Familial Felty's syndrome

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Blendis, L. M., Lloyd Jones, K., Hamilton, E. B. D., and Williams, R. (1976). *Annals of the Rheumatic Diseases*, 35, 279–281. Familial Felty's syndrome. A family is described in which the mother and 2 of the 5 children had Felty's syndrome, a pattern of inheritance suggesting a dominant defect and one which has not previously been reported. The family is also of interest in that the other sib had rheumatoid arthritis.

In 1924, Felty first reported splenomegaly and neutropenia occurring in 5 patients with rheumatoid arthritis. Since then many series of patients with this syndrome have been described (De Gruchy and Langley, 1961; Barnes, Turnbull, and Vernon-Roberts, 1971; Blendis and others, 1970; Moore and others, 1971). However, controversy persists as to whether these patients are suffering from a variant of rheumatoid arthritis or from a distinct clinical syndrome of which rheumatoid arthritis is but one aspect. Recently we have described 5 patients with Felty's syndrome and an unusual histological abnormality of the liver, namely nodular regenerative hyperplasia of the liver, which resulted in one of these patients dying from bleeding oesophageal varices (Blendis and others, 1974). In this paper we describe the inheritance of Felty's syndrome within a family which provides further evidence for it being considered as a specific clinical entity.

The Family

As well as the proband (L. L.) two other members of the family, the mother (L. C.) and an elder brother (F. C.), have been diagnosed as having Felty's syndrome (Figure). A sister has rheumatoid arthritis (R. W.), another sister probably has osteoarthritis (C. A.), while the fifth sib has no obvious arthropathy.

PROBAND (L. L.)

In 1960 a 43-year-old woman was admitted to King's College Hospital with fever, pain, and swelling of the knees, wrists, and elbows, the history dating back to 1943. No rheumatoid nodules were detected on examination, but the spleen was palpable. Rose-Waaler titre was 1:1024. Sedimentation rate was 25 mm/h, haemoglobin 8.5 g/dl, and the white blood count $2.2 \times 10^9/l$ with 31% neutrophils. No LE cells were found.

In 1966 she had cellulitis surrounding a septic spot on the arm and in 1967 she was readmitted for investigation following recurrent mouth ulcers and weight loss (Table).

FIGURE Family pedigree

Accepted for publication November 19, 1975.

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Table *Haematological and serological findings in 3 patients with Felty's syndrome*

Patient	Date of investigation	Age (years)	Sex	Haematology			Rheumatology			Complications	
				Hb (g/dl)	W B C ($\times 10^9/l$)		Platelets ($\times 10^9/l$)	Nodules	ESR		Titre of sheep cell agglutination test
					Total	Neutrophils (%)					
Propositus (L. L.)	1967	58	F	11.7	1.7	120	200	0	40	1024	Skin sepsis
Mother (L. C.)	1968	86	F	11.9	1.1	80	120	+	123	1024	Sjögrens syndrome
Elder brother (F. C.)	1974	68	M	12.4	1.6	520	200	+	83	256	Pleural effect

A splenectomy was carried out and a wedge biopsy of the liver taken. This, as well as a needle biopsy carried out in 1968, showed lymphocytic infiltration in the hepatic sinusoids with a minor degree of lymphocytic infiltration and fibrosis in the portal tracts. Since 1968 she has continued to have recurrent skin sepsis but has had few joint symptoms. In 1972 the white blood count was $2.4 \times 10^9/l$ with only 7% neutrophils.

SISTER (R. W.)

This 63-year-old woman has had rheumatoid arthritis for 13 years with marked deformities of the hands and feet but no splenomegaly. She refuses blood tests or referral to hospital, treating herself with soluble aspirin.

MOTHER (L. C.)

The mother was 85 years of age when first seen at King's College Hospital in 1965 with long-standing rheumatoid arthritis which had resulted in multiple joint deformities. In addition, she had subcutaneous rheumatoid nodules and hepatosplenomegaly. A white blood cell count at that time was $1.3 \times 10^9/l$ with a neutrophil count of 7%, and the sedimentation rate was 113 mm/h. In 1968 there was little change in the haematological findings, liver function tests were normal, and the sheep cell agglutination test was considerably raised (Table). She died in 1969 from bronchopneumonia.

BROTHER (F. C.)

The brother, 57 years old, was admitted to King's College Hospital in 1964 with a 6-month history of polyarthritis and a right pleural effusion due to rheumatoid disease. Rheumatoid nodules were present and the Rose-Waaler titre was 1:256. Other investigations included a sedimentation rate of 124 mm/h, with haemoglobin 8.4g/dl and white count $7.0 \times 10^9/l$. LE cells were negative on three occasions.

