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The natural course of juvenile rheumatoid arthritis

A Study of Two Hundred Thirty Cases

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THE natural course of juvenile rheumatoid arthritis was studied from the clinical data of 230 patients having this disease. The patients were examined and treaetd at the Cleveland Clinic during the period of June 1952 through December 1968. The mode of onset, the clinical course, and the pattern of the disease were analyzed, and a classification was made conforming to the types of clinical features.

Criteria for diagnosis

The criteria for diagnosis were those of the American Rheumatism Association (A.R.A.) for evaluating adults, and have been modified to conform to the manifestations of juvenile rheumatoid arthritis.[1] Of the criteria listed below, 1 through 4 or 4 and 5 are essential for the diagnosis of juvenile rheumatoid arthritis.

1. Arthritis of one or multiple joints for at least six weeks, or for less than six weeks in the presence of one ot the following features: (a) evanescent rash; (b) ankylosis; (c) iritis; (d) flexion contractures; (e) muscular atrophy; (f) anemia; (g) leukocyte count of 18,000 or more per cubic millimeter, without any other identifiable cause; (h) pain or stiffness in the cervical spine, with or without radiographic changes in zygapophysial joints of the neck.

2. Constitutional symptoms—fever, weakness, weight loss.

3. Increased sedimentation rate, or increased content of serum glycoproteins and plasma fibrinogen.

4. Exclusion of rheumatic fever, periarteritis nodosa, systemic lupus erythematosus, dermatomyositis, tuberculous synovitis, lymphoma, and leukemia.

5. Persistent pyrexia in the absence of any other identifiable cause, gel reaction of 1- to 2-hour duration or longer, at least one of the items (a) through (h) in criterion 1, and criterion 3. In this group, (a) in criterion 1, the typical evanescent rash, was of greatest diagnostic value.[2]

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Clinical data

Age at onset and sex ratio. Range of age at onset for juvenile rheumatoid arthritis has arbitrarily been chosen from birth through the sixteenth year. It seems likely that juvenile rheumatoid arthritis cannot be adequately defined by age of onset. Some juvenile rheumatoid arthritis with adult pattern of the disease begins as early as the age of six years, and some rheumatoid arthritis having features peculiar to childhood, begins in the late teens. In our series the age range at onset of juvenile rheumatoid arthritis was from 4.5 months through 16 years (to seventeenth birthday), the mean age at onset being 8.7 years. The sex ratio was about 1 male to 2 females.

Mode of onset. The onset was classified as sudden, gradual, or insidious. Sudden onset (in 49 patients) began with a temperature higher than 102 F, chills, usually but not necessarily associated with polyarthritis or monarticular arthritis, often accompanied by lymphadenopathy and infrequently with mild splenomegaly. Gradual onset (in 38 patients) was represented by pyrexia of 100 to 102 F and smoldering articular manifestations. Insidious onset (in 143 patients) was represented by slow progression of the disease with no fever or chills and few constitutional symptoms.

Clinical pattern and course of juvenile rheumatoid arthritis. Three types of juvenile rheumatoid arthritis were recognized: Still's type, with four subtypes; polyarticular type; and pauciarticular type.

Still's type. This is characterized by a sudden onset, i.e., spiking and usually intermittent fever of 102 F or higher, with or without lymphadenopathy and splenomegaly, associated with articular manifestations at the same time, or joint symptoms that develop subsequently, and usually affecting peripheral joints and the neck. This group included 50 patients (22 percent of 230 patients), with an average age of 6.4 years at onset. Twenty-three patients (almost half) had the typical evanescent rash, and in some it recurred.

Subtype 1, characterized by fever of unknown origin without synovitis; the 11 patients in this group all posed difficult diagnostic problems. Still's type was evidenced by increased sedimentation rate, serum glycoprotein content and leukocyte count, and morning gel reaction. A therapeutic response to antirheumatic treatment, namely, abolition of gel reaction, and return to the normal range of temperature and of results of laboratory tests was taken as additional evidence for the diagnosis.

