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LONG-TERM OUTCOME AMONG PATIENTS WITH JUVENILE RHEUMATOID ARTHRITIS

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1. ABSTRACT

Juvenile rheumatoid arthritis (JRA) is a chronic inflammatory disease primarily affecting the joints but also extra articular tissue. The long-term outcome of JRA has different aspects, which include disease outcome, mortality, iridocyclitis and stature. Several studies, which have addressed these issues, are reviewed in this article. In addition, functional, educational and employment status of patients with JRA are also reviewed. To facilitate better understanding of these various studies, a description of the terminology used in defining disease is provided. Several of the instruments that are available for assessing outcome among patients are described. The role of laboratory and radiological evaluation in predicting outcome is also addressed.

2. INTRODUCTION

Juvenile rheumatoid arthritis (JRA) is due to chronic inflammation primarily of joints and also extra-articular sites. Acute inflammation and acute exacerbations of chronic inflammation contribute to short term disability among patients. However, the chronic inflammatory process in the synovium, cartilage, bone and supportive soft tissue results in damage to these tissues. One of the central paradigms concerning JRA is that 80% of children can be expected to be free of inflammation by the time they reach adulthood. Another paradigm is that 80% of children with JRA will grow up without deformities (1,2). These views have been challenged in the recent years. Studies in adults with rheumatoid arthritis and children with JRA have shown that the proportion of patients with disability increases with age (1,3-5).

The outcome among patients with JRA can be viewed differently. The outcome of the joint in terms of synovial, cartilage and bony pathology is different from health status and functional outcome, which also includes quality of life, vocational and psychosocial outcome. To better understand the outcome of JRA, it is necessary to review the terminology used to describe juvenile arthritis and activity of disease. The term juvenile chronic arthritis (JCA) used in Europe includes polyarticular arthritis, pauciarticular arthritis, systemic arthritis, juvenile ankylosing spondylitis, psoriatic arthritis and arthritis associated with inflammatory bowel disease (IBD). The patients must be under 16 years of age and must have had arthritis for at least 3 months to be considered to have JCA. The term juvenile rheumatoid arthritis used in North America includes pauciarticular arthritis, polyarticular arthritis which is subdivided into seronegative and seropositive forms and systemic arthritis. This nomenclature excludes patients with juvenile ankylosing spondylitis, psoriatic arthritis and arthritis associated with IBD. At onset, patients must be under 16 years of age and must have had objective arthritis for at least 6 weeks.

The International League of Associations for Rheumatology [ILAR] presented in 1995, a proposal for developing criteria for classification of idiopathic arthritides. The onset must be before the sixteenth birthday

Table 1. Proposed classification for idiopathic arthritides of childhood. [ILAR]

1	Systemic arthritis
2	Polyarthritis – Rheumatoid factor positive
3	Polyarthritis – Rheumatoid factor negative
4	Oligoarthritis
5	Extended oligoarthritis (1 to 4 joints in the first 6 months, more than 5 joints after 6 months)
6	Enthesitis related arthritis
7	Psoriatic arthritis

and the duration of arthritis must be at least 6 weeks. Classification is made 6 months after the onset. Arthritis may remain unclassified between 6 weeks and 6 months. The classification is presented in table 1 (6).

Terms used to define activity of disease include active, stable, inactive and in remission. Active is the term used to indicate increasing number of joints with active synovitis irrespective of therapy. Stable denotes stable number of joints, but requiring medication. Inactive refers to no evidence of active synovitis and or active extra-articular features and without medication for less than 2 years. In remission denotes no evidence of active synovitis and or active extra-articular features 2 or more years without medication (7).

3. MEASURES OF OUTCOME

Traditionally the Steinbrocker classification has been utilized to measure long-term outcome among patients with JRA (8). It classifies patients into four functional classes (table 2). There is a wide range of disability included in these classes. For instance a patient with total joint replacement may be in functional class I or II. Recognition of the need to incorporate estimates of physical, social and mental functioning into health assessment has resulted in the development of measurement instruments that evaluate health status, functional status, disability and quality of life. The instruments that have been used in the rheumatic diseases of children include the CHAQ, JAFAS, JAFAR, JASI, CHAIMS, CAHP and JAQQ (9).

