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Research Article

Factors Effective in Persistent Penicillin Allergy

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Abstract

Objectives: The present study investigates the factors effective in the continued sensitivity to penicillin of people with penicillin allergies.

Methods: Included in the study were patients who presented with penicillin allergies and defined penicillin allergies between July 1, 2013 and December 31, 2015. The sample was divided into two groups, being: those with continued sensitivity, and those with a previous history of allergy to the group of drugs who can now use them without problems after undergoing diagnostic tests performed following the National Guidelines for Approach to Clinical Drug Hypersensitivity to those with suspected penicillin allergy, and these two groups of patients were compared. 14, 2 and 4.

Results: Among 70 patients with penicillin allergies, 14 were excluded due to irrelevant histories or incomplete tests. Among those with complete test results (n=36), 17 (47%) showed no persistent allergy, while 13 (36%) had persistent allergies via skin tests, and 6 (17%) via oral provocation tests after negative skin results. Persistent allergies typically developed within 5 years of initial reaction, ceasing after 7 years.

Conclusion: Allergic evaluations should be made based on detailed patient histories, skin tests and oral provocation tests so as not to limit the use of penicillin unnecessarily in those with a history of penicillin allergy lasting longer than 5 years.

Keywords: Allergy persistence, drug hypersensitivity, penicillin allergy

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An adverse drug reaction was defined in 1969 by the World Health Association as a reaction that is "noxious and unintended, and which occurs at doses used in man for prophylaxis, diagnosis or therapy".[1] Adverse drug reactions develop in 10–20% of hospitalized patients and in 7% of the general population, although only 15% of adverse drug reactions are due to drug hypersensitivity.[2]

Drug reactions can be considered significant health problems given their association with life-threatening conditions, extended hospitalizations and increased treatment costs. Adverse drug reactions in patients are increasing in parallel with the increased use of drugs. Such reactions are serious problems that affect physicians' prescriptions, and lead to the use of alternative treatments that are less effective, more toxic and more expensive, with lengthier treatment durations, while contributing also to an increase in bacterial resistance.[3]

Among the drugs most frequently associated with drug hypersensitivity are beta-lactam (BL) antibiotics and nonsteroidal anti-inflammatory drugs. Adverse reactions to BL antibiotics are most frequently associated with penicillin, and can be seen in any age group. The rate of penicillin allergy is 1–10%, while the prevalence of life-threatening anaphylaxis is in the range of 0.02–0.05%.[4] Penicillin allergies can present with a broad spectrum of symptoms, from mild urticaria to anaphylaxis, and may also include the findings of all other allergic diseases, contributing to anxiety in both physicians and patients when prescribed.

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Reactions are classified as early or delayed, depending on the timing of the hypersensitive reaction. Early reactions occur within the first 6 hours following the application of the antibiotic, and mostly in the first hour, while delayed reactions can occur at any time 1 hour after the start of treatment.[5]

Real drug allergies were identified in less than 40% of the patients who presented to a hospital with suspected drug allergies based on diagnostic tests.[6] Diagnostic tests are required to verify the diagnosis when atypical signs are present and when significant time has passed since the last reaction in cases with a suspicious history. In vitro and in vivo tests are used for the diagnosis of drug allergies.[7,8] Skin tests are performed initially where possible, being quick, simple and inexpensive, followed by drug provocation tests (DPT) if these tests produce negative results. The sensitivity of skin tests is higher than in vitro tests.[6,7] Prick/Intradermal (IDT) tests are performed in cases with early reactions based on the patient history, and patch tests and late readings of IDT tests for delayed reactions in the patient history.[9] Drug provocation tests are the final option for diagnosis, and are performed when no results can be obtained from the other steps.[6,10]

Beta-lactam allergies are the most frequently reported of all drug allergies, and are reported spontaneously in at least 10% of patients, although 90% of these patients were found to have no allergy and were observed to be able to tolerate penicillin.[11,12] Furthermore, 80% of patients with IgE-mediated penicillin allergy lose their penicillin sensitivity after 10 years after refraining from use with skin tests largely converting to negative.[13,14] It is unknown, however, in which patients skin tests become negative. The present study evaluates the factors contributing to the persistence of sensitivity in patients who define penicillin allergy.

