

Serum IgE as an important aid in management of allergic bronchopulmonary aspergillosis

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Differentiating patients with allergic bronchopulmonary aspergillosis (ABPA) from patients with asthma who have immediate skin reactivity to Aspergillus fumigatus may be difficult when the characteristic clinical and laboratory findings of ABPA are absent. This article describes the response of ABPA patients to corticosteroid therapy. After treatment of the acute stage of the disease with corticosteroid therapy, all ABPA patients had $\geq 35\%$ reduction of the total serum IgE within 2 mo. In 30 exacerbations of ABPA in 15 patients, there was $\geq 35\%$ reduction of the total serum IgE in 24 exacerbations within 2 mo. Of the six exacerbations with $< 35\%$ reduction of total serum IgE, noncompliance to medical therapy was clearly documented in three exacerbations. In one exacerbation with a slowly resolving pulmonary infiltrate, 6 mo of corticosteroid therapy was required before the total IgE decreased 35%. The total serum IgE and its response to corticosteroid therapy is a sensitive marker in ABPA and can be considered an important aid in management of ABPA. Failure to achieve $> 35\%$ reduction of total serum IgE by 2 mo with the administration of corticosteroid therapy in patients highly suspected of ABPA should make one either question the diagnosis of ABPA or consider noncompliance of the patient to medical management with corticosteroids. (J ALLERGY CLIN IMMUNOL 74:68, 1984.)

During the past 14 yr, the number of reported cases of ABPA has risen secondary to increased awareness by physicians and to improved diagnostic criteria for identifying the disease.^{1, 2} The diagnosis of ABPA usually does not present a problem when the complete clinical picture is present in the acute stage of the disease. The clinical diagnostic features of ABPA include (1) asthma, (2) history of pulmonary infiltrates, (3) blood eosinophilia, (4) immediate skin reactivity to Af antigen, (5) elevated serum IgE concentration, (6) precipitating antibodies against Af antigen, (7) central bronchiectasis, and (8) elevated serum IgE and IgG antibodies to Af (compared to asthmatic patients with immediate skin reactivity to Af).^{3, 4} Other features may include a positive sputum culture for Af, a history of expectoration of brown plugs, and late (Arthus type) skin reactivity to intracutaneous testing with Af antigen.

Abbreviations used

ABPA: Allergic bronchopulmonary aspergillosis
Af: *Aspergillus fumigatus*

However, it is not uncommon for asthmatic patients without ABPA to demonstrate the first four criteria. For example, up to 25% of asthmatic patients may demonstrate immediate skin reactivity to Af.⁵ Although the serum IgE is markedly elevated in most patients with ABPA, asthmatic patients without ABPA may also demonstrate elevated serum IgE values. Precipitating antibodies against Af antigen may be weakly positive or even negative at the time of diagnosis in ABPA, and these antibodies may be observed in up to 10% of asthmatic patients.⁵ Late (Arthus type) skin reactivity is demonstrated in only one third of ABPA patients.¹ Positive sputum cultures for Af are uncommon in individual ABPA cases and, furthermore, many patients with ABPA do not produce sputum even during exacerbations with pulmonary infiltrates. Central bronchiectasis may not be present particularly in early cases of ABPA, and bronchography of the lungs may be hazardous in the corticosteroid-dependent asthmatic. In children sus-

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TABLE I. Change in total serum IgE after diagnosis of ABPA and prednisone treatment of the acute stage

Patient	Initial IgE*	2 mo IgE	% Change IgE	Patient	Initial IgE	2 mo IgE	% Change IgE
1	58,000	19,500	66	21	6,520	2,278	65
2	32,000	7,800	76	22	5,377	3,516	35
3	20,192	10,262	49	23	4,988	2,616	48
4	18,760	3,670	80	24	4,255	1,380	65
5	17,724	5,500	68	25	4,000	2,235	45
6	13,146	3,428	74	26	3,679	1,431	61
7	13,000	7,000	46	27	3,655	1,129	69
8	12,980	6,118	53	28	3,614	1,150	68
9	12,457	6,943	56	29	3,400	1,100	68
10	12,459	7,659	39	30	2,991	1,616	46
11	12,421	1,436	89	31	2,070	639	69
12	11,119	6,774	39	32	1,900	1,102	42
13	10,350	4,945	53	33	1,894	999	42
14	10,210	6,470	37	34	1,883	970	75
15	9,995	2,803	74	35	1,696	880	48
16	9,704	3,240	67	36	1,664	514	69
17	9,430	2,443	74	37	1,491	905	39
18	8,510	3,600	58	38	1,427	656	54
19	8,271	3,997	52	39	810	164	80
20	7,360	2,990	59	40	697	242	65

*Total serum IgE (ng/ml).

pected of ABPA, general anesthesia is required for this procedure.

