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BRIEF ARTICLE

Clinical analysis of high serum IgE in autoimmune pancreatitis

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Abstract

AIM: To clarify the clinical significance of high serum IgE in autoimmune pancreatitis (AIP).

METHODS: Forty-two AIP patients, whose IgE was measured before steroid treatment, were analyzed. To evaluate the relationship between IgE levels and the disease activity of AIP, we examined (1) Frequency of high IgE (> 170 IU/mL) and concomitant allergic diseases requiring treatment; (2) Correlations between IgG, IgG4, and IgE; (3) Relationship between the presence of extrapancreatic lesions and IgE; (4) Relationship between clinical relapse and IgE in patients treated with steroids, and (5) Transition of IgE before and after steroid treatment.

RESULTS: IgE was elevated in 36/42 (86%) patients. Concomitant allergic disease was observed in seven patients (allergic rhinitis in three, bronchial asthma in three, and urticaria in one). There were no significant correlations between IgG, IgG4, and IgE (r = -0.168 for IgG, and r = -0.188 for IgG4). There was no significant difference in IgE in the patients with and without extrapancreatic lesions (526 ± 531 IU/mL *vs* 819 ± 768 IU/mL, P = 0.163), with and without clinical relapse (457 ± 346 IU/mL *vs* 784 ± 786 IU/mL, P = 0.374). There was no significant difference in IgE between before and after steroid treatment (723 ± 744 IU/mL *vs* 673 ± 660 IU/mL, P = 0.633).

CONCLUSION: Although IgE does not necessarily reflect the disease activity, IgE might be useful for the diagnosis of AIP in an inactive stage.

Key words: IgE; IgG4; IgG; Autoimmune pancreatitis

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INTRODUCTION

Autoimmune pancreatitis (AIP) is a unique, benign pan-

creatic disease characterized by irregular narrowing of the pancreatic duct, swelling of the pancreas, lymphoplasmacytic infiltration and fibrosis, and favorable response to steroid therapy[1-8]. Serologically, elevation of IgG and IgG4 is the most remarkable characteristic in this disease[9-12]. A recent study showed that IgM and IgA were decreased in AIP[13]. There has been no detailed clinical analysis of IgE, although some clinicians have noted elevated serum IgE in AIP or IgG4-related diseases[14-17].

In most allergic diseases, total serum IgE levels do not reflect disease activity; however, in allergic bronchopulmonary aspergillosis, it is reported that IgE is a useful marker for therapeutic monitoring[18-21]. The expression of T-helper type 2 (Th2) cytokines [interleukin (IL)-4, IL-5, and IL-13] are upregulated in the affected tissues of AIP[22]. Both IgG4 and IgE production are dependent on help by Th2; therefore, all IgG4-inducing antigens are also efficient IgE inducers[23]. As IgG4 reflects the disease activity of AIP[12], it is reasonable to expect that IgE is also related to the disease activity of AIP and could become a clinically useful marker. Thus, we decided to clarify whether IgE is related to the disease activity of AIP from various viewpoints.

MATERIALS AND METHODS

Patients

Between 1997 and 2009, 67 patients were diagnosed as having AIP at the University of Tokyo hospital and affiliated hospitals. All the patients fulfilled the diagnostic criteria of AIP proposed by the Mayo Clinic[3] or the revised criteria by the Japan Pancreas Society[4]. Serum IgE was measured in 48 patients before steroid treatment. As the method of measurement was different in six patients, these patients were excluded. Thus, 42 patients whose IgE level was measured by the same method before steroid treatment were enrolled in this study. Of the 42 patients, 33 were men and nine were women. The mean age of onset was 65 years old. Thirty-seven patients received steroid treatment. Prednisolone at an initial dose of 30-40 mg/d was administered for 2-4 wk in most cases. It was then tapered by 5 mg every 2-6 wk until 10 mg/d, and 2.5-7.5 mg/d was continued as maintenance therapy in principle.

This retrospective study was approved by the review board of our institute.

Methods

Serum IgE was measured by fluorescence enzyme immunoassay. To evaluate the relationship between IgE levels and disease activity, we examined (1) frequency of high IgE (> 170 IU/mL) and concomitant allergic diseases requiring treatment; (2) correlations among IgG, IgG4, and IgE; (3) relationship between the presence of extrapancreatic lesions and IgE; (4) relationship between clinical relapse and IgE in patients treated with steroids; and (5) transition of IgE before and after steroid treatment.

