Follow-up study of 100 cases of juvenile rheumatoid arthritis

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Although juvenile rheumatoid arthritis (JRA) was first described by Cornil (1864) and by Still (1897), the paediatrician often encounters aetiological, diagnostic, and prognostic problems.

The purpose of the present follow-up study is to review our experience of this disease in recent years in an attempt to add to our knowledge of its natural history and in particular to clarify the long-term prognosis of JRA and the factors affecting it. As far as we can ascertain the previous review articles in Britain on JRA were published by Colver (1937), Ansell and Bywaters (1959), and Schlesinger, Forsyth, White, Smellie, and Stroud (1961). To-day most would agree that Still's disease is but one part of a larger spectrum of rheumatoid disease in adults and children (Bywaters, 1971; Calabro and Marchesano, 1967), although age at onset still seems to be an important factor in its presentation and evolution.

Patients and methods

We have studied JRA in 100 patients who were admitted to the Royal Hospital for Sick Children, Glasgow, between 1942 and 1970. All but five were examined personally, and full information was obtained from the paediatrician or general practitioner about the rest.

We have followed in our study the diagnostic criteria of Ansell and Bywaters (1959):

- (1) The disease must begin before the age of 16 years.
- (2) There should be inflammatory involvement of four or more joints for a minimum period of 3 months.
- (3) If less than four joints are involved, biopsy of the synovial membrane should show histological changes compatible with rheumatoid arthritis.
- (4) Other causes of arthritis should be excluded.

A definite diagnosis of JRA was made on admission in 88 patients who satisfied these criteria. There were another sixteen patients who at the time of their discharge from hospital were considered to be suffering from 'probable' juvenile rheumatoid arthritis. Twelve out of these sixteen cases were diagnosed on follow-up as definite cases of JRA, and in the remaining four the diagnosis still remains in the 'probable' category. In another six patients, initially diagnosed as cases of JRA, some other diagnosis has been reached on follow-up (systemic lupus erythematosus, acute lymphoblastic leukaemia, pulseless disease (Takayasu's disease), nail-patella-syndrome, transient synovitis of right hip, and traumatic arthritis of right knee). We have, therefore, excluded these ten cases and

also patients with any form of connective tissue disease from this study.

We have chosen to divide our patients with juvenile rheumatoid arthritis (JRA) or 'Still's disease' into three major clinical sub-groups, according to the mode of onset of their symptoms. If the onset was acute with primarily systemic manifestation (fever, typical rash, splenomegaly, lymphadenopathy, leucocytosis, neck involvement, and arthralgia), the condition was termed 'early-onset' JRA as it tended to occur in younger children, in spite of an overlap in age-distribution with that termed 'late-onset' JRA. The distribution is shown in Fig. 1.

FIG. 1. Distribution of age at the onset of symptoms in 100 patients with JRA

The patients with early-onset JRA were usually toxic, listless, and irritable. This is the type which other authors have described as Still's disease or juvenile chronic polyarthritis (Calabro and Marchesano, 1968; Robinson, 1969; Ansell, 1972).

Those with insidious onset, polyarthritis, and little systemic involvement have been grouped as cases of 'late-onset' JRA (labelled 'Adult type JRA' by Calabro and Marchesano, 1968; Robinson, 1969), and those with single joint involvement as cases of 'monoarticular-onset' JRA. Among those with late-onset JRA is included a boy with Bruton's type hypogammaglobulinaemia who later developed arthritic symptoms. Synovial membrane biopsy was performed in all monoarticular-onset JRA patients except one, in whom, however, the Waaler-Rose test was positive. The joints involved in cases of monoarticular-onset were the knee in seven patients, the ankle in one, and the wrist in one. Monoarticular-onset JRA patients had few, if any, systemic manifestations. The incidence of each of the three types is shown in Table I (overleaf).

Table I Type of onset of juvenile rheumatoid arthritis in 100 cases

Type	No. of patients	Sex	Age range (yrs) (Mean)	No. of patients with systemic features			
				Fever	Rash	Splenomegaly	Lymphadenopathy
Early-onset	44	Male	26	27	22	19	28
		Female	18				
Late-onset	47	Male	19	14	1	3	7
		Female	28				
Monoarticular-onset	9	Male	3	3	0	0	0
		Female	6				
Total	100	100		44	23	22	35

In our series of 100 cases under review, there were 52 girls and 48 boys. Duration of follow-up has ranged from over 20 years to less than 1 year, but only five have been observed for less than 1 year (Fig. 2). The age at onset varied from 9 months to 12 years 7 months. There were two patients who presented with unexplained fever. A positive family history of rheumatoid arthritis was elicited in the close relatives of twelve patients.