In 1965, the patient was found to be neutropenic with a white count of $3.0 \times 10^9/l$ (42% neutrophils). In 1969 x-rays of the joints showed erosions, the sedimentation rate was 83 mm/h, and for the first time he was noted to have an enlarged spleen. Rose-Waaler titre was 1:256 and the antinuclear factor was negative. He was last seen in 1974 because of diverticulitis. Investigations at the time being essentially unchanged (Table).

SISTER (C. A.)

The eldest sister is 70 years old. For 2 years she has been complaining of joint pains, at first in her knees and then in her finger joints in association with stiffness and swelling. On examination there was bony swelling of many of the proximal interphalangeal joints and of the first, second and third metacarpophalangeal joints of both hands. X-rays of the hands and feet showed degenerative changes only in the affected joints, and the sedimentation rate was normal. The Rose-Waaler test was positive to a titre of 1:16, but the antinuclear factor was negative.

SISTER (M. D.)

The youngest sister is 55 years old. She was seen this year because of pain in her left shoulder. She has no evidence of a polyarthritis or splenomegaly. Her white blood count is $5.6 \times 10^9/l$, and erythrocyte sedimentation rate 6mm/h. Both the Rose-Waaler test and antinuclear factor are negative.

Discussion

The occurrence of Felty's syndrome in three first-degree relatives of the same family has to our knowledge never been reported. There are two possible explanations for this familial involvement. Firstly, Felty's syndrome may be a variant of a condition caused by a transmissible agent. However, the 3 patients presented clinically over a period of 9 years, making an infectious cause unlikely. Furthermore, despite an intensive search such an agent has yet to be identified in rheumatoid arthritis. If Felty's syndrome was truly infectious in origin, it is surprising that similar family histories have not been reported previously. The second explanation that the familial occurrence represents inheritance as a dominant gene seems more likely. However, as yet no cases have occurred in the next generation. The type of family pedigree described here is typical of a new dominant mutation, although differentiation of a truly dominant from intermediate inheritance is difficult.

It is surprising that for such a common condition as rheumatoid arthritis the question of its inheritance remains a subject of dispute. From a number of recent reviews of the genetics of rheumatoid arthritis (Blumberg, 1960; Bywaters, 1963; Cobb, 1965; Lawrence, 1967; Boyle and Buchanan, 1971) the majority opinion appears to be that the frequency within families of the disease as a whole was not significantly greater than that of the controls. However, there does appear to be significant familial clustering of the severe erosive and seropositive disease (Ziff and others, 1958). For example, in seropositive rheumatoid patients the incidence of disease in first-degree relatives was four times that in controls, while in seronegative patients the familial incidence was not significantly different (Lawrence and Ball, 1958). Since patients with Felty's syndrome tend to have both erosive joint disease and to be seropositive one would not be surprised to find familial clustering of this syndrome, if it is indeed a distinct entity. In contrast, one would be surprised to find inheritance of the same variant of rheumatoid arthritis. The presence of rheumatoid arthritis in another member of the family could be explained by familial clustering of either variants of the rheumatoid arthritis or of related conditions as found for Sjögren's syndrome (Burch, Bunim, and Bloch, 1963)

and lupus (Ansell and Lawrence, 1963). Nonetheless, the occurrence of Felty's syndrome and rheumatoid arthritis in the same family is unusual.

Although splenomegaly is found in up to 5% of patients with rheumatoid arthritis, the relationship of Felty's syndrome to rheumatoid arthritis is uncertain. The occurrence of nodular regenerative hyperplasia of the liver in Felty's syndrome has already been mentioned (Blendis and others, 1974). Not a single instance of this abnormality was found in a post-mortem study of 51 patients with rheumatoid arthritis, which included 2 patients with splenomegaly. The other distinguishing feature of Felty's syndrome is the neutropenia which may precede other manifestations including the arthritis, and which may be due to a sequestration of neutrophils by the spleen (Wright and others, 1951), maturation arrest of the granulocyte series in the marrow (Hutchinson and Alexander, 1954), leucocyte IgG antibodies against the white blood cells (Rosenthal and others, 1974), or decreased production or activity of granulopoietic factors (Gupta, Robinson, and Albrecht, 1975).

We thank Dr. Kataria for allowing us to see and investigate patient, L. C., who was in St. Francis' Hospital under his care. We are grateful to Dr. Jack Singer, Department of Genetics, Guy's Hospital, and Professor E. G. L. Bywaters for advice and criticism.

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