The CHAQ (Childhood Health Assessment Questionnaire) comprises two components: disability and discomfort. The final score ranges from 0-3, with 0 representing no disability. The CHAQ has been validated and has been shown to be reliable (10). This instrument also has good convergent validity with excellent correlations with Steinbrocker's functional class, active joint count, disease activity index and degree of morning stiffness. It has also been validated in Irish, Portuguese, Italian, Dutch and Spanish cohorts, still maintaining reliability, validity and parent child correlation (9).

JAFAS (Juvenile Arthritis Functional Assessment Scale) is an observer based scale requiring standardized simple equipment and is administered by a trained health professional. The child's performance of 10 physical tasks is timed and it can be administered in about 10 minutes (11). The JAFAR (Juvenile Arthritis Functional Assessment Report) is a patient or parent completed report. This has a score range of 0 to 46, with a lower score indicating better function. This instrument however cannot be administered to children under 7 years of age.

JASI (Juvenile Arthritis Self-report Index) focussed on physical activity in children with JRA over 8 years of age. This is scored from 0 to 100, with higher scores indicating better function. This being a comprehensive questionnaire takes time to complete. It does not attempt to measure overall health or quality of life. The CHAIMS (Childhood Arthritis Impact Measurement Scale) has a physical disability dimension and a pain dimension. This instrument has not been widely used. It is scored from 0 to 10, with a higher score indicating worse function.

The JAQQ (Juvenile Arthritis Quality of Life Questionnaire) is an instrument to measure physical and psychosocial function, quality of life and be applicable to all age groups. An essentially different questionnaire is completed by each patient because of its unique scoring system. This makes comparison between groups difficult. The CAHP (Childhood Arthritis Health Profile) is a self administered parent report consisting of three modules, generic health status measures, JRA specific health status measures and patient characteristics. This is a new instrument and further data are awaited. In view of its reported discriminative ability, this will be useful as a tool for longitudinal studies (9).

4. DISEASE OUTCOME

It is now understood that for identifying truly long-term outcome, a long duration of follow up is essential. A study by Scott *et al* in adults with rheumatoid arthritis (RA) has shown that the functional outcome declined considerably in patients between 10 and 20 years of follow up (3). After 20 years of follow up, 47% of the cohort was disabled, 35% were dead and only 18% were in functional class I and II. Studies in adults with RA have also shown that the outcome is dependent on the selection of study population. Among hospitalized patients, 59% were in functional class III or IV, while 30% of outpatient and 20% of patients from the general population were likely to be moderately or severely incapacitated after 20 years (12).

There have been several studies looking into long-term outcome among patients with JRA. Besides looking at functional outcome, there are some studies that look into psychosocial aspects and quality of life. Jeremy *et al* reported in 1968, follow up of 46 adult patients with JRA with a mean duration of disease of 18 years (13). Severe hip disease was present in 18 patients (39%). Eleven patients (23.9%) were in functional classes III and IV.

In 1966, Laaksonen reported the outcome of patients followed for a mean duration of over 16 years (4). At three to seven years of follow up 12% of the patients were in Steinbrocker functional class III and IV. This

Table 2. Steinbrocker classification of functional capacity in Rheumatoid arthritis

Class I	Complete functional capacity with ability to carry on all usual duties without handicaps
Class II	Functional capacity adequate to conduct normal activities despite handicap of discomfort or limited mobility of one or more joints.
Class III	Functional capacity adequate to perform only few or none of the duties of usual occupation or of self-care
Class IV	Largely or wholly incapacitated with patient bedridden or confined to wheelchair, permitting little or no self-care.

increased to 48% when these patients were followed 16 or more years from onset. Ansell *et al* reported in 1976, their cohort of patients who had been followed for a mean duration of greater than 15 years (14). They reported 23% were in functional class III and IV. Hanson *et al* in 1977, reported that 28% of patients followed for five to twenty five years, with a mean duration of follow up of 10 years, were in class III and IV (15).