FIG. 2 Duration of follow-up

The functional status of the 91 surviving members of our series have been grouped as follows:

- Grade I Helpless
- Grade II Chair/bed existence
- Grade III Moderate limitation of function
- Grade IV Slight limitation of function
- Grade V No limitation of function

DISEASE COURSE AND CURRENT FUNCTIONAL STATUS

We have described the course of the disease as intermittent when the periods of inactive disease were interspersed with a few weeks or months of flare-up of active disease. The monocyclic course was characterized by active disease lasting less than 2 years from the onset and terminating in remission without recurrence or sequelae; continuous or unremitting polyarthritis was used to indicate those in whom the active disease lasted for more than 2 years. The course of the disease and functional status of our 100 patients is shown in Table II.

The relationships of functional status, residual deformities, disease activity or inactivity, and mortality to the age at onset, to the mean duration of disease activity, and to the follow-up period from onset is shown in Table III (opposite).

Table II Relationship to mode of onset and course of disease

Relationship	No. of patients	Current functional status				Clinical disease		Died
		V	IV	III	II	Inactive	Active	
To mode of onset:								
Early-onset	44	22	5	6	3	32	4	8
Late-onset	47	33	7	6	0	40	6	1
Monoarticular	9	8	0	0	1	9	0	0
To course:								
Monocyclic	26	22	0	0	0	22	0	4
Intermittent	72	41	12	11	3	58	9	5
Continuous (Unremitting polyarthritis)	2	0	0	1	1	1	1	0
Total	100	63	12	12	4	81	10	9

Table III Relationship between various parameters

Relationship	No. of patients	Current functional status				Residual deformities	Clinical disease		Died
		V	IV	III	II		Inactive	Active	
To age at onset (yrs):									
0-5	46	27	4	5	4	16	37	3	6
6-9	30	20	3	4	0	9	24	3	3
10-15	24	16	5	3	0	11	20	4	0
To duration of disease (yrs) (mean)									
< 1 (5 months)	19	14	0	0	0	5	14	0	5
1-12 (4)	81	49	12	12	4	31	67	10	4
To follow-up period from onset:									
< 1	5	1	0	0	0	1	1	0	4
> 2	26	17	4	2	1	5	21	3	2
> 5	32	19	5	5	1	13	26	4	2
> 10	27	20	2	4	0	11	24	2	1
> 20	10	6	1	1	2	6	9	1	0
Total	100	63	12	12	4	36	81	10	9

Monocyclic course

Out of the 26 patients with monocyclic course, of which 22 are alive (Table II) the disease became inactive in fourteen cases in less than 6 months from onset, in five cases after 1 year from onset, and in three cases after 18 months from onset. Eleven of these patients are now adults. It is interesting that in none of the 22 patients has there been limitation of function (Grade V) or other sequelae. Relapses have not occurred in any of these patients over a period of observation ranging from 1 year to 27 years. The ultimate outcome, however, cannot be predicted in all of them because relapses can occur even after several years of remission.

Intermittent course

The intermittent type has been observed in 72 cases and the duration of activity has ranged from 1 year to 14 years (Table II). Of these five died and in nine cases the disease is currently active.

The course of the disease is highly unpredictable and there is no way to foretell which of these patients will relapse and when or whether the disease has completely burnt itself out. In this group 33 patients are now adults.

The poor functional status and residual deformities of several of these patients may be related to the duration and frequency of periods of activity.

Continuous course (unrelenting polyarthritis)

The course of polyarthritis was unrelenting in two female patients. In one patient the disease has been active for 8 years from the onset. In the other patient the active disease lasted for 14 years from onset but it has been quiescent over the past 6 years. The current functional status of these patients is Grade II and III respectively.

In our series, therefore, nine patients died and in ten cases the disease is still clinically active while in 81 the disease remains inactive.

Of the 91 surviving members there has been no limitation of function (Grade V) in 63 and they are at present living normal lives. None of our cases was classed as helpless (Grade I). In three patients with monoarticular-onset JRA, the disease progressed from a single joint to other joints. The parameters which have affected the functional status of our patients are shown in Tables II and III.

RESIDUAL DEFORMITIES

These were seen in 36 cases. Spindling of fingers was present in 25, crippling deformities of fingers in seven, micrognathia in five, flexion contractures of elbows in fifteen, deformity of hips in three, and of the knees in one. Residual deformities were more common in early-onset than late-onset JRA (55 and 32.5 per cent. respectively). In general they were related to the duration of the disease (Table III). None of those whose disease remained monoarticular showed residual deformity. All five patients who have micrognathia show radiological changes of temporomandibular joint involvement, presumably responsible for the growth disturbance of the mandible.

