min	10min	20min	30min	50min
Latex sheet extract solution	8×13/42×42	14×14/42×70	14×14/42×82	20×30/42×90	18×18/40×70
Banana flesh	negative	10×10/15×20	negative	negative	negative
Avocado flesh	negative	negative	negative	negative	negative
Distilled water	negative	negative	negative	negative	negative

(unit:mm)

2. Results of "use" testing with 1finger of a latex glove

Material	5min	20min
White Latex Surgical Gloves	erythema,wheal and itching	slight erythema

3. Results of "use" testing with a low-latex glove

Material	20min
LATEX DENTAL GLOVES	negative

Table 2. Results of scratch and patch testing of case 2

1. Results of scratch testing

Material	20min	50min
Latex sheet extract solution	wheal and flare	wheal and flare
Distilled water	negative	negative

2. Results of patch testing

Material	con.	48h	72h
Professional gloves	as is	+	+
Latex sheet	as is	+	+
Plastic gloves	as is	-	-
Rinderon VG ointment	as is	-	-
Dermovate ointment	as is	-	-

Efficacy of O_2 and vancomycin in a case of pneumatosis cystoides intestinalis after incomplete remission with O_2 and tinidazole

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Abstract

An 80-year-old man with monoclonal hypergammaglobulinemia, developed upper abdominal distention and mild hematochezia. Computed tomography revealed intramural gas cysts in the wall of the transverse and descending colons. He demonstrated a mild form of immune deficiency and human leukocyte antigens, Cw3-DR4, were probably homozygotes. The complaints and clinical findings improved following a combination of oxygen inhalation and administration of vancomycin after incomplete remission with oxygen and tinidazole.

Key words : Pneumatosis cystoides intestinalis
Benign monoclonal hypergammaglobulinemia
Vancomycin

Introduction

Pneumatosis cystoides intestinalis (PCI) is a reratively rare condition characterized by multiple intramural pockets of gas involving any portion of the gastrointestinal tract and occasionally the mesenteric attachments. Pneumatosis in adults frequently has a benign course and prognosis. It was first described in the 18th century by Duvernoi, J. Hunter and Jenner[1].

Two theories on the etiology exist, mechanical and bacterial. Several underlying diseases or conditions have been reported for the pathogenesis, involving intestinal obstruction, connective

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tissue diseases, chronic obstructive lung diseases, administration of immunosuppressive drugs, and the exposure to some organic chemical compounds for industrial use[2].

We describe a case of PCI, where the combination of oxygen and vancomycin therapy was effective, although there was no evidence for its bacterial etiology.

Case Report

An 80-year-old man, diagnosed with monoclonal gammopathy of undetermined significance (IgG, κ type) in 1978, had been demonstrating abdominal distention and mild hematochezia since 1991. No abnormalities of the colon were radiographycally found (Fig.1-a). The complaints were persistent. In 1994, colonoscopy revealed the appearance of submucosal cyst-like lesions protruding into the lumen of the transverse and descending colons. Radiolucent collections of gas were clustered along the distorted contours of the barium-filled colon in a radiographic study at this time, but obstructive lesions were not found (Fig.1-b). Computed tomography of the upper abdomen confirmed the localization of the intramural air-filled cysts in the colon, indicating features of pneumatosis cystoides intestinalis (PCI).

The patient had never been exposed to any industrial organic chemical, e.g. trichloroethylene, nor to any kind of pesticide or herbicide since 1990, when he had not yet manifested PCI. Chest roentgenogram suggested mild hyperinflation of the lungs, but the vital capacity was 2440㎖(81.6%) and $FEV_{1.0}$ was 2290㎖ (93.9%T), which were incompatible with chronic obstructive pulmonary disease. No fibrotic change was seen. Raynaud's phenomenon, scleroderma, Gottron sign, heliotrope rash, butterfly rash, and photosensitivity were not found. Autoantibodies, including anti-scl-70 Ab, anti-Jo-1 Ab and anti-DNA Ab, were negative, except for a low positive titer of anti-nuclear Ab (X80, speckled type) (Table1).Therefore, systemic sclerosis, systemic lupus erythematosus and dermatomyositis were neglected.

Immunoelectrophoresis of the serum and the urine depicted a monoclonal hypergammaglobulinemia pattern of γ and κ types. The ratio of plasma cells to the total nuclear cells of the bone marrow was 0.6 %. This ratio had been about the same for 16 years. Other immunological examinations showed some mild immune abnormalities; serum IgA was 67 mg/dℓ, lymphocyte count in the peripheral blood was diminished (624-989/$\mu\ell$), lymphoblastogenesis stimulated by concanavalin A had slightly decreased to 1.77, and the Mantoux reaction by purified protein derivative was negative. We also examined human leukocyte antigens. Only Cw3 and DR4 were expressed at C and DR loci respectively, suggesting a homozygote of Cw3-DR4 haplotype (Table1).

Although anaerobic bacteria, including clostridium, did not grow in the culture study of the fecal specimen, we assumed an infectious process of anaerobic bacteria in the colon. As oxygen was recommended

as the first choice therapy, considering the risk of using antibiotics[3], 2 ℓ/min of oxygen was inhaled for 4 hours everyday. Then, administration of tinidazole was added to the oxygen therapy. One cycle of the chemotherapy consisted of oral administration of 1000 mg per day for 2 days and no antibiotics for the following 7 days. Five cycles resulted in improvement of the abdominal expansion and hematochezia. However, the subdiaphragmatic gaseous clusters at the splenic quadrant in the plain films, did not disappear. Alternatively, 2000 mg of vancomycin was intravenously injected for 7 consecutive days, while the oxygen therapy continued, and the radiolucent clusters disappeared. This was confirmed by a barium enema (Fig.1-c), computed tomography and colonoscopy. The immune abnormalities, however, did not improve. As the patient urgently required a prophylactic oxygen therapy, 2 ℓ/min of oxygen is administered for 4 hours every day,and no recurrence is so far observed.