Stoeber reported in 1981, the outcome of 433 patients followed for an average of 15 years (range 10-22 years) with JCA (16). Among patients with systemic onset JCA, 13.4% were in functional classes III and IV. Among patients with pauciarticular onset arthritis, none were in class III or IV. In 1984, Rennebohm *et al* reported 9% of patients to be in functional class III and IV at 10 years of follow up (5). The same cohort of patients was followed for 15 to 20 years and the results were reported by Levinson (1). Seventeen percent of the patients were in functional class III or IV. These studies once again show that truly long term outcome can be identified only when the follow up is also over a long period. In a meta-analysis of 10 studies of patients with JRA followed for an average of ten years or more, Wallace and Levinson, found that as many as 31% of the patients were in functional class III and IV, after averaging the data from these different studies, weighting them for the number of patients (1,2).

Activity of the disease is another aspect of JRA. Active JRA at follow up of 10 years ranged from 31% (14) to 55% (15). Data from 1991 by Levinson and Wallace reveal that 45% had active JRA at ten years of follow up, based on a meta-analysis of 10 studies (1,2). These studies came from tertiary centers mostly and may be biased toward the severe cases.

David *et al* followed 43 patients with JCA for over ten years (17). The mean duration was 19.7 years (range 10-39 years). The patients were adult hospital attendees. Hence, the study is biased towards those with severe disease and hospital follow up. Ninety five percent of the patients were taking NSAIDs. No disability was reported by 26% while 60% of the patients reported mild disability, corresponding to Steinbrocker functional class II. The remaining 14% of the patients were in classes III and IV. Seventy two percent of all patients in this series needed total hip replacement. Bilateral total knee replacement was done in 12% and total shoulder replacement in 9%.

Some recent studies suggest more favorable figures. In 1996, van der Net *et al* reported the results of their study with 23 patients who had polyarticular JCA with mean duration of disease for 4.6 years (range 0.7-13.7 years (18). Twenty patients (87%) were on medication at evaluation, by definition active or stable. The outcome was studied using CHAQ (Dutch Version), JAFAR and JAFAS as the instruments. They report that the median scores were all less than 20% of the maximum possible score. However, the mean duration of disease in this cohort is shorter than those in other studies and only follow up will confirm if this trend continues.

Anderson Gare *et al*, in 1995 reported follow up of 124 patients with JCA (7,19). The authors performed a cross sectional study of all patients with JCA born between 1968-1972 and were evaluated during 1984-1988 in a region of Southwestern Sweden. The median age of the patients was 17.7 years and the median duration of disease was 7.1 years. The authors used incidence data from a previous study for JCA in the same region from which they were able to extrapolate the number of patients who had gone into remission prior to their study period (20). They estimated 97.3% to be in functional class I or II. Only 5 patients were in class III and 1 patient in class IV, in their cohort of 124 patients. The mean duration of follow up was 7.1 years. This study also used CHAQ and found median scores of 0.19 (actual scores ranged from 0-2.75 on a scale of 0 to 3). The patients with active or stable disease had higher scores than those with inactive disease or in remission. This study differs from others in that it is a population-based study in contrast to many other studies, which are referral center based.

In 1997, Ruperto *et al* presented their findings of follow up of 227 patients with a mean duration of follow up of 15 years (21,22). This study also evaluated quality of life. The disability index was measured by using HAQ or CHAQ. 85% of the patients scored from 0-0.5 (maximum score 3) indicating no or mild limitation in daily activities. This suggests that a very large proportion of patients with JRA have little or no residual functional disability in the long term. However 30% of the patients indicated that they had moderate or severe pain at the time of the study, 31% reported low level of pain and 39% had no pain. These figures present an optimistic outlook for patients with JRA. One important point to note is that in this study, only those patients were included who had been seen by rheumatologists at tertiary care centers within six months of onset of their disease. Thus, they are likely to have undergone therapy appropriate for the period of diagnosis, early on.

5. MORTALITY

Ansell and Wood in 1976, in a series of 240 patients with juvenile chronic polyarthritis, reported 7% mortality (14). This represented a ten-fold increase in

mortality over the general population in the age groups studied. Amyloidosis and infection accounted for more than two thirds of the deaths. The mortality in Stoeber's series was 4.2% in total, but 13.8% in the systemic group (16).

