PENICILLIN ALLERGY IN RHEUMATOID ARTHRITIS WITH SPECIAL REFERENCE TO SJØGREN'S SYNDROME

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An increased prevalence of penicillin allergy has been noted in certain connective tissue disorders, in particular polyarteritis nodosa (Rose and Spencer, 1957) and systemic lupus erythematosus (Harvey, Shulman, Tumulty, Conley, and Schonerich, 1954). There is, to our knowledge, no reported study of the prevalence of penicillin allergy in rheumatoid arthritis, although an increased prevalence has been observed in patients with Sjögren's syndrome, including those individuals with co-existing rheumatoid arthritis (Bloch, Buchanan, Wohl, and Bunim, 1965).

In this paper we have studied the prevalence of penicillin allergy in patients with rheumatoid arthritis, in particular to ascertain whether penicillin allergy was related to Sjögren's syndrome complicating rheumatoid arthritis or to rheumatoid arthritis *per se*.

Materials and Methods

298 patients with definite or classical rheumatoid arthritis (Ropes, Bennett, Cobb, Jacox, and Jessar, 1958), who had had previous penicillin therapy, were questioned regarding related allergic phenomena. 161 (53 per cent.) of these patients had a positive sheep cell agglutination test and all exhibited articular erosions on radiological examination of the joints.

In addition to the age and sex of the patient, subcutaneous nodule formation and salivary gland enlargement (Bloch and others, 1965) were recorded.

All of the patients were carefully examined for evidence of Sjögren's syndrome (Bloch and others, 1965).

Keratoconjunctivitis sicca.—An ophthalmological examination for keratoconjunctivitis sicca was performed

by the method described by Williamson, Cant, Mason, Greig, and Boyle (1967). In each patient a Schirmer I tear test was carried out, using standardized sterile paper strips* in an atmosphere between 60 and 70°F. and a relative humidity greater than 40 (Williamson and Allison, 1967). Patients were considered normal if wetting of the paper exceeded 15 mm. after 5 minutes.

In patients with a subnormal Schirmer I tear test a Schirmer II test was performed: this test is identical to the Schirmer I test, except that lacrimation is stimulated with a 10 per cent. solution of ammonia held 6 inches from the nose.

The Rose Bengal test was performed by instilling a 1 per cent. solution of the dye into the conjunctival sacs, followed by normal saline irrigation and examination with a Zeiss or Haag-Streit slit lamp for punctate or filamentary keratitis.

Keratoconjunctivitis sicca was said to be definitely present when the Schirmer II tear test was subnormal and the Rose Bengal dye showed a punctate or filamentary keratitis on slit-lamp examination. In patients with a subnormal Schirmer II test but without evidence of keratitis, a diagnosis of "possible" keratoconjunctivitis sicca was made.

Oral Symptoms.—Each patient was carefully questioned regarding a history of xerostomia and related oral symptoms of Sjögren's syndrome (Bloch and others, 1965). "Symptomatic" xerostomia was diagnosed when the patient admitted to having a dry mouth, but had no reduction in salivation or associated difficulty in mastication requiring increased fluid intake. These patients' mouths were normal on clinical examination, and parotid salivary studies (using a modified Carlsson-Crittenden cup with an inner chamber diameter of 10 mm., an outer chamber diameter of 20 mm., and a depth of 4 mm.) were within the normal range. The inner chamber of this cup fits over the end of Stensen's duct, and suction is exerted on the outer chamber to hold the cup in position and prevent the leakage of saliva, which passes down a tube into a collecting vessel.

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Sialography was performed by the hydrostatic technique of Park and Mason (1966). The contrast medium is allowed to flow into the parotid duct from a reservoir held 70 cm. above the patient's head. Filling was stopped when the patient experienced pain due to distension of the gland. This technique overcomes the major hazards of injection sialography. For instance, underfilling rarely occurs as the film is taken while the contrast medium is still flowing and the pressure, therefore, maintained. Overfilling also is extremely unusual because an almost constant pressure is employed in all cases. Degrees of abnormality were based on the criteria of Bloch and others (1965).

Penicillin Allergy

This was recorded when the patient experienced a definite skin eruption, angioneurotic oedema, asthma, or a clinical picture resembling serum sickness with fever, painful swollen joints, myalgia, and lymphadenopathy following exhibition of penicillin or a penicillin drug analogue (Goodman and Gilman, 1955). Postadministration phenomena, for example, nausea, vomiting and diarrhoea, or generalized malaise, were not included.