COMPLICATIONS

In our series there were only three patients, two of early-onset and one of late-onset, who developed complications. Both patients with early-onset JRA developed secondary amyloidosis 6 and 7 years after diagnosis which was confirmed by rectal and liver biopsy. Of these one also developed unilateral iridocyclitis and cataract 4 years after the onset of disease. One patient with late-onset JRA developed

Table IV Details of nine patients with juvenile rheumatoid arthritis who died

No.	Sex	Age at onset of disease (yrs)	Age at death (yrs)	Type	Course of disease	Cause of death
1	M	4 3/12	8	Early-onset	Intermittent	Acute hepatic necrosis
2	F	8 7/12	15	Late-onset	Intermittent	Chronic glomerulonephritis, left heart failure, hypertension, renal failure
3	F	8	16	Early-onset	Intermittent	Septicaemia (<i>Candida albicans</i> isolated from abscesses in lung, liver, spleen and kidneys)
4	M	1 2/12	13	Early-onset (Waalser-Rose positive)	Intermittent	<i>E. coli</i> septicaemia, secondary amyloidosis, nephrosis, renal failure, pulmonary oedema
5	M	9	10	Early-onset	Intermittent	Widespread liver damage
6	F	3 7/12	4 1/12	Early-onset	Monocyclic	Bronchopneumonia
7	M	4 2/12	4 3/12	Early-onset	Monocyclic	Septicaemia, terminal pneumonia
8	M	2	2 9/12	Early-onset	Monocyclic	Acute periportal hepatic necrosis, myocarditis and pericarditis, terminal septicaemia, acute bronchopneumonia, oesophageal candidiasis
9	F	3 1/12	3 5/12	Early-onset (Waalser-Rose positive)	Monocyclic	Septicaemia (<i>Strept. haemolyticus</i> and <i>Staph. pyogenes</i> grown from splenic culture), polyserositis

iridocyclitis, cataract, and band keratopathy 4 years after the onset of disease. In all three cases, the course of the disease was intermittent. None of the patients with monoarticular-onset JRA developed complications.

DEATHS

In our series there were nine patients who died (Table IV), five within 1 year of the onset of disease. One died more than 10 years after the onset of the disease with amyloidosis, renal failure, and superimposed septicaemia. The mortality seems related to the age at onset and to the mode of onset of disease rather than to other parameters (Tables II and III). The main causes of mortality in our series have been septicaemia and hepatic necrosis.

The only case of late-onset JRA (Case No. 2 in Table IV) who died showed evidence at autopsy of chronic glomerulonephritis, hypertension, and renal failure. These findings cast some doubt on the diagnosis of juvenile rheumatoid arthritis, but repeated investigations in life failed to demonstrate the LE cell phenomenon nor did the *post mortem* findings show any feature suggestive of SLE. There were no deaths in the monoarticular-onset group. A *post mortem* examination was performed in all who died.

RHEUMATOID FACTOR

The most consistently used test for rheumatoid factor at the time of admission of our patients was the sheep cell agglutination or Waaler-Rose test. The Waaler-Rose test was positive in six out of seventy patients (8.6 per cent.) in a titre of 1:64 or

more. Out of these six seropositive patients, three were of early-onset, two of late-onset, and one of monoarticular-onset JRA. In four of these patients the age at the onset of symptoms was more than 10 years and in the other two less than 3 years. Two patients died, and of the remaining four the disease is quiescent in two and active in two.

The number is too small for conclusions to be drawn, but the fact that seropositivity was more frequent in children in whom the disease started in their later childhood accords with the findings of other authors (Sievers, Ahvonen, Aho, and Wager, 1963; Cassidy and Valkenburg, 1967; Zutshi, Ansell, Bywaters, Epstein, Holborow, and Reading, 1969). The Waaler-Rose and latex-fixation tests were performed at the follow-up examination in the four living cases and in all of them were found to be negative. All the patients who were seronegative at the time of diagnosis were retested (both Waaler-Rose and latex-fixation) at follow-up and none became seropositive. In addition immunoglobulins (IgG, IgA, and IgM) and β_{1C}/β_{1A} globulins were determined and are the subject of another communication (Goel, Logan, Barnard, and Shanks, 1974).