Baum and Gutowska reported mortality rate among JRA patients from a wide variety of causes 1.1% in 1976 (23). In Cincinnati, data was collected prospectively from 1966 to 1989. There were 5 deaths among 472 patients, giving a mortality rate of 1.06% (1,2). In England there were 18 deaths among 2100 patients with JCA, giving a mortality rate of 0.86% (1,2). Levinson and Wallace in 1991, reported mortality statistics compiled from surveying 22 US and 1 Canadian pediatric rheumatology centers. Among 11287 patients there were 33 deaths, yielding a mortality rate of 0.29% (1,2). Any of these figures are considerably higher than the standardized mortality figure of 0.08% for the age groups 1 to 24.

Two thirds of the deaths in the United States and 10/18 of the deaths in the United Kingdom occurred in patients with systemic JRA. In the United Kingdom, 10 of the deaths were attributed to renal amyloidosis. Amyloidosis is rare in patients with JRA in the United States. The prevalence of amyloidosis is reported to vary between different centers. British and German centers have higher prevalence compared with the centers in United States (24). In Poland, the prevalence was reported to be 10.6%. Patients with systemic JCA have the highest prevalence of amyloidosis. Renal failure is the main cause of death in patients with amyloidosis. Regression of amyloidosis has been reported (24). A study from Finland reported a decrease in the number of deaths from secondary amyloidosis in patients with JRA (25). Between 1969-79 amyloidosis accounted for 42% of all causes of deaths in patients with JRA compared to 17% between 1980-90. The last death due to amyloidosis was reported to have been in 1983.

6. IRIDOCYCLITIS

Iridocyclitis or uveitis seen with pauciarticular JRA is usually chronic with long periods of active ocular inflammation, remissions and recurrences. It can occur six months to four years before the onset of arthritis. This process can go undetected until sight is impaired. Iridocyclitis can recur, even when the joint disease is in remission. Undetected and untreated, it can eventually lead to loss of vision with band keratopathy, cataracts, synechiae and glaucoma. Periodic slit-lamp examinations are the best means of detection of chronic iridocyclitis. The iridocyclitis seen with juvenile ankylosing spondylitis is usually an acute painful condition, which begets prompt attention. Uveitis can have a significant impact on the outcome of patients with JRA. Kanski *et al* reported a 20% incidence of iridocyclitis (26). The majority of the patients (77%) were under eight years of age when the iridocyclitis was diagnosed. A study reported that the prevalence of eye disease in patients with JRA had decreased from 45% in 1975 to 13% in 1989 (27).

Anderson Gare *et al* reported an incidence of uveitis of 8.9% out of 124 patients (7,19). Out of this, 2.4% had chronic uveitis, all in ANA positive girls. Six boys and two girls had acute uveitis. Two boys and one girl with acute uveitis were reported to be HLA B27 positive. None of the patients in this series had developed severe impairment of vision. One patient who did not report for follow up in their study was reported as having severely impaired vision resulting from uveitis. Rosenberg reported prevalence of blindness in JRA with uveitis of 12% (28). Ruperto *et al* in 1997, reported that 27 out of 122 children (22%) had eye disease (21,22). Eye disease was reported to affect their daily functioning in 56% of these 27 patients.

To answer the question of whether iridocyclitis influences the articular outcome of JRA, Cimaz *et al* studied 29 patients with Pauciarticular JRA and chronic iridocyclitis (29). Patients with symptomatic iridocyclitis and follow up less than five years were excluded from their study. Controls were 89 patients with pauciarticular JRA without iridocyclitis. They reported that only 41% had a completely normal articular exam after extended follow up. They found no statistically significant difference between the two groups in indicators of disease severity. These included progression from pauciarticular to polyarticular JRA after six months, hip involvement, radiographic evidence of erosions in any clinically involved joint and severe functional disability defined by Steinbrocker class III or IV or total joint replacement. The only 2 patients in class IV had severe uveitis, with glaucoma in both and cataracts in one. They concluded that uveitis does not improve articular prognosis in patients with pauciarticular JRA.