Control Subjects

These were in-patients or out-patients of the general medical and surgical departments of various hospitals in Glasgow. 298 such subjects, matched for age and sex, were included in this study. None had clinical evidence of Sjögren's syndrome, rheumatoid arthritis, or other

connective tissue disease, nor had any of these patients been attending hospital as a direct result of penicillin allergy.

Age of Patients and Controls

The mean age and age range of the male and female patients with rheumatoid arthritis and the control subjects are shown in Table I, together with their age distribution in decades. The age distribution in decades is identical in both groups, and the mean ages and age ranges are very similar.

Serological Methods

Antinuclear factor (ANF) was detected by the indirect immunofluorescence techniques of Beck (1961), using rat liver as substrate. Sera were initially tested at a dilution of 1 in 16 and positive sera were then titrated in quadrupling dilutions till an end-point of nuclear staining was obtained.

Rheumatoid factor was determined by the sheep cell agglutination test (Ziff, Brown, Lospalluto, Baden, and McEwen, 1956); screening was carried out at a dilution of 1 in 32, positive sera being titrated at doubling dilutions.

Results

The prevalence of penicillin allergy, as defined overleaf, is shown in Table II. It can be seen that 63 of the 298 patients with rheumatoid arthritis

TABLE I
AGE AND SEX DISTRIBUTION OF PATIENTS WITH RHEUMATOID ARTHRITIS AND CONTROL SUBJECTS

Group	Sex	No. of Cases	Age (yrs)		Age Distribution in Decades						
			Mean	Range	0-19	20-29	30-39	40-49	50-59	60-69	70-79
Rheumatoid Arthritis (298)	Male	108	47.8	15-78	3	14	18	19	31	19	4
	Female	190	48.6	16-71	11	20	23	31	50	43	12
Controls (298)	Male	108	46.9	14-75	3	14	18	19	31	19	4
	Female	190	49.1	17-79	11	20	23	31	50	43	12

TABLE II
PENICILLIN ALLERGY IN PATIENTS WITH RHEUMATOID ARTHRITIS AND CONTROLS, BY AGE AND SEX

Group	Total with Penicillin Allergy		Sex	No. of Cases	Penicillin Allergy								
	No.	Per cent.			Age Distribution in Decades								
					0-19	20-29	30-39	40-49	50-59	60-69	70-79		
Rheumatoid Arthritis (298)	63	21·1	Male	108	21	19·4	0/3 (0%)	0/14 (0%)	6/18 (33·3%)	1/19 (5·3%)	8/31 (25·8%)	4/19 (21·1%)	2/4 (50%)
			Female	190	42	22·1	1/11 (9·1%)	5/20 (25%)	1/23 (4·3%)	7/31 (22·6%)	14/50 (28·0%)	11/43 (25·3%)	3/12 (25·0%)
Controls (298)	38	12·8	Male	108	15	13·9	1/3 (33·3%)	2/14 (14·3%)	2/18 (11·1%)	3/19 (15·8%)	4/31 (12·9%)	3/19 (15·8%)	0/4 (0%)
			Female	190	23	22·1	0/11 (0%)	2/20 (10%)	5/23 (21·7%)	4/31 (12·9%)	5/50 (10%)	5/43 (11·6%)	2/12 (16·7%)

(21.1 per cent.) were allergic to penicillin, compared with only 38 of the 298 control subjects (12.8 per cent.). This difference is statistically significant ($\chi^2 = 7.45$; $P < 0.01$). Table II also shows that there is a higher prevalence of penicillin allergy in both male (19.4 per cent.) and female (22.1 per cent.) rheumatoid patients than in male (13.9 per cent.) and female (12.1 per cent.) control subjects. However, only in the female patients with rheumatoid arthritis is this difference statistically significant ($\chi^2 = 6.69$; $P < 0.01$). The distribution of penicillin allergy with regard to its prevalence in each decade follows no consistent pattern, and it would thus appear that penicillin allergy is probably not related to age.