Subtype 2, characterized by fever of unknown origin initially, with subsequent development of arthritis; there were 18 patients in this group.

Subtype 3, characterized by fever and joint manifestations occurring simultaneously; there were 18 patients in this group.

Subtype 4, characterized by polyarticular disease that subsequently changed into Still's type; there were three patients in this group.

Polyarticular type. This is characterized by involvement of multiple joints, without significant pyrexia and usually with insidious onset. There were 114

patients (50 per cent of 230 patients) with polyarticular type of juvenile rheumatoid arthritis. The majority had an insidious onset, but in 36 the disease changed from Still's type into the polyarticular type (these are categorized under Still's type). Only 10 patients with polyarticular disease had evanescent rash, most of whom were less than 10 years old. In five patients, rheumatoid nodules developed during the course of the disease; all were more than 10 years old and the majority were around the age of puberty (mean age, 13 years). One of the five patients had rheumatoid factor, another did not, and latex fixation tests were not performed in the others. Two of the 114 patients had Raynaud's phenomenon, and one patient had Stevens-Johnson syndrome. The polyarticular disease metamorphosed into the pauciarticular type in three patients.

Pauciarticular type. This is characterized by involvement of one or more joints up to a total of four, usually larger ones. There were 66 patients (28 percent of 230 patients) in this group. The mode of onset was insidious in 61 patients, and in five patients it had started with Still's type. In nine patients the pauciarticular type metamorphosed into the polyarticular type during the course of the disease. Only four patients had evanescent rash.

Clinical course of each type of juvenile rheumatoid arthritis

Table 1 details the clinical courses of the various types of juvenile rheumatoid arthritis in the series of 230 patients. The overall remission rate was 50 percent—60 percent in the Still's type; 44 percent in the polyarticular type; 56 percent in the pauciarticular type. Of the patients who had no remission, nine (5 percent of the total) remained in functional classes III or IV* (according to the A.R.A. criteria, the classes with the least favorable prognosis), and 76 patients (45 percent of the total) were in functional classes I or II, and one patient died.

Still's type. Of the 50 patients having Still's pattern, 12 each had a monocyclic† course[3] with one acute attack of arthritis and subsequent control of the disease within two years. Six of those patients had remissions, and six were lost to follow-up study.

Eleven patients had a polycyclic course with periods free from symptoms. At the time of review, three patients were in remission.

Twenty-five patients had persistent disease; one patient had a progressive course and was still in functional class III at the beginning of the third year of follow-up study. Fifteen patients had persistent but not progressive courses. Eight of them went into remission; the others were in functional classes I or II (A.R.A. criteria—the classes with the most favorable prognosis). Of nine patients with persistent disease that showed exacerbations from time to time, three

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* *American Rheumatism Association functional capacity classification: class I, ability to carry on all normal duties without any difficulty; class II, ability to carry out normal activities despite some handicaps; class III, activities are limited to only few or some of the normal duties; class IV, bedridden or confined to wheelchair.*

† *Monocyclic means one attack of the disease terminating in remission in less than two years. Polycyclic means intermittent remission and exacerbation. Persistent means that the disease persists in active form. Remission means that disease activity abates and remains inactive without therapy or with only minimal treatment for at least one year.*

Table 1.—*The clinical courses and types of juvenile rheumatoid arthritis in 230 patients*

Type of juvenile rheumatoid arthritis	Number of patients		Clinical course	Number of patients		
	Total	Subtotal		In remission	In functional classes III or IV	Lost to follow-up study
Still's	50					
		12	Monocyclic	6	0	6
		11	Polycyclic	3	0	3
		1	Persistent, progressive	0	1	0
		15	Persistent, nonprogressive	8	0	1
		9	Persistent, with flare-up	3	2 (one died)	2
		2	(Single examination)	–	–	2
Polyarticular	114					
		4	Monocyclic	2	0	2
		32	Polycyclic	11	2	5
		2	Persistent, progressive	1	0	0
		57	Persistent, nonprogressive	25	1	9
		11	Persistent with flare-up	1	3	0
		8	(Single examination)	–	–	8
Pauciarticular	66					
		7	Monocyclic	4	0	3
		16	Polycyclic	6	0	6
		1	Persistent, progressive	0	0	0
		32	Persistent, nonprogressive	15	0	6
		5	Persistent with flare-up	1	0	0
		5	(Single examination)	–	–	5
Total	230			86	9	58