We have been able to demonstrate that there is a dramatic fall in the total serum IgE with the institution of corticosteroid therapy in patients with ABPA.⁶ Associated with this decline in total serum IgE, there is also a clearing of pulmonary lesions and control of asthma and other constitutional symptoms. Since exacerbations of ABPA are correlated with a twofold or greater rise in total serum IgE, and in most cases the total serum IgE rises before the development of a pulmonary infiltrate, serial-IgE determinations of total IgE are of importance in management of these patients.⁷

Since the differentiation of patients with ABPA from patients without ABPA who demonstrate some of the criteria of ABPA may be difficult, other parameters may be of value in separating these groups of patients. We report here evidence that a decline of >35% in the total serum IgE with the institution of corticosteroid therapy over a 2-month period occurs in ABPA. This change in IgE is important in the initial diagnosis of patients with ABPA and in monitoring therapy for recurrent exacerbations of ABPA.

PATIENTS AND MATERIAL

ABPA patients

Extensive clinical evaluation has been performed on 40 patients ranging in age from 8 to 67 yr with ABPA who have been diagnosed and managed by the Allergy-Immu-

nology Section of Northwestern University Medical School. At initial evaluation or during a period of observation, all patients demonstrated the primary diagnostic criteria for ABPA.^{3, 4} Therapy was instituted in these patients on initial diagnosis of the disease with prednisone 0.5 mg/kg/day as a single morning dose for 7 to 14 days at which time the same dosage was changed to a single-dose, alternate-day regimen, and this dosage was maintained for a minimum of 3 to 6 mo. Patients were considered to have an exacerbation of ABPA when there was a twofold or greater rise in their total serum IgE accompanied by a new infiltrate on chest roentgenograms and not explained by infection or other causes. Therapy for recurrent exacerbations in these patients was similar to the therapy administered for the acute stage of the disease.

Total serum IgE

Total serum IgE was measured by a double-antibody radioimmunoassay method.⁸ The serum-IgE level was obtained at the initial presentation of the patient to our service and on a monthly or bimonthly basis subsequent to this.

IgG and IgE antibody to Af

The IgG and IgE antibody to Af was estimated by the solid-phase, polystyrene-tube radioimmunoassay as previously described.⁹

RESULTS

The response of ABPA patients, presenting in the acute stage of the disease, to the administration of corticosteroid therapy is illustrated in Table I. All 40 patients had >35% reduction in the total serum IgE

TABLE II. Change in total serum IgE with prednisone after exacerbations of ABPA

Patient	Exacerbations	Initial IgE*	2 mo IgE	% Change IgE	
1	1	16,320	9120	44	
	2	23,324	15,045	35	
	3	23,299	12,200	52	
	4	31,269	12,947	62	
	5	22,692	11,872	48	
	6	28,800	13,500	53	
	7	19,524	23,788	0	23,488†
	8	31,000	28,000	9	12,097‡
2	1	4,150	940	83	
	2	1,641	1,184	28	681†
3	1	1,281	642	50	
4	1	9,600	2,200	78	
	2	6,164	2,481	60	
5	1	10,660	3,540	67	
	2	10,250	15,500	0	4,600§
	3	8,160	6,720	18	3,760§
6	1	21,721	5,964	73	
	2	11,229	9,455	16	5,477§
7	1	5,610	1,150	80	
	2	2,400	1,206	50	
8	1	1,279	583	54	
9	1	2,621	337	87	
10	1	12,000	6,300	48	
	2	8,400	4,200	50	
11	1	1,600	481	70	
12	1	8,400	3,840	54	
13	1	6,394	3,500	45	
14	1	20,000	11,500	43	
	2	24,618	10,931	56	
15	1	3,624	950	74	

*Total serum IgE (ng/ml).

†Four month IgE.

‡Six month IgE.

§Three month IgE; noncompliance with prednisone was suspected.

by 2 mo. Twenty of 40 patients had >60% reduction of the total serum IgE by 2 mo. Thirty-five of 40 patients had >40% reduction of IgE by 2 mo.