The relationship of penicillin allergy to Sjögren's syndrome is shown in Table III. Of the 298 patients with rheumatoid arthritis, 54 (18.4 per cent.) had Sjögren's syndrome. Of these 54 patients with Sjögren's syndrome and rheumatoid arthritis, 22 (40.7 per cent.) had penicillin allergy, whereas of the 244 patients with rheumatoid arthritis alone only 41 (16.7 per cent.) had evidence of penicillin allergy. This difference is highly significant ($\chi^2 = 15.196$;

$P < 0.001$). The prevalence of penicillin allergy in patients with Sjögren's syndrome and rheumatoid arthritis is significantly higher ($\chi^2 = 19.59$; $P < 0.00025$) than that in the control subjects. However, the prevalence of penicillin allergy in those with rheumatoid arthritis alone is not significantly higher than the prevalence in the control subjects ($\chi^2 = 1.769$). It would thus appear that the increased prevalence of penicillin allergy in rheumatoid patients is related to the presence of co-existing Sjögren's syndrome, rather than to rheumatoid arthritis itself. When the distribution of penicillin allergy was examined in relation to the age distribution in decades, it was seen that no patient with rheumatoid arthritis under the age of 40 years had evidence of Sjögren's syndrome; thus the apparent increased prevalence of penicillin allergy in patients over the age of 40 years is accounted for by the fact that Sjögren's syndrome occurs in this age group.

The relationship of penicillin allergy to clinical and laboratory findings in patients with rheumatoid arthritis uncomplicated by Sjögren's syndrome is shown in Table IV. No relationship was found

TABLE III
PENICILLIN ALLERGY IN RHEUMATOID ARTHRITIS RELATED TO SJÖGREN'S SYNDROME

Group	Total with Penicillin Allergy		Sex	No. of Cases	Penicillin Allergy								
	No.	Per cent.			No.	Per cent.	Age Distribution in Decades						
							0-19	20-29	30-39	40-49	50-59	60-69	70-79
Rheumatoid Arthritis and Sjögren's syndrome (54)	22	40.7	Male	15	4	26.7				0/1	3/8 (37.5%)	1/6 (16.7%)	
			Female	39	18	46.2				1/5 (20%)	10/16 (62.5%)	6/16 (37.5%)	1/2 (50%)
Rheumatoid Arthritis Alone (244)	41	16.7	Male	93	17	18.3			6/18 (33.3%)	1/18 (5.6%)	5/23 (21.7%)	3/13 (23.1%)	2/4 (50%)
			Female	151	24	15.9	1/11 (9.1%)	5/20 (25%)	1/23 (4.3%)	6/26 (23.1%)	4/34 (11.8%)	5/27 (18.5%)	2/10 (20%)

TABLE IV
PENICILLIN ALLERGY IN 244 PATIENTS WITH RHEUMATOID ARTHRITIS WITHOUT SJÖGREN'S SYNDROME, RELATED TO CLINICAL AND LABORATORY FEATURES

Clinical and Laboratory Features	Number of Cases	Penicillin Allergy		Significance
		Present	Absent	
Sex Distribution				
Male	93	17	76	Not significant
Female	151	24	127	
Possible Keratoconjunctivitis Sicca*	62	14	48	Not significant
Symptomatic Xerostomia*	28	6	22	Not significant
Subcutaneous Nodules	48	13	35	$\chi^2 = 4.51$ $P < 0.05$
Sheep Cell Agglutination Test	115	25	90	Not significant
Antinuclear Factor Test	47	14	33	$\chi^2 = 7.01$ $P < 0.01$

*For definition see text

between the presence of penicillin allergy and "possible" keratoconjunctivitis sicca, "symptomatic" xerostomia, salivary gland enlargement, or the positivity or titre of the sheep cell agglutination test. A significant correlation was noted, however, between penicillin allergy and the presence of subcutaneous nodules ($\chi^2 = 4.51$; $P < 0.05$) and the presence of a positive test for antinuclear factor ($\chi^2 = 7.01$; $P < 0.01$). No relationship was noted between penicillin allergy and the titre of antinuclear factor.

No significant correlation was noted between the presence of penicillin allergy and the presence of xerostomia, salivary gland enlargement, abnormal sialograms, or the positivity or titre of rheumatoid or antinuclear factors in the 54 patients with rheumatoid arthritis complicated by Sjögren's syndrome.