Methods

A search of the archives of the Allergy and Immunology Outpatient Clinic was made for the period between July 01, 2013 and December 31, 2015, and the medical records of patients with penicillin allergies were analyzed retrospectively. Excluded from the study were patients aged less than 18 years, pregnant women, patients undergoing treatment for cancer and those with a history of penicillin allergy who refused to undergo the necessary multiple-stage diagnostic tests. The demographic data of the patients and other information, such as the presence of atopy and multi-drug allergies, were recorded and evaluated.

All patients who underwent the evaluation were subjected to skin tests (prick and intradermal tests); drug provocation tests if the skin tests were negative (DPT); and 5 days of oral penicillin regularly b.i.d. if the EAACI and DPT were negative. The skin tests were conducted using a DAP penicillin skin test kit (DIATER lab, Madrid, Spain) including Benzyl penicilloyl octa-l-lysine (0.04mg-PPL) and sodium Benzylpenilloate (0.5 mg-MD), with each active ingredient given on different days. Amoxicillin/amoxicillin-clavulanate/ampicillin/ampicillin-sulbactam tests were also conducted using the vial form (20–25 mg/ml), being the sole commercial formula present in the country. Intradermal tests were applied in line with the defined concentrations and orders determined in the National Guide of Approach to Drug Hypersensitivity.[15]

The test solutions were prepared on the day of application.

DPT was applied, as each drug in different days, in accordance with the National Guide to patients who recorded negative skin test results (Prick and intradermal), in the absence of any contraindication.

A cut-off value of 0.35 kUA/l was determined for positive specific serum IgE levels against Fenoksimetilpenisilin (penicillin V) and benzylpenicillin (penicillin G) which were studied as service encounter at the laboratory of this hospital between 01.07.2013 and 30.12.2015 (An ELISA approach was used for the analysis, for which a kit with the Astra Biotech GmbH trademark was acquired. The test was finalized using a Robonik Readwell -Touch Automatic Elisa Plate Analyser device).

Ethics Board approval was obtained from the local ethics board dated April 29, 2016 and numbered 2016/15.

Statistical Analysis

The statistical analyses were performed using IBM SPSS Statistics for Windows (Version 20.0. Armonk, NY: IBM Corp.). The distribution of data was checked with a Kolmogorov-Smirnov test. Data with a non-normal distribution were expressed as median±interquartile range (IQR) and minimum-maximum values. A Chi-square test was used for the comparison of categorical data, and a Mann-Whitney U Test for the between-group comparison of parametric variables. P values lower than 0.05 were considered statistically significant.

Findings

Included in the retrospective evaluation were a total of 70 cases (25 male; 45 female) between the ages of 18 and 70 years and who presented to the outpatient clinic of the Immunology and Allergy. Subsequently, 14 cases were excluded from the study due to the incompatibility of their past medical history with a hypersensitivity reaction, two cases who declined to undergo the skin tests, four cases whose tests at the time of the study were incomplete, although they were planned to be performed, and 14 cases who were unable to undergo the diagnostic tests due to the emergence of a need for alternative drugs. The demographic and clinical data of the 36 patients whose medical records were fully accessible are summarized in Table 1.

Table 1. Demographic and clinical characteristics

	n
Sex	
Female	24
Male	12
Age	
18–30	5
31–40	8
41–50	13
51–60	7
51–70	3
Accompanying chronic diseases	
Depression	5
Diabetes mellitus	5
Hypertension	5
Thyroid disease	4
Heart Disease	3
Other	11
Accompanying allergic diseases	
Allergic rhinitis	10
Asthma	4
Non-penicillin drug allergy	8
Food allergy	1
Bee sting allergy	2
None	18
Family history	
Yes	3
None	33