had remissions. In one patient (onset of disease at the age of 16 years) generalized amyloidosis developed and he died five years after the onset of arthritis; autopsy confirmed the diagnosis of amyloid disease. Two patients of the total group of 50 were examined only once; their clinical courses are not known.

Polyarticular type, constituted 114 patients whose clinical courses are listed in *Table 1.*

Pauciarticular type, formed a group of 66 patients; their clinical courses are shown in *Table 1.*

Although the overall remission rate was 50 percent, it is likely that the true rate is higher than this, because patients with remission have been prone to be lost to follow-up study and thus would not be included in the favorable group. The remission rate rises sharply for the first four years of the disease (*Fig. 1*). After this it levels off at about 50 percent for the remainder of the period of follow-up; patients with the most persistent and severe juvenile rheumatoid arthritis account for this prolonged course and low remission rate, features rather characteristic of adult rheumatoid disease.

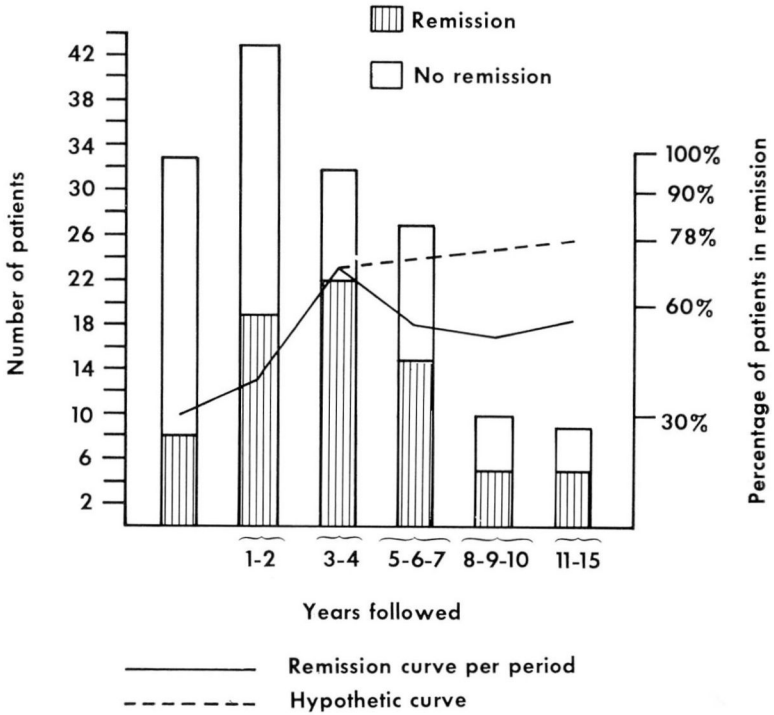

Fig. 1. Graph showing correlation between remission of juvenile rheumatoid arthritis and duration (in years) of active disease.

Laboratory findings

The most useful laboratory determination was the sedimentation rate, which was definitely increased in 104 (58 percent) of the 178 patients on whom the test was performed, and the glycoproteins (serum polysaccharides) which were increased in 129 (68 percent) of 188 patients. Those who had normal values of the above tests had been on treatment before examination at the Cleveland Clinic. Abnormal serum protein electrophoretic patterns were shown in 87 (76 percent) of 114 patients. The abnormalities consisted of increased γ-globulin and (or) increased β- and α_2-globulins, and, in certain cases, of decreased serum albumin values.

Rheumatoid factor[4-6] was present in 14 (10 percent) of 140 patients who were tested. Latex fixation titers ranged from 1:16 to 1:5120. The majority of patients having rheumatoid factor had the polyarticular type of juvenile rheumatoid arthritis. Those patients' ages ranged from 3 to 17 years, an average of 12.4 years. A majority (80 percent) of seropositive patients had erosive disease affecting cartilage and bone, identifiable on roentgenograms.

