

Specific IgG antibodies in sera in patients with penicillin allergy

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Abstract The role of IgG antibodies in inducing or modifying allergic reaction has not been sufficiently clarified. The objective of this investigation is to elucidate the relationship between IgG antibodies and penicillin allergy, between IgG and IgE antibodies in allergic patients. Enzyme-linked immunosorbent assay and Radioallergo-sorbent test were used to examine eight kinds of specific IgG and IgE antibodies, including major antigenic determinants: benzylpenicilloyl (BPO), ampicilloyl (APO), amoxicilloyl (AXO) and phenoxomethylpenicilloyl (PVO), and minor antigenic determinants: benzylpenicillanyl (BPA), ampicillanyl (APA), amoxicillanyl (AXA) and phenoxomethylpenicillanyl (PVA), in the sera of 249 patients with penicillin allergy. Except BPA-IgG, seven kinds of antigenic determinants IgG antibodies levels were significantly higher than that of control group ($P < 0.05$). Positive rates of specific IgG and IgE were 47.0 and 57.8%, while positive rate of IgE and IgG together was 77.9%. The positive rate of IgG antibodies to major antigenic determinants (42.2%) was significantly higher than that of minor antigenic determinants (8.8%) ($P < 0.05$). The positive rate of IgG antibodies of patients with typical clinical symptoms after penicillin administration when skin tests were negative was significantly higher than that of patients with positive skin test ($P < 0.01$). There were no

differences between the IgG positive rates to three kinds of determinants and that of all of eight kinds. The study indicates that IgG may be important in penicillin allergy with negative skin test and IgG antibodies to major antigenic determinants probably play a more important role in the process of allergic reaction.

Keywords Penicillin · Allergy · IgG · IgE · Enzyme-linked immunosorbent assay

Introduction

Penicillins and other β -lactam antibiotics are generally nontoxic, however, the reported allergic incidence occurring in patients receiving these medications poses a continuing clinical problem [1]. These compounds are heterocycle, of low molecular weight, that bind covalently to different macromolecules, such as body proteins, forming hapten-carrier complexes capable of inducing an immunological response and therefore an allergic reaction [2].

Penicillin allergy is associated with high serum levels of immunoglobulin E (IgE) and with an unbalance in cellular and humoral immunity. Some authors associated IgE levels with the severity of the disease. Although the pathogenic role of IgE in allergic diseases is well established, about 40% patients with penicillin allergy present normal IgE levels, according to the our previous results [3–5]. The IgE system is not the only one activated in this condition. The T cell system is involved, because IgE production is strongly if not absolutely dependent on T cell help. These active T cells promote the synthesis not only of IgE, but also IgG1 and IgG4 [6].

It is known that IgG represents 75% of the total circulating immunoglobulins and its half-life is much longer

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than IgE. Four subclasses of IgG have been identified with antiserum preparations against proteins from different human myelomas. They received the denominations of IgG1, IgG2, IgG3, and IgG4 according to serum concentrations in normal subjects. The humoral immune response to a certain antigen may be restricted to one subclass. IgG1 can be classified two types. One is anaphylactic IgG1, the other is non-anaphylactic IgG1. The difference in the anaphylactic property between them seems to be primarily due to binding to the mast cell surface [7].

Several investigators have attributed a protective activity to IgG and IgG subclasses, mainly IgG4, which is produced as a result of a prolonged antigenic exposure. Some authors believe that the IgG4 subclass antibody could neutralize the antigen or block the antibody, and thereby aid immunotherapy [8]. While other groups considered that IgG may mediate allergy. In adults, atopic disease and chronic allergen exposure are associated with higher levels of aeroallergen-specific IgG4, which appears to be promoted by TH2 (IL-4) cytokines [9–11]. It has been also speculated that IgG may play a role in the pathogenesis of food allergy [12, 13].

The double actions of IgG antibodies in allergy may be resulted from different antigen, different time of allergy and different subjects, etc. IgG antibodies to penicillin have been studied by different groups using different methods and with variable results [14–16]. It had been reported that the presence of specific IgG antibodies to penicillin in sera of subjects, whether or not allergic to penicillin, indicates immunity to penicillin. It was also been suggested that they may be able to prevent anaphylactic shock in penicillin-allergic subjects by their blocking ability. Recently, Torres et al. [17] observed that specific BPO-PLL and AXO-PLL IgG antibodies were higher in allergic patients than those of control subjects, but no difference between patients with urticaria and anaphylactic shock. Adkinson [15] found that 60% of subjects taking short course of penicillin developed IgG antibody.