Table 2. Characteristics of the described reaction

	n
Responsible drugs in the medical history	
Amoxycillin-clavulanate	22
Amoxycillin	2
Penicillin	10
Ampicillin Sulbactam	3
Time of Eruption of the Reaction	
1 hour	16
1–24 hours	17
Data absent	3
Systems involved described in the medical history	
Skin/mucosa signs	31
Upper respiratory tract signs	7
Lower respiratory tract signs	8
Cardiovascular system signs	6
Gastrointestinal system signs	5
Neurological signs	10
Recovery after reaction	
At home	12
At hospital	24
Duration between the last reaction and penicillin skin tests	
1–6 months	9
6–12 months	7
1–5 months	12
5–10 months	2
>10 months	4

The drugs causing the reaction in the described cases, the time of the eruption of the reaction, the systems involved, information on recovery after the reaction and the time between the last reaction and the skin tests are summarized in Table 2.

Results of Skin and Oral Provocation Tests

All 36 cases underwent tests with major and minor determinants, and seven were found to be (+) while 29 were (-). Of the 27 patients who underwent an amoxicillin-clavulanic acid vial test, five were found to be (+) while 22 were (-). Of the 20 patients who received OPT with amoxicillin, five were found to be (+) while 15 were (-). Of the 17 patients who received OPT with amoxycillin-clavulonic acid, all were found to be (-). Of the 24 patients who underwent an amoxycillin vial test, eight were found to be (+) while 16 were (-). Of the 14 patients who received OPT with ampicillin, one was found to be (+) while 13 were (-). Of the 12 patients who underwent an ampicillin-sulbactam vial test, all were found to be (-). Of the 14 patients who received OPT with ampicillin-sulbactam, all were found to be (-). Of the 18 patients who received 5-day OPT with benzathine penicillin, all were found to be (-). The allergic evaluation phases and the results of the penicillin allergy evaluations are presented in Figures 1 and 2, respectively.

The mean age of the cases with persistent and non-persistent penicillin allergies were 46±20 years and 48±12 years, respectively (p=0.04). As a result of the non-homogeneous nature of the age variable, the median age in the two groups was compared, revealing no significant difference. Furthermore, no significant differences were noted in the sex, the presence of accompanying chronic or allergic diseases, past medical histories of individual non-penicillin drug allergies, and drug allergies in the family histories of the cases with persistent and non-persistent penicillin allergies.

The variety of the drugs in the past medical histories and the total number of reactions encountered in the two groups were not significantly different. The presence of any systematic involvement other than the skin/mucosa at the time of the initial reaction was also similar between the two groups. No difference was noted in the time between the eruption of the reaction and drug intake (first 1 hour