With regard to allergic diseases, only diseases that required treatment during follow-up were counted. There are many extrapancreatic lesions in AIP; however, in this study, only representative and definite lesions, including sclerosing cholangitis[7,8,24], retroperitoneal fibrosis[8,25], sclerosing sialadenitis[17], interstitial pneumonia[26], and tubulointerstitial nephritis[27] were counted. With regard to the number of extrapancreatic lesions, we used the number of extrapancreatic lesions that were observed when IgE was measured. We do not regard intrapancreatic biliary stricture as an extrapancreatic lesion, because it is influenced by pancreatic edema[24]. We defined "clinical relapse" as AIP-related symptomatic unfavorable events; i.e. obstructive jaundice from distal bile duct stenosis due to exacerbated pancreatitis with pancreatic swelling, increased levels of biliary enzymes caused by sclerosing cholangitis (in which extrapancreatic biliary strictures were confirmed on imaging findings), retroperitoneal fibrosis, interstitial pneumonia, and interstitial nephritis (for which simple observation seemed very inadequate and remission induction therapy was introduced). Concerning clinical relapses and IgE, we analyzed patients whose follow-up after the initiation of steroid treatment was more than 6 mo. With regard to the transition of IgE, IgE measured before steroid treatment and during maintenance steroid treatment (2.5-7.5 mg prednisolone/d) were compared.

Statistical analysis

Categorical variables were compared by the χ^2 or Fisher exact test, where appropriate. Continuous variables were reported as mean ± SD and compared by the Student *t* test, Welch *t* test, or paired *t* test, where appropriate. A *P* value of < 0.05 was considered statistically significant. Statistical analyses were performed by the statistical software JMP 7.0.1 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Frequency of high IgE and concomitant allergic diseases

The clinical profiles of 42 patients with AIP are summarized in Table 1. Serum IgE was elevated in 36/42 (86%). The average value of IgE was 679 ± 675 IU/mL (range, 67-3000 IU/mL). No patient had concomitant parasitosis. Concomitant allergic diseases were observed in seven patients, comprising allergic rhinitis in three, bronchial asthma in three, and urticaria in one. There was no significant difference between the average IgE values of these seven patients and those of the other 35 patients (970 ± 775 IU/mL *vs* 621 ± 650 IU/mL, $P = 0.216$). The frequency of high IgE was 100% (7/7) in these patients, and 63% (29/35) in the others; however, this difference was not statistically significant ($P = 0.567$).

Correlations between IgG, IgG4, and IgE

The values of IgG and IgG4, which were measured at the same time as IgE before steroid treatment, were used in this analysis. Elevation of IgG and IgG4 were observed in 20 (47%) and 39 (93%) patients, respectively. The correlation coefficient of IgG and IgE was -0.168 (not significant, $P = 0.290$). The correlation coefficient of IgG4 and IgE was -0.188 (not significant, $P = 0.235$). The correla-

Table 1 Clinical profiles of 42 patients with autoimmune pancreatitis

Patient	Sex	Age	IgE (< 171 U/mL)	IgG (870-1800 mg/dL)	IgG4 (< 135 mg/dL)	Total bilirubin (0.3-1.3 mg/dL)	Concomitant allergic diseases	Extrapancreatic lesion associated with AIP
1	F	58	670	2542	592	0.6	AR	-
2	M	63	650	2055	691	3.0	AR	-
3	F	53	500	1527	143	7.9	AR	SA
4	M	64	490	2457	670	0.5	BA	-
5	M	56	1800	1712	436	0.5	BA	-
6	F	43	340	1036	223	0.9	BA	-
7	M	74	2339	1481	98	0.9	Urticaria	RF
8	F	70	480	2190	133	5.8	-	-
9	M	57	120	3793	1420	10.6	-	RF
10	M	55	480	1419	320	1.7	-	-
11	M	61	270	1878	410	0.4	-	SC
12	M	66	1200	1620	310	0.5	-	SA
13	M	79	170	1585	420	3.3	-	SC
14	M	73	290	1647	360	5.4	-	-
15	M	79	410	1404	554	0.7	-	-
16	M	76	1000	1728	65	14.1	-	SC
17	F	72	650	2384	1400	1.6	-	SA
18	F	65	190	1511	374	0.6	-	-
19	M	68	290	1656	253	2.0	-	SC
20	M	61	940	1448	578	1.6	-	-
21	F	61	640	2177	354	0.4	-	-
22	M	58	2289	1973	481	6.9	-	-
23	M	71	1915	2318	470	0.6	-	-
24	M	61	69	2215	974	0.5	-	SA
25	M	65	91	3032	1260	5.4	-	SC, RF
26	M	64	330	1730	361	0.4	-	SC
27	M	66	1330	1849	270	4.7	-	-
28	F	64	328	2898	456	12.8	-	SC
29	M	69	440	1875	270	8.7	-	-
30	M	73	70.3	2395	393	0.4	-	RF
31	M	67	660	1683	230	0.6	-	-
32	M	72	3000	1579	455	0.5	-	-
33	M	61	467	1301	331	2.9	-	-
34	M	40	320	1996	650	1.0	-	RF
35	M	62	480	1368	236	0.5	-	SC, SA
36	M	71	267	1827	458	1.3	-	-
37	M	59	625	1876	139	0.5	-	RF
38	M	73	302	2834	1800	0.5	-	SA
39	F	76	426	1458	543	0.9	-	RF
40	M	76	943	1840	431	0.7	-	SC
41	M	59	67	1338	140	0.7	-	-
42	M	64	198	1709	232	10.2	-	-

AIP: Autoimune pancreatitis; AR: Allergic rhinitis; BA: Bronchial asthma; SA: Sialadenitis; RF: Retroperitoneal fibrosis; SC: Sclerosing cholangitis.