In this paper, we reported the levels of specific IgG antibodies against BPO-HSA, BPA-HSA, APO-HSA, APA-HSA, AXO-HSA, AXA-HSA, PVO-HSA and PVA-HSA in patients with urticaria, anaphylactic shock, positive skin test and other symptoms, and established the relationships among the presence of specific IgG and IgE antibodies and the clinical manifestations.

Materials and methods

Subjects studied

The study included 249 patients (age with a range from 12 to 80, mean $\pm$ SD 22.54 ± 9.83) with penicillin allergy

and 88 healthy volunteers (age with a range from 16 to 60, mean $\pm$ SD 22.86 ± 6.72). All subjects were mainly recruited from the first affiliated hospital of Zhengzhou University. Among them, patients with penicillin G (PG), ampicillin (AMP), and amoxycillin (AX) allergy were 223, 13, and 13, respectively. To obtain information about their illnesses, the time, and nature of previous apparently allergic reactions, a detailed form was developed. Among them, 130 patients had various clinical manifestations of allergy after penicillins administration when skin tests were negative, and 119 patients had positive skin test. According to allergic symptoms, 130 patients could be divided into anaphylactic shock group, urticaria group and other symptoms group. According to the time interval between drug administration and the onset of symptoms, reactions to betalactams have generally been classified as immediate and non-immediate reactions. Immediate reactions occur within the first hour (Table 1). Their sera of 88 control subjects with no previous allergic reactions to drugs. All of them had no history of allergic diseases, cancer, cardiovascular disease or other atopic diseases. They or their guardians gave informed consent to participate in this study, which were approved by the ethics committee.

Blood samples were drawn from each subject at the time of the clinical manifestations and/or at the time of positive skin test. After clotting for 2 h at room temperature the sera were separated and stored at -20°C until the in vitro tests were performed.

Table 1 The clinical data of 249 patients with penicillin allergy

Group	<i>n</i>	Positive rate of IgE [<i>n</i> (%)]
Gender		
Male	144	86 (59.7)
Female	105	58 (55.2)
According to the results of skin test		
Positive skin test (PST)	119	72 (60.5)
Negative skin test (NST) ^a	130	72 (55.4)
According to allergic symptoms		
Anaphylactic shock	43	24 (55.8)
Urticaria	73	38 (52.1)
Other symptoms ^b	14	10 (71.4)
According to allergic type		
Immediate reactions (IR)	74	41 (55.4)
Non-immediate reactions (NIR)	56	31 (55.4)
Total	249	144 (57.8)

^a NST patients with typical clinical symptoms after penicillin administration when skin tests were negative

^b Other symptoms referred to all allergic symptoms except anaphylactic shock, urticaria, e.g. angioedema, rhinitis, bronchospasm and maculopapular eruption, etc.

RAST for detection of IgE against penicillins

Major and minor antigenic determinant paper disks were made by ourselves, including major antigenic determinants: benzylpenicilloyl (BPO-PLL), ampicilloyl (APO-PLL), amoxicilloyl (AXO-PLL) and phenoxomethylpenicilloyl (PVO-PLL), and minor antigenic determinants: benzylpenicillanyl (BPA-PLL), ampicillanyl (APA-PLL), amoxicillanyl (AXA-PLL) and phenoxomethylpenicillanyl (PVA-PLL). The tests were performed as previously reported [3]. Values over the mean +2.33 SD of the results in the control group would be considered positive against the corresponding allergen.

ELISA for detection of IgG against penicillins

Major and minor antigenic determinants included BPO-HSA, BPA-HSA, APO-HSA, APA-HSA, AXO-HSA, AXA-HSA, PVO-HSA and PVA-HSA. Penicilloylation of HSA was carried out following the method of Zhao [18]. The ELISA was performed according to published procedure [19]. Absorbance (A) was read at 490 nm. Values over the mean +2.33 SD of the results in the control group would be considered positive against the corresponding allergen.

Statistical analysis

The statistics package SPSS10.0 running on Windows XP Professional was used for the analysis. The results were analyzed with the analysis of variance (ANOVA), the independent sample *t* test and Chi-square test. A 95% ($P < 0.05$) confidence level was used to determine statistical significance.

Results

The positive rates of specific IgG antibodies

Except BPA-IgG, other IgG antibodies levels against seven kinds of antigenic determinants were higher than those in

control ($P < 0.05$). When we established the categories of IgG positive or negative according to the cutoff point (mean + 2.33 SD), we found that 47.0% (117/249) of the patients were positive to IgG.