One patient had an abundance of lupus erythematosus cells. Thirteen patients (having juvenile rheumatoid arthritis) each had lupus erythematosus cells

Table 2.—*The 12 diseases accompanying juvenile rheumatoid arthritis in 14 of 230 patients*

Disease	Number of patients	Remarks
Hypogammaglobulinemia	2	
	1	16-year-old girl, with jacksonian seizures, bronchiectasis, splenomegaly, chorea, and herpes zoster; γ-globulin, 0.18 g per 100 ml
	1	γ-globulin, 0.04 g per 100 ml
Diabetes mellitus	2	Acute onset at ages 8 yr and 11 yr
Fibrous dysplasia, and testicular atrophy	1	—
Bilateral congenital dislocation of hips	1	—
Osteochondritis deformans juvenalis	1	—
Postnecrotic cirrhosis (viral)	1	—
Turner's syndrome, and rheumatic heart disease	1	—
Mongolism	1	—
Chronic ulcerative colitis	3	One had polyarticular arthritis, one pauciarticular arthritis, and one spondylitis
Systemic lupus erythematosus	1	—

definitely present but not abundant; two patients were less than two years old, and the others ranged between 10 and 16 years of age.

Accompanying diseases

Twelve types of accompanying disease were found among 14 patients in the series of 230 (*Table 2*). There were two patients with hypogammaglobulinemia; one patient had a serum γ-globulin level of 0.18 g per 100 ml, and the other had a serum γ-globulin level of 0.04 g per 100 ml. In the latter patient, immunoglobulins IgA and IgM have been absent, and IgG has been less than 100 mg per 100 ml of serum (normal from 500 to 1500 mg). Arthritis in this patient has been persistent for almost six years with a normal sedimentation rate but with elevated serum glycoprotein and plasma fibrinogen.[7] Both patients with γ-globulin deficiencies had persistent disease with flare-ups. The three patients with colitic arthritis had presenting symptoms of juvenile rheumatoid arthritis for some time before the ulcerative colitis was diagnosed.

Complications

Table 3 shows the number and various kinds of complications occurring among all the patients. The patients having hypercortisonism had all been treated with large doses of steroids before their examinations at the Cleveland Clinic.

In *Figures 2 and 3* the retarded growth and the fairly normal growth in chil-

Table 3.—*The 16 complications of juvenile rheumatoid arthritis in 110 of 230 patients*

Complications	Number of patients
Contractures	36
Joint effusion	20
Retarded growth	22
Iatrogenic hypercortisonism	17
Adrenal failure due to withdrawal of steroid therapy	2
Pes planus	3
Hallux valgus	1
Septic arthritis	1
Aseptic necrosis (hip)	1 (aged 6 yr)
Kyphosis	1
Cutaneous ulcers of leg	1
Amyloidosis (fatal)	1
Cataract (posterior subcapsular)	1
Myocarditis	1
Hypertrophic osteoarthropathy (juvenile)	1
Salicylate intoxication	1

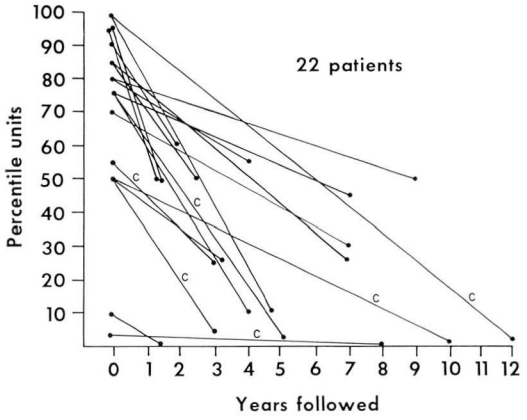

Fig. 2. Graph showing the change with time of expected growth (height and weight) expressed in percentile units, of 22 patients having gross retardation owing to juvenile rheumatoid arthritis.