Ten percent of patients with JRA were reported to have chronic anterior uveitis (30). Risk factors are female sex, young age, pauciarticular onset, ANA positivity and rheumatoid factor negativity. Wolf *et al* studied 51 JRA patients with uveitis. In their series, the average age at onset of arthritis was 4.4 years and the average age of onset of uveitis was 6.8 years. 82% of patients were girls and 83% were ANA positive. Nearly half of those with pauciarticular onset had polyarticular course. The degree of ocular inflammation on initial examination was predictive of long term visual acuity and ocular complication. Patients with uveitis as their initial manifestation of JRA carried a poorer visual prognosis (67% of these eyes had visual loss) than those with arthritis as the first manifestation of JRA (6% of eyes had eventual visual loss.) Untreated iridocyclitis resulted in irreversible injury and visual acuity loss in as little as two years. Sixty one percent of eyes with active uveitis had 20/40 or better vision after the extended follow up period. Average follow up time was reported to be 12.7 years, with minimum follow up of one year. Range was not reported.

Cabral *et al* reported 49 patients in their series who had uveitis (31). Forty-one patients were females. Thirty-nine patients had JRA, 6 had psoriatic arthritis, 3 had juvenile ankylosing spondylitis and 1 had sarcoidosis. After follow up for a mean duration of 8.5 years from

diagnosis, there were 82 affected eyes. 70/82, (85%) had vision of 20/40 or better. Synechiae occurred in 20 eyes, (13 patients), cataracts in 17 eyes (12 patients) and glaucoma in 7 eyes (5 patients). They identified four factors as being significantly associated with development of complications. These were 1) diagnosis of uveitis prior to or at the time of onset of arthritis, 2) symptomatic at onset, 3) chronic course of uveitis and 4) diagnosis of juvenile psoriatic arthritis.

In 1997, Dana *et al* reported the result of their study of 43 patients with JRA associated iridocyclitis (32). They found that the mean duration of iridocyclitis was 146 months with females suffering from significantly longer duration of active disease. Visual acuity at presentation, use of systemic NSAIDs, older age of disease onset and male sex strongly correlated with a final visual outcome of 20/40 or better. Seventy percent of the patients experienced visual improvement with therapy. Chalom *et al* reported in 1997, results from retrospective analysis of 760 patients with JRA from four centers (33). The prevalence of uveitis was 9.3%. Visual complications developed in 31% of patients with uveitis. Complications were more common in ANA negative patients.

7. PSYCHOSOCIAL OUTCOMES

Several studies have looked into the psychosocial outcome of patients with JRA for long periods. In 1976, Hill *et al* reported the outcome of 58 patients diagnosed with JRA with a mean follow up of 14.5 years (34). Findings regarding friendship and leisure activities revealed that two thirds of the patients reported not being restricted in forming friendships. One third of the patients had fewer friends and reported being more dependent on family members for their social activities. Another study of 39 children with JCA aged 7 to 16 years found that the subjects had a median Lipsitt self concept scale score of 86, that expected for a healthy population (35).

In a review Miller noted that children with rheumatic diseases tended to do well in both psychological and social development and function. Patients who have strong social support system, particularly maternal competence are said to be the ones who do best (36).

David *et al* reported in 1994 the outcome of 43 patients with JCA for over ten years (17). The authors used Beck's Depression Inventory and found that 7% of the patients had mild depression and 21% had moderate to severe depression. The results of responses to the general health questionnaires were similar to those, which may be found in a random sample of population. The scores did not significantly correlate with disability. This study also focussed on social issues. Among the patients, 68% perceived that their disease had no effect on their ability to form relationships. Only 24% felt that the disease had no effect on their work life and 20% felt that the disease had no effect on their home life. 64% of the patients operated an automobile and had full independence with travel.

A study published in 1997, (21,22) reported the outcome in terms of overall well being of 122 patients. Forty two percent of the patients reported a score of 0 (Scale of 0 to 3, lower the better) while only 2% reported a score greater than 1.5, corresponding with a low level of well being. Out of the 118 patients who were over 18 years of age and answered the quality of life scales questionnaire, 77% reported that they were delighted or pleased with the outcome. Seventeen percent were mostly satisfied. One patient with systemic onset JRA was mostly dissatisfied and nobody reported being unhappy or terrible. The authors concluded that a very high percent of patients who had childhood onset of arthritis classify themselves as having a high quality of life. The authors do point out that many of those studied could not remember when they did not have arthritis because onset was very early in life. Thus it is possible that their overall concept of a high quality of life may be different from individuals who have been disease free for much of their life.