The positive rate of IgG antibodies in patients with negative skin test (63.8%, 83/130) was significantly higher than that of IgG antibodies to those with positive skin test (28.6%, 34/119, $P < 0.01$). In terms of allergic symptoms, there were no difference in positive rates of IgG antibodies among anaphylactic shock group, urticaria group, and other symptoms group. The same was true in that to male and female.

The results showed no difference in the positive rate of IgG antibodies between immediate and non-immediate hypersensitivity reaction.

The positive rates of eight kinds of specific IgG antibodies

The IgG positive rates of eight kinds of antigenic determinants in different groups were presented in Table 2. Among eight kinds of specific IgG antibodies, the positive rate of BPO-IgG was the highest (19.7%), followed by APO-IgG (16.5%), and that of BPA-IgG was the lowest (0.80%).

The positive rate and the kind of specific IgG antibodies

The positive rate in patients with only one specific IgG antibody (BPO-IgG) screened was 19.7%, however that in patients with all eight kinds of specific IgG examined was 47.0%. Meanwhile, we found that there were no difference between the IgG positive rate to three (include BPO, APO, AXO) kinds of determinants and that of all of eight kinds. The results indicated that the total positive rate of IgG antibodies increased according to the enhanced kinds of determinant and had a steady trend (Fig. 1a).

The major antigenic determinants included benzylpenicilloyl (BPO), ampicilloyl (APO), amoxicilloyl (AXO) and phenoxomethylpenicilloyl (PVO), and minor antigenic determinants included benzylpenicillanyl (BPA),

Table 2 The positive rate of IgG antibodies to different antigenic determinants with different allergic symptoms in 130 patients

Group	<i>n</i>	Positive rate of IgG (%)								Total
		BPO	BPA	APO	APA	AXO	AXA	PVO	PVA	
Anaphylactic shock	43	34.9	0	16.3	4.6	18.6	2.3	11.6	0	65.1
Urticaria	73	27.4	0	30.1	0	24.7	1.4	13.7	1.4	64.4
Other Symptoms	14	50.0	0	0	0	0	7.1	0	0	57.1
Positive skin test (PST)	119	5.9	1.7	10.1	2.5	6.7	9.2	5.0	2.5	28.6
Total	249	19.7	0.8	16.5	2.0	13.6	5.6	8.4	1.6	47.0

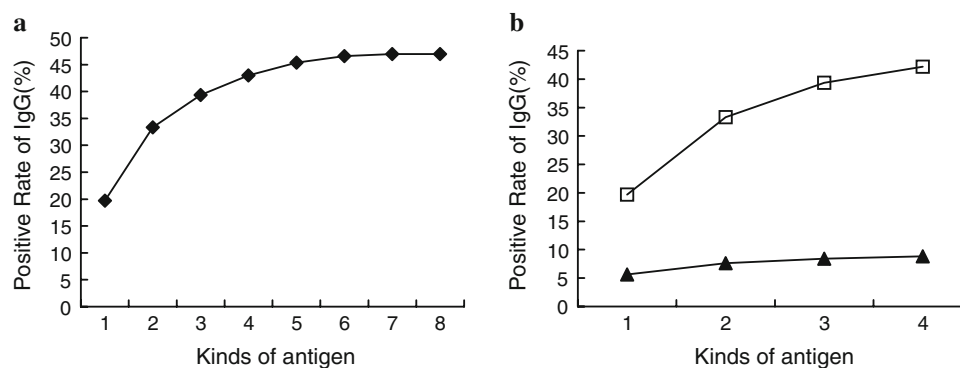


Fig. 1 The cumulative positive rates of IgG antibodies. **(a)** The cumulative positive rates of IgG against eight kinds antigens (the antigens were BPO, APO, AXO, AXA, PVO, APA, PVA and BPA by turns). **(b)** The cumulative positive rates of IgG against four kinds

major antigens (*square* the antigens were BPO, APO, AXO, PVO) and against four kinds minor antigens (*triangle* the antigens were AXA, APA, PVA and BPA to IgG, by turns)

Table 3 The positive rates of IgG antibodies against major and minor antigenic determinants in patients with different symptoms

Group	n	Positive rate of IgG	
		A (%)	B (%)
Anaphylactic shock	43	62.8*	7.0
Urticaria	73	64.4*	2.7
Other symptoms	14	50.0*	7.1
Positive skin test	119	20.2	13.4
Total	249	42.2*	8.8