dren with juvenile rheumatoid arthritis are compared. The lag ranged betweeen 3.5 and 30 percentile units, an average growth failure of 11.6 percentile units per annum in comparison with the expected normal. Any growth lag of more than 25 percentile units throughout follow-up study was considered as retarded growth. There were 22 patients with notable growth retardation. Only six of them had had iatrogenic hypercortisonism (marked as "c"). Forty-three patients had either normal growth or growth mildly stunted (less than 25 percentile

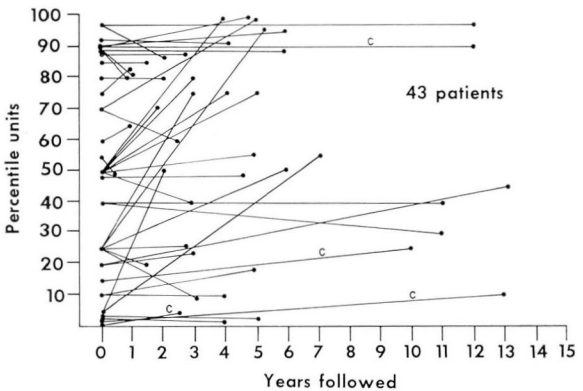

Fig. 3. Graph showing the change with time of expected growth (height and weight), expressed in percentile units, of 43 juvenile rheumatoid arthritis patients not having gross retardation.

Table 4.—*Roentgenographic findings correlated with rheumatoid factor in 122 of 230 patients with juvenile rheumatoid arthritis*

	Number of patients	Soft-tissue swelling, demineralization, and narrowing of joint spaces	Erosion and/or cyst	Rheumatoid factor present, number of patients
	92	Present	Absent	3
	30	Present	Present	11
Total	122			14

units), four of whom had hypercortisonism sometime during the course of the disease.

Roentgenographic findings

Roentgenograms have been of little diagnostic help, as the specific changes occur rather late in the course of disease and only in a minority of patients,[8,9] but have provided valuable prognostic signs for extremely severe disease. According to roentgenograms of the 122 patients on whom such studies were made (*Table 4*), 30 had erosive disease or cystic lesions, or both, usually with demineralization, cartilage lysis manifested by narrowing of the joint spaces, and soft-tissue swelling. Ninety patients had only soft-tissue swellings, demineralization (usually severe) and narrowing of joint spaces. Two patients had, in addition, retarded bone growth as shown on roentgenograms. The majority of pa-

tients (11 of 14) with rheumatoid factor had erosive and/or cystic disease; the ages of these patients ranged from 3 years to 17 years, with the mean age being 10 years.

Treatment

Medical treatment for systemically ill patients consisted of rapid induction of response by administering small doses of nitrogen mustard into the tubing of an intravenous setup containing 5 units of adrenocorticotropic hormone in 250 ml of dextrose and saline. This was followed by maintenance therapy using an antimalarial drug and salicylates,[10] often supplemented by mild antidepressant medication. Selected patients were maintained, in addition, on small doses of cytotoxic drugs and/or corticosteroid preparations. The cytotoxic drugs used included various alkylating agents and folic acid antagonists but no purine analogues. A physiotherapy program in the hospital and at home was a standard feature of this combined chemotherapeutic program. No contraindication to moderate doses of indomethacin has been encountered. No serious complications occurred while this chemotherapeutic program was followed.

Several patients with protracted, destructive disease underwent corrective orthopedic surgery, or synovectomy for persistent erosive synovitis (*Table 5*).

Comments

The natural course of juvenile rheumatoid arthritis is rather unpredictable at the onset of the disease. It is most frequently characterized by periods of exacerbation and suppression. Suppression of disease manifestations resulting from chemotherapy may be difficult to distinguish from spontaneous remission that eventually may occur. There were metamorphoses from one type to another, with the exception of pauciarticular type changing to Still's type. These changes have no acceptable explanation at present.