Table 2 Correlations between IgG, IgG4, and IgE

	Correlation coefficient	*P* value
IgG and IgE	-0.168	0.290
IgG4 and IgE	-0.188	0.235
IgG and IgG4	0.698	< 0.0001

tion coefficient of IgG and IgG4 was 0.698, which was significant ($P < 0.0001$) (Table 2).

Relationship between the presence of extrapancreatic lesions and IgE

Extrapancreatic lesions were observed in 20 patients (48%). Two patients had two lesions, and 18 patients had one lesion. Sclerosing cholangitis, retroperitoneal fibrosis, and sclerosing sialadenitis, were observed in nine, seven, and six patients, respectively. The IgE levels of the patients with and without extrapancreatic lesions were compared, and the same analysis was performed for IgG and IgG4. The results are shown in Table 3. IgG tended to be related to the presence of extrapancreatic lesions, although statistical significance was not attained ($P = 0.093$). No such tendency existed for IgE.

Table 3 Comparison of IgE, IgG, and IgG4 between patients with and without extrapancreatic lesions

	Patients with extrapancreatic lesions (n = 20)	Patients without extrapancreatic lesions (n = 22)	*P* value
IgE (IU/mL)	526 ± 531	819 ± 768	0.163
IgG (mg/dL)	2065 ± 644	1775 ± 396	0.093
IgG4 (mg/dL)	588 ± 505	392 ± 161	0.110

Table 4 Comparison of IgE, IgG, and IgG4 between patients with and without clinical relapses

	Patients with clinical relapses (n = 5)	Patients without clinical relapses (n = 28)	P value
IgE (IU/mL)	457 ± 346	784 ± 786	0.374
IgG (mg/dL)	1898 ± 424	1915 ± 579	0.953
IgG4 (mg/dL)	266 ± 157	558 ± 429	0.148

Table 5 Transition of IgE, IgG, and IgG4 before and after steroid treatment

	Before	After	P value
IgE (IU/mL) (n = 29)	723 ± 744	673 ± 660	0.633
Proportion of high IgE	26/29	23/29	0.470
IgG (mg/dL) (n = 30)	1891 ± 566	1155 ± 315	< 0.0001
Proportion of high IgG	14/30	1/30	0.0002
IgG4 (mg/dL) (n = 28)	557 ± 429	229 ± 112	0.0002
Proportion of high IgG4	27/28	20/28	0.0248

Normal range, IgE: < 171 IU/mL, IgG: 870-1800 mg/dL, IgG: < 135 mg/dL.

Relationship between clinical relapse and IgE in the patients treated with steroids

There were 33 patients whose follow-up period was more than 6 mo. The mean follow-up period was 52 mo (range, 8-141 mo). Clinical relapse was observed in five patients. The style of clinical relapse was pancreatitis in two, interstitial pneumonia in two, and sclerosing cholangitis in one. Their relapses occurred 16 mo after the initiation of steroid therapy on average (range, 3-26 mo). The mean follow-up period was the same between the patients with and without clinical relapse (53.0 mo *vs* 51.8 mo, $P = 0.929$). IgE levels of the patients with and without clinical relapse were compared, and the same analysis was performed for IgG and IgG4. The results are shown in Table 4. Neither IgE, IgG nor IgG4, were related to later clinical relapses.

Transition of IgE before and after steroid treatment

IgE measured before steroid treatment and during maintenance therapy could be compared in 29 patients (Figure 1). IgE increased in 10, and decreased in 18. There was no significant difference in IgE between before and after steroid treatment (723 ± 744 IU/mL *vs* 673 ± 660 IU/mL, $P = 0.633$). Abnormally high IgE (> 170 IU/mL) was observed in 90% (26/29) before steroid treatment, and in 79% (23/29) after steroid treatment ($P = 0.470$). By contrast, IgG and IgG4 did show significant differences before and after steroid treatment (Table 5).