The response of ABPA patients presenting with an exacerbation of the disease to the administration of corticosteroid therapy is illustrated in Table II. Thirty exacerbations of ABPA have been diagnosed and treated in 15 patients. One patient (patient 1) had accounted for eight of the 30 exacerbations. In 18 of 30 exacerbations, there was $\geq 50\%$ reduction in the total serum IgE by 2 mo. In 24 of 30 exacerbations of ABPA, there was $\geq 35\%$ reduction in the total serum IgE by 2 mo.

In six of 30 exacerbations of ABPA, there was <35% reduction in the total serum IgE by 2 mo. In three of these exacerbations (patients 5 and 6), a careful review of their therapy was made because of no improvement in their clinical symptoms. In these two

patients, a review of their medication revealed an admittance of noncompliance to the prescribed corticosteroid regimen. It was subsequently noted in these two patients that the total serum IgE had not decreased by 2 mo. In these three exacerbations there was >45% reduction in the total serum IgE by 3 mo and improvement in their clinical symptoms. Of the other three exacerbations (patients 1 and 2) of ABPA with <35% reduction in the total serum IgE by 2 mo, there was >55% reduction of the total serum IgE in two exacerbations by 4 mo. In one of these two exacerbations (patient 2), clinical evaluation and total serum IgE were obtained bimonthly because of distance from our institution. After 4 mo of corticosteroid therapy, this patient had complete resolution of his pulmonary infiltrate. In one exacerbation (patient 1), 6 mo of corticosteroid therapy was required to attain >35% reduction in the total serum IgE.

DISCUSSION

The diagnosis of ABPA does not present a problem when the characteristic clinical and laboratory findings of ABPA are observed, particularly if repeated positive sputum culture for Af, hyphae of Af in sputum, or characteristic radiographic changes of ABPA are present. The diagnosis becomes more difficult when the major criteria are not clearly present or when the clinical, laboratory, and radiographic findings have been altered by prior corticosteroid therapy to control symptoms of asthma. The patients who are most difficult to differentiate from ABPA are those who demonstrate mold-sensitive asthma. These patients may demonstrate immediate skin reactivity to Af and other molds and commonly have eosinophilia and a history of pulmonary infiltrates. Also, precipitating antibody to Af and elevated total serum IgE may be present in these patients. The differentiation of ABPA from this group of patients is imperative because an early diagnosis of ABPA has the potential to result in intervention and the possible prevention of progression to a more chronic disease or eventual fibrotic lung disease.

In all patients presenting with the acute stage of ABPA, there was $\geq 35\%$ reduction in the total serum IgE by 2 mo. This dramatic decrease in the total serum IgE to the administration of corticosteroids is a sensitive marker in patients with ABPA. Therefore, in patients strongly suspected of ABPA, a serum sample for total serum IgE and IgE and IgG antibodies to Af should be obtained before the institution of corticosteroid therapy, and the total serum IgE should be measured on a monthly basis.

The effects of corticosteroids on the total serum IgE levels have been reported.^{10, 11, 12} However, because of the diseases treated, e.g., eczema, the dosage of corticosteroids, the length of treatment with corticosteroids, and the initial levels of IgE that are not relevant to our series, these reports neither disclaim usefulness of serial IgE levels in ABPA or support it. A further observation of IgE levels in other disease states is required.

In the management of these ABPA patients during the past decade, 30 exacerbations of ABPA have been diagnosed and treated. In 24 of 30 exacerbations of ABPA, there was $\geq 35\%$ reduction in the total serum IgE after 2 mo of corticosteroid therapy. Of the six exacerbations with $< 35\%$ reduction of the total serum IgE by 2 mo, noncompliance to corticosteroid therapy in three exacerbations was clearly documented. In these three exacerbations $> 35\%$ reduction in the total serum IgE was attainable by 3 mo. In one patient (patient 1) during an exacerbation of ABPA, 6 mo of

corticosteroid therapy were required before $> 35\%$ reduction of the total serum IgE was obtained despite apparent compliance to corticosteroid therapy. The pulmonary infiltrate was slow to resolve in this exacerbation, and a period of 4 mo lapsed before there was significant improvement in the chest radiograph. This patient is unique in that he has had eight exacerbations of ABPA and requires prednisone at a dosage of 0.5 mg/kg every other day as a maintenance dose to prevent exacerbations of ABPA.

In summary, the response of the total serum IgE to the administration of corticosteroids therapy is a sensitive marker in the management of ABPA. Failure to achieve $> 35\%$ reduction of the total serum IgE to the administration of corticosteroid therapy in patients highly suspected of ABPA should make one either question the diagnosis of ABPA or consider non-compliance to corticosteroid therapy.

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