Polyarticular juvenile rheumatoid arthritis most closely resembles adult rheumatoid arthritis not only by the presence of the rheumatoid factor (in 10 percent) and the subcutaneous nodules but also in its inherent tendency to persist. Nearly all patients with active juvenile rheumatoid arthritis persisting into adulthood will have had many years of polyarticular type, even when the onset is Still's type or pauciarticular type. These two types are rather characteristic of childhood and are distinctly uncommon in adult rheumatoid arthritis.

Although pain has been reported to be absent in juvenile rheumatoid arthritis[1, 2] no examples of pain-free synovial disease occurred in the 230 patients. All of the patients showed clearly antalgic attitudes or movements even when they said they had no pain. In our experience the widely held belief that pain may be absent is an erroneous one. Teenagers tend to minimize disease symptoms that make them different from their healthy peers.

Cumulative remission rates approach 70 percent after mean duration of disease becomes three or four years; however, cumulative rates are unreliable thereafter because the available data are limited to patients having persistent and

Table 5.—*Clinical data of 13 patients with juvenile rheumatoid arthritis who underwent or were to undergo surgical treatment*

Patient, number	Sex	Age, yr: At onset of disease	Age, yr: At operation	Disease: Type	Disease: Pattern	Operation performed or indicated	Latex test	Follow-up, yr	Result, comment
1	F	16½	25	Polyarticular	Cyclic, progressive	Cup arthroplasty, left hip	1:5120	10	Good motion but some pain
2	F	12	22	Polyarticular	Cyclic, progressive	Cup arthroplasty, left hip	Not done	12	Motion still restricted but less in left hip than in right
3	F	2	8	Pauciarticular	Persistent, progressive	Posterior capsulotomy of right knee, with Kirschner wire	Not done	13	No pain, mild contracture
4	F	2	13	Pauciarticular	Cyclic, nonprogressive	Synovectomy, right and left hip	Not done	13	Better function than preoperatively
5	F	13	19–20	Polyarticular	Persistent, nonprogressive	Synovectomy (A) PIP* of left thumb, and left flexor tendon of index and middle fingers. (B) PIP and MCP† of left index and middle fingers	Negative	3	(A) Excellent, no recurrence, good function (B) Synovitis recurred but with less pain

6	M	15	7	Poly-articular	Persistent, nonprogressive	Synovectomy, ankle and subtalar joints, right peroneal, tibial posterior tendons	Negative	7	Less pain, better motion, no recurrent arthritis in ankle
7	F	13	6	Poly-articular		Synovectomy indicated	Negative	15	—
8	F	1¼	11	Pauci-articular	Persistent, nonprogressive	Synovectomy indicated	Negative	6	—
9	F	12	5	Pauci-articular	Cyclic, nonprogressive	Synovectomy indicated	Not done	5	—
10	F	6½	11	Poly-articular	Persistent, progressive	Synovectomy indicated	Not done	3	—
11	F	1	14	Poly-articular	Persistent, progressive	Cup arthroplasty, left, right hips indicated	Negative	13	—
12	M	6	16	Poly-articular	Persistent with flare-up	Cast for correction of contractures of knees	Not done	10	Contractures corrected
13	M	10	7	Poly-articular	Cyclic, nonprogressive	Cast for correction of contractures of knees	Not done	7	Contractures corrected

* PIP—proximal interphalangeal joint.
† MCP—metacarpophalangeal joint.

often severe juvenile rheumatoid arthritis of long duration.[11] In this latter group, remissions occurred in about half during each three-year period succeeding a five-year anniversary of onset.