Discussion

In this study we have shown that patients with rheumatoid arthritis, in particular female patients, have a higher than expected prevalence of penicillin allergy (Table II). On closer examination, however, this association has been shown to be due not to rheumatoid arthritis itself, but to the presence of co-existent Sjögren's syndrome. The reason why female patients have a higher prevalence of penicillin allergy is probably due to the fact that they have a higher prevalence of Sjögren's syndrome. Thus, in this study, fifteen of the 108 male rheumatoid patients (13.9 per cent.) had Sjögren's syndrome, compared with 39 of 190 female patients (20.5 per cent.). This difference is not significant. No definite relationship was observed between penicillin allergy and the age of the patient, although it is of interest to note that only patients over the age of 40 years had Sjögren's syndrome (Table III).

It is of interest that the patients with rheumatoid arthritis uncomplicated by Sjögren's syndrome showed no evidence of increased allergy to penicillin in relationship to the presence of "possible" keratoconjunctivitis sicca or "symptomatic" xerostomia, both of which have been alleged to be evidence of subclinical Sjögren's syndrome on the basis of their association with the presence of salivary duct auto-antibody (MacSween, Goudie, Anderson, Armstrong, Murray, Mason, Jasani, Boyle, Buchanan, and Williamson 1967). It would also appear that the presence of penicillin allergy may be related to

the severity of the rheumatoid disease process in patients who do not have evidence of Sjögren's syndrome, since the presence of subcutaneous nodules and antinuclear factor were both significantly related to the occurrence of penicillin allergy in these patients (Table IV). It should be noted, however, that no such relationship was observed in patients with rheumatoid arthritis complicated by Sjögren's syndrome.

Patients with Sjögren's syndrome, whether associated with rheumatoid arthritis or not, have been shown to manifest a high incidence of allergic reactions to drugs, including penicillin (Bloch and others, 1965). In this study we have confirmed that patients with rheumatoid arthritis and Sjögren's syndrome have an increased likelihood of developing allergy to penicillin. It should be noted that in this study the diagnosis of Sjögren's syndrome was based solely on the ophthalmological finding of keratoconjunctivitis sicca in sixteen of the 54 patients (29.6 per cent.), and that more than half of these had not been diagnosed previously by other hospital physicians. It would thus appear of practical value to screen patients with rheumatoid arthritis as a routine for keratoconjunctivitis sicca, and to avoid penicillin therapy.

Summary

298 patients with rheumatoid arthritis who had received penicillin therapy were questioned regarding allergy to this drug. Penicillin allergy was found in 63 (21.1 per cent.) of these patients compared with 38 (12.8 per cent.) of 298 controls carefully matched for age and sex ($P < 0.01$). Closer study revealed that this increase was associated with Sjögren's syndrome complicating the arthritis. It is concluded that patients with rheumatoid arthritis should be carefully examined for evidence of Sjögren's syndrome, and that penicillin therapy should be avoided, if possible, in those manifesting evidence of this syndrome.

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L'allergie causée par la pénicilline dans la polyarthrite rhumatoïde concernant spécialement le syndrome de Sjögren

RÉSUMÉ

298 malades atteints de polyarthrite rhumatoïde qui avaient reçu un traitement à la pénicilline ont été questionnés au sujet de l'allergie à ce médicament. L'allergie à la pénicilline a été trouvée chez 63 (21,1 pour cent.) de ces malades comparé à 38 (12,8 pour cent.) des 298 témoins spécialement choisis quant à l'âge et le sexe ($P < 0.01$). Une étude plus approfondie a révélé que cette augmentation était associée au syndrome de Sjögren compliquant l'arthrite. Il a été conclu que les malades atteints de polyarthrite rhumatoïde devraient être soigneusement examinés pour les signes cliniques du syndrome de Sjögren, et que le traitement à la pénicilline devrait être évité, si possible, chez ceux manifestant des signes de ce syndrome.

Alergia a la penicilina en la poliartritis reumatoide con especial referencia al síndrome de Sjögren

SUMARIO

298 pacientes con poliartritis reumatoide, que habían recibido tratamiento con penicilina, fueron interrogados con relación a la alergia a esta droga. Se descubrió alergia a la penicilina en 63 (21,1 por ciento) de estos pacientes, comparado con 38 (12,8 por ciento) de 298 testigos seleccionados cuidadosamente para que coincidiesen en edad y sexo ($P < 0,01$). Un estudio más detallado reveló que este aumento estaba asociado con el síndrome de Sjögren, que complica la poliartritis. Se llega a la conclusión de que los pacientes con poliartritis reumatoide deberían ser cuidadosamente examinados en busca del síndrome de Sjögren y que la terapia de penicilina debiera ser evitada, de ser posible, en los pacientes que manifesten indicios de este síndrome.