A study published recently followed 44 patients and 102 age and sex matched controls, who had no known or suspected rheumatic or connective tissue diseases (37). Mean duration of follow up was 24.7 years (range 7 to 38). Presence of active arthritis was reported by 65.9% of patients, but only 15.9% reported seeing a physician regularly for their symptoms. The HAQ was used to measure functional outcome. Abnormal scores on the HAQ were reported to be significantly higher among patients who had JRA compared to the controls. Patients with JRA also reported more physical disability compared with controls as indicated by significantly lower scores in physical subscales of the health status questionnaire. A significant difference was not found in the number of patients who were married compared to controls (55% Vs 59%).

8. EDUCATION AND EMPLOYMENT

Although the vast majority of patients with JRA attend school full time, a significant number miss more than the national average for days absent from school (38). In the study of Lovell *et al,* 8 patients out of 303 were receiving homebound education. However the academic achievement of these patients was good. In Cincinnati, by age 25, 27% of the patients followed had completed four of more years of university, compared to only 7% of the general population in Cincinnati metropolitan area (39). Prolonged absences from school has been reported especially those with more severe disease and functional classes III and IV (34). In Hill's series of 58 patients, educational achievement of the study group was reported to be higher than the population. Twice as many had completed at least one year of university. (31.1% Vs 15.8%). The percent of patients employed was 62%, and an additional 14% were active homemakers. The percentage of unemployed patients was almost the same as that for the general population in British Columbia, where the study was done. The average yearly income in the subjects was higher than the general population in British Columbia.

David *et al* reported that 21% attained higher or university education (17). 66% of the patients were employed. Thirty percent reported they were unemployed and felt it was due to their disease. Miller *et al* reported in 1982, the results of follow up of 121 patients (40). Of these, 109 (90%) reported that they had little or no disease. However, 51 patients (42%) simultaneously indicated that they were still seeing a physician for joint disease. On the whole the patients were functioning well. In the same series of 121 patients, 37% were working full time, 20.7% were in school full time, 19% were in school and working and 11.5% were married women at home. Patients with polyarticular onset had lower monthly salaries. Fifty patients were compared to their siblings and were found to have comparable education, salaries and proportionate number of marriages and children.

Peterson *et al* reported in their series, a significant increase in the rate of unemployment in the patients compared with controls (37). The subjects also reported less ability for physical exercise compared to controls. They found, however, that the percentage of individuals completing high school annual income among wage earners and health insurance status was not significantly different between cases and controls.

9. STATURE

Growth disturbance occurring in children with chronic arthritis was first noted by G.F. Still. In his landmark article in 1896, he mentioned "general arrest of development that occurs when the disease begins before the second dentition" (41). Children with JRA can have short stature at presentation. On the other hand, crossing of percentiles can also be seen. Short stature is seen mostly with systemic JRA and also with polyarticular JRA. Factors contributing to the shortening of stature include activity of the disease, side effect from medications, poor nutritional status, severe temporomandibular joint disease, vertebral fractures and contractures of knees.

In 1956, Ansell and Bywaters noted that children with active disease were more likely to have a short stature (42). In Laaksonen's series of 544 children, heights were significantly lower than normal (4). Growth retardation was more marked in children with prolonged duration of disease. Bernstein *et al* reported their study of 31 children with JRA (43). A significant decrease in growth rate was observed in children with systemic JRA. They also found that higher than expected number of children were below the third percentile prior to onset of disease. Patients with JRA treated with steroids had significantly increased growth retardation than did SLE patients who were treated with steroids.

van der Net *et al* reported in their group of 23 patients with polyarticular JCA, only 2 patients were greater than 2 standard deviations below the mean height for Dutch children (18). One patient had Down's syndrome and the other was on prednisone therapy. Anderson Gare *et al* reported that among the 124 patients they studied, none were greater than two standard deviations below the mean height for Swedish children (7,19). It should be noted that the prevalence of systemic JRA in their series was only 3.2%.

Height data was obtained from the Cincinnati database of the American Rheumatism Association medical information service (ARAMIS). Data from 156 patients followed past the age of 18 revealed that on the whole 17% of the patients were below the 5^{th} percentile. Fifty percent of those with systemic onset, 16% of those with polyarticular onset and 11% of those with pauciarticular onset were below the 5^{th} percentile (44).