The outcome of juvenile rheumatoid arthritis can be categorized in several ways. (1) Functional capacity is normal to good (A.R.A. classes I and II) in 95 percent of patients, with only 5 percent in functional capacity classes III and IV, all of whom derive from Still's type or polyarticular juvenile rheumatoid arthritis. (2) Although iritis was noted in approximately 8 percent of this series, no blindness has developed. (3) Of 230 patients, one died (0.4 percent) (a single case of generalized amyloidosis). (4) Moderate to severe growth disturbance was seen in 22 patients, and mild stunting of growth in many more. Severe dwarfism was seen in only 2 or 3 percent, the consequence of persistent severe polyarticular and systemic juvenile rheumatoid arthritis usually beginning before the seventh year of life. Major dwarfism may correct itself when remission takes place at least two years before puberty. (5) Persistence of juvenile rheumatoid arthritis into adulthood occurs in only from 5 to 10 percent of patients, but data in our series do not justify an exact estimate. (6) No systematic studies of psychiatric well-being have been made of these patients. Although depression, withdrawal, and hostility are much in evidence during active disease, the clinical impression does not suggest that imbalance will occur later. Classroom achievements are good to superior by 99 percent of these children, although social skills may be somewhat delayed. We are impressed with the greater than expected frequency of parental psychopathology.[1]

Features suggestive of good prognosis are, indeed, obscure. The only two items evident are (1) benignity of course (absence of deformity or erosion), and (2) prompt and nearly complete suppression of disease with chemotherapy. Features suggesting bad prognosis are more numerous: (1) persistent polyarticular disease, (2) deformities and bone erosions, (3) failure of symptoms to be suppressed well with chemotherapy, (4) presence of rheumatoid factor and subcutaneous nodules, (5) sustained elevation of γ-globulin, (6) hip cartilage lysis, (7) notable hostility of either parent toward the child.

Protracted activity of juvenile rheumatoid arthritis with erosive changes and an unremitting course is a severe disease. Aggressive chemotherapy and surgical treatment ameliorate the process and appear to improve the functional outcome without exposing the child to the dangers of excessive dosage of corticosteroids.

Summary

The natural course of juvenile rheumatoid arthritis in 230 patients under treatment was evaluated. The duration of follow-up in this retrospective study ranged from a single examination to periodic examinations during 16 years.

The onset of juvenile rheumatoid arthritis was sudden in 22 percent, gradual in 16 percent, and insidious in 62 percent of the patients. The age at onset ranged from 4½ months to the seventeenth birthday, the mean age being 8.7

years. The sex ratio is 1 male to 2 females, virtually identical to that in adult rheumatoid arthritis populations.

The course of juvenile rheumatoid arthritis was variable, being monocyclic in 11 percent, polycyclic in 28 percent, and persistent in 61 percent. The persistent course may be further described as progressive or nonprogressive, or punctuated by episodic exacerbations.

Three types of clinical pattern were recognized: (1) Still's type in 22 percent, usually with an abrupt febrile onset in the young child (mean age 6.4 years); (2) polyarticular juvenile rheumatoid arthritis in 50 percent, often with an insidious onset in late childhood (mean age 13 years); (3) pauciarticular juvenile rheumatoid arthritis in 28 percent, the onset of which is typically insidious but dispersed throughout the years of childhood. Still's type may be difficult to diagnose owing to a dissociation of the febrile reaction from other features. Four subtypes of Still's type appeared in the 50 patients as follows: (1) fever of unknown origin without synovitis in 11 patients, (2) fever of unknown origin with subsequent development of arthritis in 18 patients, (3) fever occurring simultaneously with arthritis in 18 patients, and (4) polyarticular juvenile rheumatoid arthritis later metamorphosing into febrile Still's disease in three patients. The rash of juvenile rheumatoid arthritis is helpful in the diagnosis of Still's type, subtypes 1 and 2. The rash occurs in half of the patients with Still's type but only in 9 percent of those with polyarticular and 6 percent of those with pauciarticular type.

The remission rate was almost 70 percent in three to four years of follow-up study, but thereafter the rate remains at 50 percent. Ninety-four percent of patients whose progress was followed were in functional classes I or II, with only 6 percent in functional classes III or IV. At the time of review the mortality rate was 0.4 percent. Severely stunted growth occurred in from 2 to 3 percent of patients.

An aggressive chemotherapeutic program for severe and intractable disease, physical therapy and rehabilitation, and surgical intervention in prolonged, destructive cases of juvenile rheumatoid arthritis seem warranted.

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