Discussion

Priest and Goldstein classified pneumatosis cystoides intestinalis (PCI) into 2 clinical groups, depending on the co-existence of associated lesions of the gastrointestinal tract[4]. When no other gastrointestinal abnormalities are present, the disease is considered primary or idiopathic. The second group has a broad variety of lesions in the gastrointestinal tract. The former occurs mostly in adults, and the colon, particularly the left side, is involved. Our patient falls into this category. The small intestine is involved more commonly in the latter group.

Priest et al. also summarized 2 theories regarding the etiology; mechanical and bacterial. Any mechanical obstruction of the intestine could give rise to PCI. Akamatsu et al. proposed trichloroethylene as a cause of PCI, because PCI patients were observed in fine mechanical industrial factories. Our patient, however, had never been exposed to this organic compound, nor showed any intestinal obstruction.

A number of experiments support the bacterial theory[4-6]. It is interesting that some autoimmune diseases such as scleroderma, dermatomyositis and lupus erythematosus, and Crohn's disease[7-10], are associated with PCI. Use of immunosuppressive drugs may also be accompanied by PCI[11]. In our patient, a mild form of immune deficiency was demonstrated, probably in relation to benign monoclonal hypergammaglobulinemia, suggesting vulnerability to bacterial infection. For this reason, we tried the combination therapy of oxygen and tinidazole, the latter is a derivative of metronidazole and is reported to be effective for protection against anaerobic bacterial infections[12]. The therapy was incomplete, and we, therefore, changed it to oxygen and vancomycin, which were satisfactory. This indicated that PCI, in our case, may have been induced by a bacterial mechanism, although there was no direct evidence for bacterial infection. This is the first case in which vancomycin was effective for PCI.

There have been no reports describing the relationship between HLA types and PCI or benign monoclonal hypergammaglobulinemia. Our case expressed the HLA haplotype of Cw3-DR4, probably a homozygote. As Cw3-DR4 is well known to be significantly linked to rheumatoid arthritis, this haplotype might be associated with some immune abnormalities, which presents an opportunity for anaerobic bacteria. Further studies should be done to elucidate the pathological mechanism of this disease.

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Table 1. Immunological Examination

CRP	0.1mg/dℓ	TPHA	negative
ASLO	0 IU/mℓ	Mantoux Reaction by PPD	
RF	4 IU/mℓ		negative
Immunoglobulins	21.8%	Lymphoblastogenesis	
IgG	3040 mg/dℓ	PHA	2.10
IgA	55 mg/dℓ	Concanavalin A	1.77
IgM	134 mg/dℓ	Fraction of Lymphocytes	
IgE	73 IU/mℓ	CD4 (+) CD8 (-)	29.5 %
Immune Complex (C1q binding)		CD4 (+) CD8 (+)	0.2 %
	12.9 μg/mℓ	CD4 (-) CD8 (-)	32.5 %
C3	63 mg/mℓ	CD4 (-) CD8 (+)	0.9 %
C4	22 mg/dℓ	Total SmIg*	37.6 %
CH50	37.1 %	SmIg G	33.3 %
LE Phenomenon	negative	SmIg M	8.2 %
ANA	X80 (speckled)	SmIg A	3.5 %
anti-DNA AB (EIA)	5 IU/mℓ	SmIg D	5.0 %
anti-SM Ab (EIA)	‹1.0×1	SmIg κ	21.3 %
anti-SS-A Ab (EIA)	‹1.0×1	SmIg λ	19.1 %
anti-SS-B Ab (EIA)	‹1.0×1		
anti-RNP Ab (EIA)	‹1.0×1	HLA	
anti-SCL-70 Ab (EIA)	‹1.0×1	A Loci	24,33
anti-Jo1 Ab (EIA)	‹1.0×1	B Loci	44,62
Thyroid Test	‹X100	C Loci	w3, Blank
Microsome Test	‹X100	DR Loci	4, Blank

Abbreviation *Sm:membrane surface

編集後記

今年はエルニーニョ現象に起因すると思われる異常気象が世界各地で続発しているようで群馬県でも4月の平均気温が2.7度も高く、前橋気象台観測史上最高とのことです。異常といえば、日本経済も低迷を極め今後も不安定傾向が持続すると専門家は予想しているようです。この原因を国民ではなく政府や大蔵省の無能力さに押しつけて何となく納得していた編集子も不摂生がたたり体調を崩してしまい、今年の桜はしかも雪を被った桜を病室から観ることになってしまいました。幸い、大過なく順調に回復しましたが、このため本誌の発行が大幅に遅れることになってしまいました。深くお詫び申し上げます。

さて平成9年度の本学会でも職業・環境性疾患の対策の方向性として関係各方面に実態を広くアピールしようとする声が高まっています。学会で担当のworking groupを編成しこれを当面の課題として取り組んだら如何とおもいます。会員諸氏のご意見をお待ちしております。なお本誌への積極的な御投稿も宜しくお願いいたします。

平成10年5月

中澤次夫　記

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