DISCUSSION

High IgE in AIP has been frequently documented[14-17], but its frequency and clinical significance were unknown. Kamisawa *et al*[14] reported that elevation of IgE was observed in 34% (12/35) of patients, and that all the patients with high IgE had present and/or past histories of allergic diseases, although none of the patients with normal IgE had such histories. In the present study, the

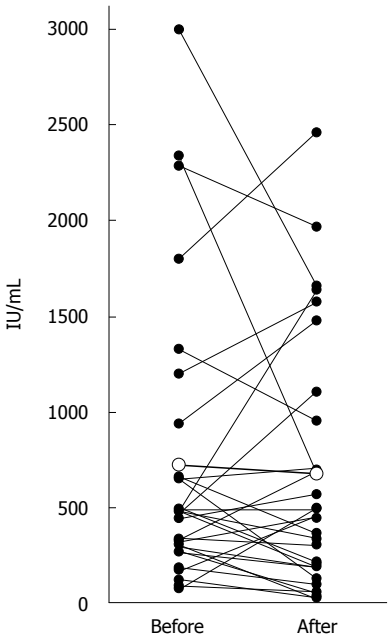

Figure 1 IgE levels measured before steroid treatment (Before) and during maintenance therapy (After) were compared in 29 patients. White circles show average values.

frequency of high IgE was surprisingly high at 86% (36/42), which might be equal to frequency of high IgG4 (73.3%-94.3%)[12]. On the other hand, unlike the previous report, there seemed no definite relationship between IgE and allergic diseases. It seemed unreasonable to count allergic diseases that occurred decades ago. In addition, it is difficult to accurately judge past histories of mild allergic diseases. Thus, we included only concomitant allergic diseases. For reference, there were at least eight patients who had past histories of allergic diseases, but no concomitant ones. Comparison between patients with (n = 15) and without (n = 27) present and/or past histories of allergic diseases showed no significant difference in mean IgE values (654 ± 605 IU/mL *vs* 693 ± 721 IU/mL, $P = 0.860$) and frequency of high IgE (93% *vs* 81%, $P = 0.395$); therefore, the presence of past allergic disease did not affect the results.

From the results shown in Table 3, IgE levels appear to be unrelated to disease activity from the viewpoint of extrapancreatic lesions. On the contrary, it is possible that high IgE is associated with lower disease activity, when considering the higher IgE levels in the group without extrapancreatic lesions, and the negative correlation coefficient of IgG (IgG4) and IgE. It is difficult to analyze the results shown in Table 4 because of the small number of patients with clinical relapses. Nevertheless, it is likely that high IgE is not a risk factor for later clinical relapses, especially considering the higher IgE levels in the group without clinical relapses. IgG4 seems a little high in the group without clinical relapses (Table 4), which is similar to previous reports[8,28].

It was of great interest whether IgE could become a useful marker for therapeutic monitoring in AIP, like IgG and IgG4. From the results shown in Table 5, we

cannot help but conclude that IgE is not a useful marker. However, this phenomenon is not strange in other allergic diseases. For example, Gunnar *et al*[18] reported that steroid treatment did not alter IgE levels in patients with atopic dermatitis. Kumar *et al*[19] showed that changes in serum IgE are not related to severity of asthma or allergic rhinitis. Exceptionally, in allergic bronchopulmonary aspergillosis, it is reported that the response of IgE (35% or more reduction) to steroid treatment is a sensitive marker in the management[20].

Although IgE does not seem to reflect disease activity, we speculate that this feature might be useful for the diagnosis of inactive AIP. Indeed, three patients in the present series showed low IgG4 (65, 98, and 133 mg/dL) at the diagnosis, but all of them showed high IgE (1000, 2339 and 480 IU/mL). When patients with a past history suggestive of AIP, such as voluntarily improved jaundice, do not show high IgG and IgG4, IgE should be measured. If IgE is also low, the possibility that their diagnosis is AIP will be low. If IgE is high, it might indicate AIP in an inactive stage.

In summary, the elevation of serum IgE is very frequent in AIP. It is also observed even in patients without other allergic diseases. IgE might not reflect the disease activity; however, it might be useful for the diagnosis of AIP in an inactive stage.

COMMENTS

Background

It is known that elevation of serum IgE is frequently observed in autoimmune pancreatitis (AIP). However, its clinical significance has not yet been clarified.

Research frontiers

This study demonstrated the frequency of high IgE in AIP, and investigated whether IgE is related to the presence of extrapancreatic lesions and later clinical relapses. In addition, the transition of IgE before and after steroid treatment was investigated to confirm whether IgE can become a marker for therapeutic monitoring.

Innovations and breakthroughs

This study confirmed the high frequency of elevated serum IgE in AIP, although IgE does not seem to be related to the disease activity.

Applications

Measuring IgE might be useful for the diagnosis of AIP especially in an inactive stage.

Peer review

These data about IgE were not positive, which means that IgE is not considered as a useful marker for AIP. However, the author revealed that many (86%) AIP patients have IgE elevation and some AIP patients with low IgG4 have a high level of IgE. IgE should be considered as one of the supportive parameters for diagnosis of AIP and the authors succeeded in clarifying that.

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