

The hazard of mould hyposensitization in children with asthma

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Summary

Of thirty-eight children, who were immunized with mould extracts, seven (19%) were withdrawn from hyposensitization due to serious side-effects clinically consistent with a type III reaction. These seven children exhibited a two- to four-fold increase in circulating precipitating-antibodies to the injected extracts, and had shown a slight increase in precipitating antibodies to the mould extracts used before hyposensitization. A further fourteen patients, also hyposensitized with mould extracts but without side effects did not develop precipitating antibodies. It is suggested that hyposensitization with mould extracts may be hazardous in children who may have a primary 'immune imbalance' with a risk of provoking type III reactions.

Introduction

Critical evaluation of allergen injection-therapy in children with asthma has not, to date, been helpful to clinicians attending allergic children. In fact, subcutaneous allergen-injections with mould extracts are unsatisfactory and their safety in children has not been sufficiently examined, for example, the incidence of immune complexes (IC) generated by the injected allergen and the clinical result. Further, because of the side effects, many clinicians have been reluctant to prescribe hyposensitization with mould extracts. This study presents the results of observations made in children with asthma subjected to a hyposensitization programme with mould extracts, and reports on the incidence of severe side-reactions associated with a simultaneous rise in precipitating serum-antibodies (PSA) to the allergens injected.

Materials and methods

Patients

During a 3 year 6 month period thirty-eight children with bronchial asthma were hyposensitized with mould extracts (ALUTARD, Allergologisk Laboratorium, Denmark). However, within 5–15 months (median 7 months), hyposensitization was withdrawn in seven (19%) due to unfavourable and mostly serious side-effects. In the thirty-eight patients, allergy to moulds was confirmed either by (1) a positive prick-test

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(more than 3 mm) and a positive RAST (more than RAST-class 2) (twenty-two patients), or (2) a positive bronchial-provocation test to the mould extract in question. Seven children exhibited severe side-effects to hyposensitization, but had no associated pulmonary-disease such as chronic bronchitis, bronchiectasis, pulmonary interstitial-disease or pulmonary complications following α -1-antitrypsin deficiency, immune deficiency or cystic fibrosis.

On entering hyposensitization the median age was 9 years 2 months (range 5 years 9 months–15 years 1 month). In the seven children withdrawn from hyposensitization, the median age was 8 years 1 month (range 6 years 4 months–11 years 4 months). In these seven patients and in fourteen of the remaining thirty-one children, investigators for precipitating serum-antibodies were carried out before entering the hyposensitization programme and at various intervals of months after immunization. The assays for detection of precipitating serum-antibodies to moulds were performed as a counter-current immune electrophoresis method (Edwards, 1980). Most of the patients were hyposensitized with a mixed extract consisting of an equal mixture of *Cladosporium herbarum* and *Alternaria iridis*, which were the most troublesome air-borne mould allergens during late summer in Denmark. In the children with side effects to the allergen injections, each exhibited a similar reaction 2–12 hr following the injection, one typical case history is cited below.

Case History

This 8-year-old boy was referred to the Allergy Unit with severe and protracted asthma, mainly in late summer. Prick tests revealed a positive reaction to *C. herbarum* and to *A. iridis*, and RAST—class 0 to the allergens was found. However, bronchial provocation-tests with the mould extracts showed a more than 20% decrease in peak flow (PEF) and forced expiratory volume in 1 sec (FEV₁) followed by active asthma. He was then put on a hyposensitization programme consisting of an equal mixture of *Cladosporium* and *Alternaria*, which was carried out by his general practitioner. For the following 6 months no side-effects to the injections occurred. Then the boy exhibited increasing symptoms of asthma, sometimes followed by an increase in body temperature. Unfortunately neither the parents nor their general practitioner informed the staff at the Allergy Unit about these symptoms until the patient had been on hyposensitization for 14 months. Then he was carefully observed at the clinic following an injection with the mould extracts. No immediate reaction was observed; however, 2 hr later he felt fatigued and restless, and during the next 3 hr, he developed a severe attack of asthma with cyanosis and a decrease in PEF and FEV₁ of more than 50%. Three hours after the injection a firm, rough nodule, blue-reddish in colour, developed at the site of the injection. For the following 2 days the boy had severe attacks of asthma with fever, which gradually subsided with inhalations of a β -2-agonist and oral Prednisone. Hyposensitization of the patient was stopped.