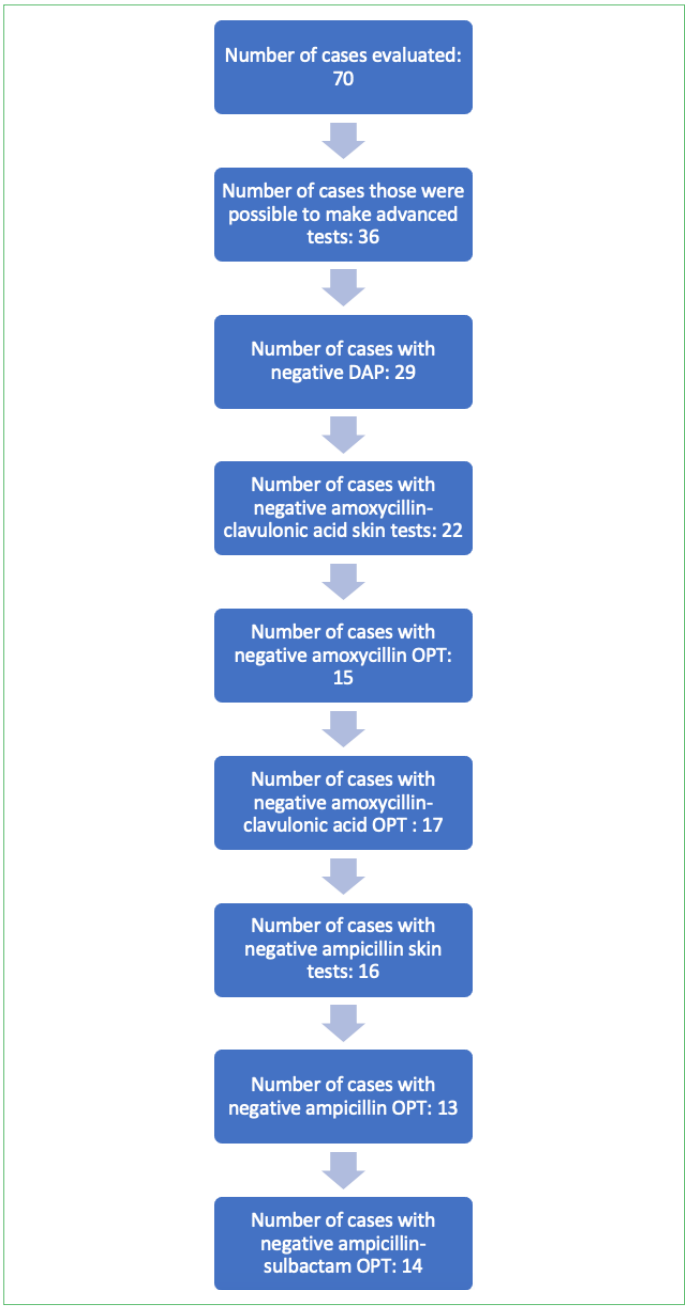

Figure 1. All phases in the allergic evaluation and the number of cases.

vs. 1–24 hours) in the cases with and without persistent penicillin allergies, while the time between the initial reaction and tests was 22.1±22.8 and 74.2±91.1 months in the cases with and without persistent penicillin allergies, respectively (p=0.022). Given the non-homogeneous nature of the above-mentioned duration variables, the median values were compared, revealing no statistically significant difference between the two groups.

Among the cases with persistent penicillin allergies, 94.7% were noted to have been evaluated within the first 5 years. No persistent case was identified when the time between

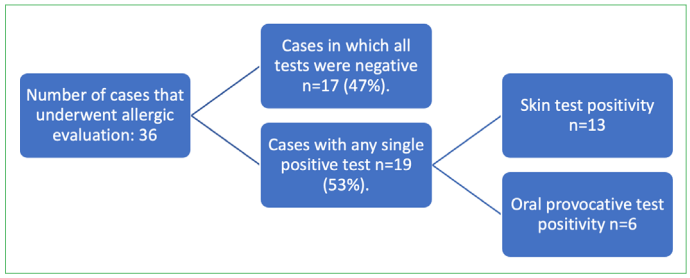

Figure 2. Results of penicillin allergy evaluation.

the development of a reaction and the conducting of tests exceeded 84 months (7 years).

The results of an evaluation of the demographic and clinical history data of cases with and without persistent penicillin allergies are presented in Table 3.

Discussion

The identification of the factors contributing to the persistence of penicillin allergies can be considered important due to the potential fatal outcomes, however, there has been no study to date investigating the factors contributing to the persistence of penicillin allergies in this country, and few studies encountered in literature addressing this subject.

Drug allergies have been reported to be 2–3 times more common in women than men in epidemiological studies of drug allergies.[16] The rate of expressing penicillin allergy in the first year of exposure in patients who were exposed to penicillin-class antibiotics was found to be about 2% and 1% in women and men, respectively in a 2014 study. The fact that two-thirds of the cases that presented to the clinic were female in the present study suggests that drug allergies were twice as common in women than in men, similar to the above-mentioned study.

There was a lack of data in literature on the mean age of patients with persistent penicillin allergy. A mean age of 15.53 years was recorded in the 19 patients with persistent penicillin allergies in the present study, and 21.82 years in the 17 patients with non-persistent penicillin allergies. The mean age of the cases with persistent penicillin allergies was lower than that of the cases without persistent penicillin allergies.