There have been very few studies looking at puberty and JRA. In a study reported by Fraser *et al,* the age of menarche in 68 patients with JRA was compared with 46 sisters of the patients, who served as controls (45). Their group consisted of 22% patients with systemic onset, 26.5% with polyarticular onset and 51% with pauciarticular onset JRA. The mean age of menarche in the subjects (13.2 years) was significantly different from that of the controls (12.5 years). Duration of disease was the single best predictor of age on menarche in JRA. However this was not statistically significant when considered singly. A delay in menarche was observed most frequently in the polyarticular onset patients.

10. PREGNANCY

Ostensen reported data, collected retrospectively in 76 pregnancies in 51 patients with JRA (46). It was found that pregnancy did not cause reactivation of the symptoms of quiescent JRA. The majority of patients with active inflammation experienced improvement or total disappearance of symptoms of arthritis in the second half of gestation. JRA was associated with a higher frequency of cesarean sections and the main reason for this was the presence of bilateral total hip prosthesis. Post partum flare was reported after 45/50 pregnancies. In general, symptoms eased or disappeared again within 2 years. Among the 76 pregnancies, 74 infants (97.4%) were healthy and of normal birth weight. One infant had low birth weight and there was one stillbirth. The median age of the children was 5 years (0.6 to 24 years) at the time of the study and all 75 children were reported to have normal physical and mental development. In another study no significance differences were found between patients with JRA and controls for the number of live births and miscarriages (37).

11. PREDICTORS OF OUTCOME

11.1. Radiographs and MRI

The risk of joint destruction increases with the duration of persistent synovitis. The first radiographic evidence of inflammatory arthritis is usually periarticular bony demineralization. The next change seen is often joint space narrowing, which is seen when the cartilage is damaged or completely destroyed. This is followed by progressive destruction characterized by erosions and subchondral cysts at the edges of articulating bones. Laaksonen reported significant correlation between joint

space narrowing and erosions and subsequent poor functional outcome (4).

The use of MRI has shown that conventional radiographs underestimate the actual damage to joints and that MRI is much more sensitive than radiographs (47). Findings demonstrated by conventional radiographs have been compared with those of MRI by several authors (48-50). Changes not seen on radiographs, including avascular necrosis, intra-articular fragments and medullary infarcts were seen on MRI. Increased frequency and severity of cartilage loss and increased severity of erosions were demonstrated by MRI compared to conventional radiographs. After 10 to 15 years of follow up, erosive changes have been reported in 55% (14) to 59% of patients (5).

Data from Cincinnati revealed that after a mean of 13.15 years from disease onset, 28% of pauciarticular, 54% of polyarticular and 45% of systemic onset JRA patients had developed joint space narrowing or erosions (2). The timing of development of radiographic changes was within 5.36 years for pauciarticular onset JRA. One half of the patients with polyarticular onset and systemic onset JRA developed radiographic changes within 2.36 years and 2.20 years, respectively (2). Data from Seattle was similar, with two thirds of the patients developing joint space narrowing and erosions at mean time of 2.63 years. In the same group of patients, it was noted that second line medication (DMARD/ SAARD) were begun after a mean of 2.63 years. These observations suggest that aggressive or remittive therapy came too late. The authors recommended that major effort at controlling the disease must be initiated before destruction become evident.

11.2. Laboratory parameters

There is no single set of laboratory parameters that can accurately predict the outcome of JRA. Persistently elevated ESR has been believed to be an ominous sign (4,51). Anderson Gare *et al* showed that ESR at onset did not correlate with the disability index using the CHAQ at follow up (7,19). However, they did find a positive correlation between ESR and C-reactive protein levels at follow up with the disability index measured by the CHAQ. Giannini *et al* have shown in clinical trials in patients with JRA, the ESR at base line shows low correlation with the number of active joints (52). Ruperto *et al* reported that the ESR produced a high odds ratio for lower quality of life (22). Odds ratio was 9.77, however, 95% confidence interval was extreme ranging between 1.22-77.8. Rheumatoid factor has been shown to be associated with a poorer outcome (7,17,19). Chronic iridocyclitis was more often associated with the presence of positive ANA.