Results

Tables 1 and 2 show the levels of precipitating serum-antibodies. In patients with severe side-effects (Table 1) the PSA-titre showed a two- or four-fold rise as compared to the initial titre. In most instances the increase in PSA was obtained only to one component of the mixed extracts. Patient No. 2 did not have a PSA test before immunotherapy. Fourteen patients without side-effects to mould hyposensitization are listed in Table 2. Most received allergen injections for a considerably longer period

Table 1. The levels of precipitating serum-antibodies in patients who exhibited severe side-effects to hyposensitization

Patients	Age (yrs)	Precipitating serum-antibodies							
		Cladosporium		Alternaria		Aspergillus		Penicillium	
		*Before	†After	Before	After	Before	After	Before	After
1	9.4	0	1:4	1:2	1:12				
2	8.3	ND	1:2						
3	11.4	0	1:2	1:2	1:8				
4	8.1	0	1:4	1:2	1:8				
5	6.4			1:2	1:8	1:2	1:2		
6	7.6	1:2	1:2	1:2	1:8				
7	8.1			1:4	1:8			0	1:4

*Before immunotherapy

†After immunotherapy

ND=Not done

Table 2. The levels of precipitating serum-antibodies to moulds in patients without side-effects to hyposensitization

Patients	Age (yrs)	Precipitating serum-antibodies							
		Cladosporium		Alternaria		Aspergillus		Penicillium	
		Before	After	Before	After	Before	After	Before	After
1	7.4	0	0	0	0				
2	15.1	0	0						
3	6.5	0	0	0	1:2				
4	9.2	0	0	0	0				
5	11.3			0	0	0	0		
6	7.3	0	0	0	0				
7	11.6					0	1:2	0	0
8	16.1	0	0					0	0
9	8.6			0	0			0	0
10	11.4	0	0	0	0				
11	11.7	0	0	0	0				
12	7.5			0	0	0	0		
13	12.5	0	0						
14	10.4	0	0						

(median 12 months) than the patients who exhibited side-effects (median 7 months), and it should be noted that the patients with side-effects often showed a slight increase in PSA before hyposensitization was initiated.

Discussion

The potential hazards of hyposensitization have been reported in different studies. Vervloet *et al.* (1980) found that only 0.1% of a total of 151 997 hyposensitizations

resulted in systemic reactions. Furthermore, Kemler *et al.* (1979) and Stein *et al.* (1978) found no evidence of circulating immune complex (IC) in patients with rhinitis and asthma who received subcutaneous injections of mould house-dust mite and pollen extracts. In contrast, Stendardi, Delespesse and Debisschop (1980) reported that about 40% of patients, who were hyposensitized with different allergens, developed detectable IC in serum simultaneously with a rise in PSA—most common in patients immunized with mould extracts, and Cano *et al.* (1977) found that atopic patients compared to normal subjects had significantly higher values of circulating IC. The highest mean-values were seen in patients who had been on long-term immunotherapy.

Several investigators (El-Hefny *et al.*, 1980; Kuuliala *et al.*, 1979; Moore & Fink, 1975) have reported considerably elevated levels of PSA in patients with asthma, and some of these authors emphasized that high titres of PSA may be found even in patients without clinical signs of type III alveolitis. Finally, substantially elevated PSA levels to pigeon serum may be present in symptomatic as well as in symptomless pigeon-breeders (Moore & Fink, 1975). Our seven patients with an increase in PSA to mould before hyposensitization and severe side-effects may reflect an 'immune imbalance' within our asthmatic group, sensitive to moulds, and this possibility is being investigated in our clinic.

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