It has been reported in literature that comorbidities can increase the risk of allergic reactions in patients, with liver disease, renal disorders and viral infections being recognized as risk factors behind adverse drug reactions. As an example, maculopapular rash following aminopenicillin has been reported to be seen more frequently alongside EBV (Epstein-Barr virus) infections and leukemia.[17,18] That said, no statistically significant association was identi-

Table 3. Comparison of cases with and without persistent penicillin allergy

	Cases with Persistent Penicillin Allergy n=19	Cases without Persistent Penicillin Allergy n=17	p
Age, Median (IQR)*	46 (20)	48 (12)	0.073
Gender (F/M)	14/5	10/7	0.301
Chronic diseases, n (%)	10 (52)	11 (65)	0.345
Allergic disease, n (%)	8 (42)	10 (59)	0.317
History of non-penicillin drug allergy, n (%)	6 (32)	2 (12)	0.153
Family history of drug allergy, n (%)	1 (5)	2 (12)	0.481
Aminopenicillin as a responsible drug in the medical history, n (%)	15 (79)	11 (65)	0.285
Total number of reactions*, month	2 (10)	1 (6)	0.057
Duration between the reaction and test*, month	14 (36)	25 (101)	0.198
Mean duration of eruption of reaction*, minute	60 (440)	45 (303)	0.928
Presence of systemic involvement other than C/M involvement, n (%)	10 (52)	11 (65)	0.463

*Expressed as IQR due to the non-normal distribution of the variables.

fied between the presence of diagnosed diseases and the presence or suspicion of drug allergy in the present study, which can be explained by the fact that the accompanying diseases, diagnosed by a physician, included such chronic diseases as CAD, malignancy and thyroid disease that did not increase the risk of drug allergies. There is, unfortunately, a lack of reliable data other than past medical history on whether the cases had any viral diseases during the reaction.

Studies performed to date have reported no significant increases in the frequency of allergic diseases in atopic patients with allergic rhinitis, allergic asthma or atopic dermatitis, either in the patient or their family history, although the possibility of more severe outcomes has been reported particularly in asthma patients when a drug reaction develops.[19]

No statistically significant association was found between the presence of diagnosed allergic disease in the past medical history of the individual and the presence of drug allergies in the cases that presented to the outpatient clinic. That said, the reaction pattern of these cases was observed to be more severe, with more frequent systemic reactions than cases with no previous allergic diseases.

The risk of the development of drug reactions has been reported to be 15 times greater in patients with a family history of such reactions.[20] An analysis of drug allergies in the family histories of the patients in the present study revealed three cases with family histories (8%) and 33 (92%) cases without. No statistically significant association was found between the presence of drug allergies in the medical histories and family histories of the patients. The lack of any statistically significant difference might associated with the small number of cases in the series.

A regression analysis performed by Wong et al.[21] in 2006 revealed no association between past clinical history, including age, sex, type of reaction, time from the application of the drug to the reaction, or time since the last reaction, and skin test positivity. Similarly, in the present study, the time from the initial reaction to the penicillin allergy evaluation tests and the time to the eruption of a reaction were found to be unassociated with penicillin persistence.

A study performed by Tannert et al.[22] in 2017 evaluating the concordance of positive skin test results and positive sIgE with clinical findings, and the need for repeat skin tests and sIgE revealed the best method for the determination of IgE-associated penicillin allergy to be a combination of positive skin tests and sIgE, or a positive OPT together with a positive case history. The results of sIgE tests were available for 13 of the 36 cases in the present study, and only three were positive. OPT and skin tests performed on two of the patients with positive sIgEs were negative. sIgE positivity was thus found not to be associated with a clinical history or skin test and OPT results.

The possibility of developing an allergy is known to increase with increased frequency of exposure to the drugs in question. The frequency of exposure to drugs by a person is directly proportional to the development of an allergic reaction.[19] No evaluation of such a condition was performed in the present study since there was a lack of adequate information on whether the patients had used the drugs previously in their medical records.