* $P < 0.05$ versus B

A antibodies to major antigenic determinants, B antibodies to minor antigenic determinants

ampicillanyl (APA), amoxicillanyl (AXA) and phenoxymethylpenicillanyl (PVA). The results about positive rates of IgG to major and minor antigenic determinants in different groups showed in Table 3. The positive rates of IgG antibodies to major and minor antigenic determinants were 42.2% (105/249) and 8.8% (22/249), respectively. The results showed that the positive rate of IgG antibodies to major antigenic determinants in patients was significantly higher than that of IgG antibodies to minor antigenic determinants ($P < 0.05$) except patients with positive skin test. Moreover, the positive rate of IgG to eight kinds of antigenic determinants was not significantly higher than that to four kinds of major antigenic determinants ($P > 0.05$).

No difference in the positive rate of IgG was found between BPO, APO, AXO-IgG examined and four major antigenic determinants examined ($P > 0.05$). To the minor antigenic determinants, the positive rate of IgG examining only AXA was not different with that examining four kinds of determinants (Fig. 1b).

Specificity and crossreactivity

The positive rates to different antigens and drugs in patients with positive IgG antibodies were shown in Table 4. The results showed that 80 patients with only one positive IgG antibody accounted for 68.4% (80/117) of patients with including any kind of positive IgG. The crossreaction positive rates were 14.5, 20.5, 24.8 and 15.4% to PG, AMP, AX and PV, respectively. The results showed that partial crossreactivity existed in different penicillin.

Association between IgG and IgE antibodies

The positive rate of detection IgG and IgE together was 77.9%. In anaphylactic shock group, urticaria group, other symptoms group and group with positive skin test group, the positive rates in patients with either specific IgG or IgE antibodies positive were 86.05, 79.45, 78.57 and 73.95%, respectively. Among 249 patients, 67(26.91%) patients were not only positive to IgE antibodies but also to IgG antibodies. Specific IgG positive rates in patients with positive and negative specific IgE were 46.53 and 47.62%, respectively (Table 5). Except BPO, AXO-IgG, no significant difference was found between two groups. Specific IgE positive rates in patients with positive and negative specific IgG were 57.26 and 58.33%, respectively. Except AXA-IgE, there was no significant difference between two groups. By Spearman test, the results showed no association between IgE and IgG antibodies.

Discussion

Penicillin allergy is mediated by immune system, in which penicillin-reactive IgE antibody is considered to be

Table 4 The positive rates of different determinants and drugs in the allergic patients with positive IgG antibodies ($n = 117$)

		PG [n (%)]		AMP [n (%)]		AX [n (%)]		PV [n (%)]		Total [n (%)]
		BPO	BPA	APO	APA	AXO	AXA	PVO	PVA	
A	Determinants	34 (29.1)	0 (0)	19 (16.2)	3 (2.6)	10 (8.5)	7 (6.0)	6 (5.1)	1 (0.8)	80 (68.4)
	Drug	34 (29.1)		22 (18.8)		18 (15.4)		7 (6.0)		81 (69.2)
B	Determinants	49 (41.9)	2 (1.7)	41 (35.0)	5 (4.3)	34 (29.0)	14 (12.0)	21 (17.9)	4 (3.4)	117 (100)
	Drug	51 (43.6)		46 (39.3)		47 (40.2)		25 (21.4)		117 (100)
C	Determinants	15 (12.8)	2 (1.7)	22 (18.8)	2 (1.7)	24 (20.5)	7 (6.0)	15 (12.8)	3 (2.6)	37 (31.6)
	Drug	17 (14.5)		24 (20.5)		29 (24.8)		18 (15.4)		36 (30.8)

A positive cases only to corresponding determinant and drug, B positive cases with including corresponding determinant and drug, C cross-reaction positive cases

PG penicillin G, AMP ampicillin, AX amoxicillin, PV penicillin V

Table 5 Specific IgG/IgE antibody positive rates in patients with positive or negative IgE/IgG antibody

Group	BPO	BPA	APO	APA	AXO	AXA	PVO	PVA	Total
A (%)	25.00	0.69	16.67	2.08	9.03	6.25	6.94	2.08	46.53
B (%)	12.38*	0.95	16.19	1.90	20.00*	4.76	10.48	0.95	47.62
C (%)	27.35	11.96	19.66	14.53	22.22	8.55	15.38	12.82	57.26
D (%)	28.79	15.91	13.64	16.67	22.73	18.94 ^Δ	13.64	12.88	58.33