This supports the statement of Scott (1952) and Bywaters, Carter, and Scott (1959) that there is no strict correlation between seropositivity and disease activity. In the latter series, in both early and late-onset JRA, some initially positive cases became negative on follow-up. This is contrary to the experience with adult rheumatoid arthritis where longer duration leads to a higher proportion of seropositivity (Brown, Bunim, and McEwen, 1949; Ball, 1952; Jacobson, Kammerer, Wolf, Epstein, and Heller, 1956).

Table V Comparison of our results of treatment with those of other series

Series	Treatment	No. of patients	Died	State of disease		Functional status			
				Active	In remission	V	IV	III	II
Ansell and Bywaters (1959)	Steroid therapy in 63	(216) Assessment in 209	9 (4)*	105 (50)	95 (46)	42 (44)	—	53 (56)	—
Schlesinger, Forsyth, White, Smellie, and Stroud (1961)	No steroid therapy Steroid therapy	37 63	2 (5) 5 (8)	2 (5) 17 (27)	33 (90) 41 (65)	18 (55) 25 (61)	10 (30) 10 (24)	3 (9) 4 (10)	2 (6) 2 (5)
Lindbjerg (1964)	No steroid therapy Steroid therapy	27 26	0 3 (11)			17 (62) 7 (25)	9 (33) 7 (25)	— 3 (11)	1 (3) 6 (23)
Present series	No steroid therapy Steroid therapy	65 35	3 (4.6) 6 (17)	4 (6) 6 (17)	58 (89.4) 23 (66)	48 (74) 15 (43)	7 (10) 5 (14)	5 (8) 8 (20)	2 (3) 2 (6)

* Number in parentheses denotes the percentage of cases.

TREATMENT

Systemic steroids were given to 35 of the children in our series and they showed a poor remission rate and functional status as compared to 65 patients who were treated with conservative measures, consisting of rest in the acute phase with salicylates and later physiotherapy (Table V). Our results are in agreement with those of Ansell and Bywaters (1959) who also reported a poor remission rate in their patients treated with steroids. However, Schlesinger and others (1961) have commended the value of steroid therapy in JRA, although 37 patients in their series who were not given steroids also showed a high remission rate. Lindbjerg (1964) reported that corticosteroids did not cut short the duration of activity of the disease, prevent complications, or alter the long-term prognosis. In our series it appears that corticosteroids can initially produce a remarkable suppression of symptoms without influencing the natural remission rate or ultimate prognosis. Corticosteroids may, therefore, be desirable in those with systemic illness and especially in those with cardiac or ocular complications. Two patients in our series with acute iridocyclitis were treated with steroids with good results.

As regards other forms of therapy, there were five patients in our series who were treated with indomethacin, two with chrysotherapy, and one each with phenylbutazone, azathioprine, cyclophosphamide, chloroquine, and D-penicillamine without noticeable benefit. Therapeutic synovectomy of the knee joint was performed in two patients with disappointing results. In all these groups the numbers are too small for clear conclusions to be drawn.

Discussion

It would seem that the prognosis of juvenile rheumatoid arthritis may be to some extent predicted by

its mode of onset (early, late, or monoarticular), the duration of disease activity, and the course of the disease. A positive rheumatoid factor and the presence of subcutaneous nodules also point to an unfavourable prognosis. Although an exact prognosis cannot be given in an individual case, the range of possibilities can be stated fairly clearly in the light of our experience.

However, remission can occur at any time, and unremitting and progressive disease that lasts into adulthood is, fortunately, uncommon although residual joint signs may persist. It is quite evident from our series that systemic manifestations, the number of complications, poor functional status, high mortality, and extensive residual deformities were more common in early-onset JRA. However, prognosis in all groups is encouraging, even although it seems better in late-onset and monoarticular-onset JRA.

The main causes of mortality in our series have been septicaemia and hepatic necrosis (Table IV). Seven of the nine patients who died were receiving steroids at the time of their infective episodes.

Cobb, Anderson, and Bauer (1953) have reported that 5 per cent. of the deaths in their series were caused by infections. An increased incidence of respiratory infections in rheumatoid arthritis has been reported (Kay, 1967; Walker, 1967). Huskisson and Dudley-Hart (1972) have recently emphasized the importance of this complication in adult rheumatoid arthritis. The observation that infection plays such a large part in causing death among patients with rheumatoid arthritis, shows the need for prompt administration of antibiotic and antifungal therapy and for especial vigilance during steroid therapy.