Previous studies in literature have reported that skin tests performed on patients who claim to have a penicillin allergy revealed actual penicillin allergies in only 10–20%,[23] which can be attributed to the fact that patients consider all side effects of a drug to be an allergic reaction, to their

incomplete recollection of the events surrounding their first reaction, and to the vanishing IgE over time.[24]

As can be seen, a detailed history can allow clinicians to diagnose true penicillin allergies and to diagnose effective antibiotics for those without real allergies. Skin tests should be performed when the clinical history of a patient whose condition requires antibiotic treatment suggests a serious allergic reaction, and penicillin desensitization should be performed when required.

Torda and Chan obtained detailed medical histories of patients in a 6-month study that were compared with the medical records, and the allergy label was subsequently removed from some 20% of the patients' case files, and the patients were duly informed. These simple methods used to identify allergies in patients free up expensive special antibiotics for patients who actually require them.[25]

Fox et al.[26] carried out an evaluation of patients with penicillin reactions in detail in a study performed in 2011, and revealed a positive medical history to be insufficient for the prediction of skin test results. Patients with negative skin tests and major and minor determinants were found to be at lower risk of rapid hypersensitivity reactions to penicillin, while desensitization with penicillin or alternative drugs was stated to be required for patients with positive skin test results.

Tests producing major and minor determinants (DAP Penicillin Diater Laboratories, Madrid, Spain) were positive in seven of the 36 patients among the 70 patients who claimed to have an allergy in their clinical history in the present study, indicating the insufficiency of clinical history for the prediction of skin test results. Patients with positive drug test results underwent alternative drug tests, and appropriate antibiotics were prescribed accordingly.

In a survey conducted by Khasawneh et al.[27] involving 192 patients who stated that they had a penicillin allergy, penicillin allergies were identified as likely present in 121 (63%) and 54 (28%) of the patients with a higher and lower possibility, respectively, while no possibility of a penicillin allergy was identified in 17 (8.9%) patients. Subsequently, 51 of the patients were re-exposed to penicillin in their lifetime, and 86.3% were found to tolerate the drug.

In general, OPT should be performed when the possibility of a drug allergy is low, since the aim is to confirm that the patient is not allergic and able to tolerate the drug.

In a survey carried out by Warrington et al.,[28] 52% of the respondent patients with negative skin tests continued to refrain from antibiotic use, and some stated that their family physicians had directed them to use alternative antibiotics. Therefore it has been a standard to perform OPT after a negative skin test to clearly exclude the diagnosis of penicillin allergy.[29]

Cutaneous drug reactions are the most frequently noted indicators of drug allergies. Most often, skin/mucosa involvement was identified in an evaluation of the observed signs in the present study, which concurs with previous studies in literature.

Conclusion

This is the first national study to scrutinize the factors affecting persistent sensitivity in people who claim to have penicillin allergies, and as such can be considered as contributing to literature.

Clinical history alone has been found to be sufficient for the removal of a penicillin allergy label from a patient in some cases as a result of the present study.

It is vital that evaluations of persistent allergies include oral provocation tests in addition to skin tests.

The mean age of the cases with persistent penicillin allergies was found to be lower than that of the cases without persistent penicillin allergies.

It was noted that the risk of persistence decreased with the increased time between the initial reaction and the penicillin allergy evaluation, and no persistence was seen after 7 years.

The most significant limitations of the present study are the fact that the initial reaction data was based solely on the patient's declaration, the absence of a healthcare system record and the low number of cases (n=36) subjected to a complete allergic evaluation.

Penicillin allergy is still the leading cause of severe/fatal anaphylaxis, although the possibility of persistent penicillin allergy is low. Persistent penicillin allergies were found to be more common among younger patients, and that we are not such limited in selecting antibiotics, especially in elderly patients with multisystem diseases, the importance of the first 5 years after the index reaction (the condition persists in almost all of them) and no persistence of allergy after 7 years. The identification of the factors behind persistent penicillin allergies is important due to the potential for fatal outcomes, and so it is suggested that the data presented in this study can serve as a guide for clinical practices, despite the limitations of the study.

Disclosures

Ethics Committee Approval: Ethics Board approval was obtained from T.C Recep Tayyip Erdoğan University, dated April 29, 2016 and numbered 2016/15.

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