A IgG positive rates in patients with positive IgE; B IgG positive rates in patients with negative IgE; C IgE positive rates in patients with positive IgG; D IgE positive rates in patients with negative IgG

* $P < 0.05$ versus A group

^Δ $P < 0.05$ versus C group

responsible for acute allergic reaction [20, 21]. However, in a number of cases, whilst symptoms suggest an anaphylactic reaction, in vivo and in vitro studies fail to show the presence of specific IgE antibodies. Our study also demonstrated it. Further information is necessary for specific antibodies of all the immunoglobulin that are present at the time of the allergic reaction. However, current data suggest that IgG can function as either a positive or negative regulator, leaving a mechanistic explanation for its association with the development of allergy unclear. To address this controversy, we studied the association between IgG to eight kinds of antigens and penicillin allergy. In particular, this study was performed to identify possible correlation between IgG and IgE in penicillin allergy.

Our study suggested that not only IgE, but also IgG, is involved in the development of penicillin allergy. This was in accordance with some previous observations and contrary to others showing protection of IgG [14–17]. Fc β R is a subunit of two related multisubunit receptor complexes, the high-affinity receptor for immunoglobulin E(IgE), Fc ϵ RI, and the low-affinity receptor for immunoglobulin G, Fc γ RIII. Allergic reactions can be initiated through both of these receptors. Clustering of Fc ϵ RI-bound IgE by multivalent allergens results in cellular degranulation and the

release of mediators of allergic reactions, including histamine, leukotrienes, and various cytokines [22]. Similarly, clustering of Fc γ RIII with IgG-containing immune complexes activates mast cells and basophils to produce anaphylactic reactions very similar to those induced through Fc ϵ RI. These may be one of reasons that lead to that both IgE and IgG levels are higher in penicillin allergic patients than that in control. With regard to IgE positive or not, no significance was found in IgG positive rates between two groups except BPO, AXO-IgG. With regard to IgG positive or not, there was no difference in IgE positive rates in two groups except AXA-IgE. That may mean the mechanisms of IgG and IgE are partial different in penicillin allergy.

Allergic reactions to penicillin have been categorized by the type of reaction, immune mechanism, and clinical syndrome, or by time of onset. Type I reactions are mediated by specific IgE antibodies and can be indicated by skin test. Types II, III, IV reactions, or idiopathic are mediated by IgG, IgM, complement and so on. The three kinds of reactions cannot be indicated by skin test [23]. These may be one of reasons that lead to that the positive rate of IgG antibodies of patients with negative skin tests was significantly higher than that of patients with positive skin test.

Torres [24] tested IgG and IgE antibodies to AX and PG and observed that IgE antibodies recognize mainly two different epitopes: the side chain and nuclear portion, but IgG antibodies only recognized the nuclear portion. Daxun [25] reported that the presence of IgE antibodies specific to the penicillin side-chain in certain patients, whereas others had IgE antibodies specific to the penicillin basic structure, which lead to clinical cross-reactions between penicillin. Our results showed the positive rates of IgG antibodies to major antigenic determinants were significantly higher than that to minor antigenic determinants. These suggest major antigenic determinants of IgG antibodies play more important role in the penicillin allergy. Torres [17] observed that positivity to minor determinants of penicillin is associated more with anaphylactic with anaphylactic shock than urticaria. The reason of variable results might due to the different control group, the antigenic determinant or/and the carrier of the antigenic determinants. In this report, we selected a control group of subjects who had not been exposed to beta-lactam antibiotics. Human IgG is divided into four subclasses based on the antigenicity of the heavy chains. Different immunoglobulin isotypes, and even the four IgG subclasses exert distinct biological activities [26]. So research about relationships between IgG subclass and penicillin allergy would be developed in the future.

Concerning on kinds of antigens tested, the results suggested that we need not test all antigens in clinic. The positive rate of detection of specific IgE and IgG together was 77.9% in penicillin allergic patients. This suggested detection of IgE and IgG antibodies together may find more penicillin allergic subjects.

There had been an increase in allergy in our society. The action of IgG was not clear, not only in penicillin allergy but also others allergic actions, for example: food allergy, asthma and so on. The action and mechanism of IgG in different allergic reactions should be further studied. The data presented in this report confirmed that penicillin allergy continued to be the most well-defined model for studying other allergy.

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