There were three deaths in this series due to hepatic necrosis which, as far as we could ascertain, was not caused by therapy. A *post mortem* examination did not reveal any obvious cause. On reviewing

the existing literature, we were unable to find any publications concerning hepatocellular necrosis in JRA as a cause of death, although massive hepatomegaly associated with abnormal liver function in JRA has been reported (Schaller, Beckwith, and Wedgwood, 1970). However, Lefkovits and Farrow (1955) reported on the histological examination of the liver tissue in fifteen patients with adult rheumatoid arthritis which they have termed 'non-specific reactive hepatitis'.

Iridocyclitis and cataract developed in 2 per cent. of our patients 4 years after the onset of disease.

Iritis is more common in children than in adults with rheumatoid arthritis; the figures for iritis in children range from 5.5 per cent. upwards, and from 3.3 per cent. to 4.7 per cent. in patients with adult rheumatoid arthritis (Sorsby and Gormaz, 1946; Godtfredsen, 1949; Stanworth and Sharp, 1956; Smiley, May, and Bywaters, 1957; Schlesinger and others, 1961; Lindbjerg, 1964).

Regular ophthalmological examinations with the slit lamp, the only means of early detection, should therefore be made, preferably every 6 months, in all patients with juvenile rheumatoid arthritis.

Rheumatoid factor has been found far less often in children than in adults with rheumatoid arthritis. Zutshi and others (1969) have reported a positive Waaler-Rose test in 15 per cent. of their patients with JRA and a higher incidence in patients with late-onset JRA. This contrasts with the 75 per cent. of adult patients and the 4 per cent. in the normal population who have a positive Waaler-Rose test (Hill and Greenbury, 1965; Alexander and McCarthy, 1966). However, a follow-up study of a population sample (Ball and Lawrence, 1963) has shown that individuals with positive agglutination tests are more likely to develop rheumatoid arthritis than individuals with negative tests. Various authors have pointed out that a persistently negative or a low titre rheumatoid factor is a good prognostic sign and, while in many cases positive and negative results may be found in the same patients, a persisting high titre suggests a poor prognosis (Schubart, Calkins, and Cohen, 1960; Kellgren and O'Brien, 1962; Ragan and Farrington, 1962).

Our own figures are lower (little more than the normal adult population, but the incidence of rheumatoid factor increases with age) and shows a roughly equal distribution in all clinical groups. However, when the rheumatoid factor is present it may be useful in assessing prognosis. In our series, of the six seropositive patients, two died, in two cases the disease is currently active, and in the other two it is inactive. It is noteworthy that, of the five patients with subcutaneous nodules, only two were seropositive. In adults, Jacobson and others (1956) found that well over 90 per cent. of their patients with nodules gave positive results.

Calabro (1966) reported that rheumatoid nodules are less common in children than in adults, occurring in about 6 per cent. of his patients. In the series of Schlesinger and others (1961), rheumatoid nodules were noted in 7 per cent. of patients. Those with rheumatoid arthritis who also have subcutaneous nodules, whether children or adults, often do less well than those without nodules (Short, Bauer, and Reynolds, 1957; Duthie, Brown, Truelove, Baragar, and Lawrie, 1964; Cohen, Eaton, Feingold, Gellis, Pryles, Teebagy, Baker, and Connelly, 1965).

Conclusions

The prognosis of JRA of all clinical types is probably better than has been thought. Adverse prognostic factors are generalized systemic manifestations and, with early-onset, the duration and frequency of periods of activity, subcutaneous nodules, positive rheumatoid factor, and a continuous course. There are features in the presentation and evolution of the disease, whether of early or late-onset, which make it difficult to adopt the current classification of adult rheumatoid into seropositive and seronegative types, each with its separate clinical pattern and differing complications. There would appear to be differences between juvenile and adult rheumatoid disease which may prove as important as their similarities.

Summary

One hundred cases of juvenile rheumatoid arthritis (JRA) have been reviewed; 44 were of early-onset, 47 of late-onset, and nine of monoarticular-onset.

81 patients are currently in remission while ten continue to have active rheumatoid disease. Nine died.

The complication of secondary amyloidosis occurred in two patients and unilateral iridocyclitis and cataract in two patients, one of whom also had band keratopathy.

The prognosis of JRA may be to some extent predicted by its mode of onset, the duration of disease activity, the course of the disease, the presence of rheumatoid nodules, and a positive rheumatoid factor. Steroids, although initially effective, had no favourable effect on the long-term prognosis of JRA and carried long- and short-term hazards.

This review reveals a favourable prognosis for the disease in general, but it seems likely that the long-term prognosis is better in late-onset and monoarticular-onset JRA.

There are differences between juvenile and adult rheumatoid disease which require further study.

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