11.3. HLA

Ruperto *et al* reported that presence of HLA DR5 correlated with the greatest risk for pain (22). HLA B5, DR3, C3 had protective effect for future disability. HLA DR1 was associated with a more favorable overall well being score. Hall *et al* studied 158 unrelated British patients (53). They reported that HLA DRW 8, C4A*4, C4B*2 and HLA B39 possibly predisposed to more severe disease. HLA DR5 frequency in ANA positive group was increased when compared with that of controls. Morling *et al* studied 104 patients (54). They found three groups of patients. D/DR5 and D/DRW8 associated group dominated by pauciarticular JRA with a rather good articular prognosis, but a higher risk of chronic iridocyclitis. A second group of D/DR4 associated group with mainly polyarticular arthritis and less favorable prognosis. The third was a HLA B27 associated group, which included patients with juvenile ankylosing spondylitis, Reiter's syndrome and unrecognized reactive arthritis. They had three patients with acute iritis, all of whom had HLA B27. In another study, frequency of HLA A2 was increased in patients with arthritis both with and without uveitis compared to the general population (31).

Sheerin *et al* studied 36 patients with HLA B27 (55). Originally 5 patients had been diagnosed as probable or definite juvenile ankylosing spondylitis. At follow up, 8 had definite, 8 probable and 11 possible JAS. They suggest that children do not manifest the type of AS seen in adults.

11.4. Other predictors

Number of joints with active arthritis, articular severity score, symmetrical arthritis and early hand involvement have been shown to have a high predictive ability for future disability and poorer overall well being (22). A young age at onset, ANA positivity and HLA C3 were reported to have a protective effect for future disability. Pauciarticular onset and HLA DR1, were both associated with a more favorable overall well being score. In another study, patients who were younger than 6 years of age at onset fared worse (14). Outcome was better in monoarticular disease, and particularly in those who presented with a limp. A better outcome was also reported in JAS. Anderson Gare *et al* reported that polyarticular disease and female sex were risk factors for future disability (7,19).

12. PERSPECTIVE

Traditionally, the management of JRA has been compared to a therapeutic pyramid, at the base of which are the NSAIDs, patient and family education in addition to physical therapy, occupational therapy and family support. Additional medications in a step-wise fashion make up the rest of the pyramid, as the disease persists longer and longer. The addition of medications such as newer NSAIDs, second line agents such as gold, methotrexate, antimalarials, cyclosporine and cyclophosphamide has increased the therapeutic options. Whether the development of biologic agents such as tumor necrosis factor receptor fusion protein usher in a new era of management of JRA and the impact of long-term outcome remains to be seen.

More therapeutic options are now available, including cytoxan and biologic agents. Methotrexate has been shown to slow down radiographic progression of JRA (56). In a study by Harel *et al,* serial radiographs were used to evaluate the response to methotrexate in 23 patients with

JRA who had bilateral wrist involvement. Of these, 17 patients responded clinically, and 11 of these demonstrated increased carpal length on radiographs. The six non-responders had progressive loss of cartilage. Even in the relatively recent study by Anderson Gare *et al*, only 3 out of 124 patients had received methotrexate (7,19). In the study by Ruperto *et al*, 21 of 122 patients had received methotrexate (21,22). Thus, it remains to be seen if the use of methotrexate earlier in the course of JRA favorably alters the long-term outcome. Also, there is not enough information regarding the role that physical and occupational therapies play in the long-term outcome.

The children and adolescents who suffer from chronic arthritis in the present era receive more aggressive medication management. There is increased research targeted at basic mechanisms of inflammation. Moreover, increased general awareness of childhood rheumatic diseases in the primary care arena may help to improve outcome in the future. Research is approaching closer to finding more effective anti-rheumatic drug therapy. Hence, medical management should try to stave off cartilage injury for as long as is possible. This might improve the outcome of JRA in the long term.

13. REFERENCES

1. Levinson, J.E & C.A. Wallace: Dismantling the pyramid. *J Rheumatol* 19, S(33) 6-10 (1992)

2. Wallace, C.A & J.E. Levinson: Juvenile Rheumatoid Arthritis: Outcome and Treatment for the 1990s. *Rheum Dis Clin North Am* 17 (issue 4), 891-905 (1991)

3. Scott, D.L, B.L. Coulton, D.P.M. Symmons & A.J. Popert: Long-term outcome of treating rheumatoid arthritis: Results after 20 year. *Lancet* 1, 1108-1111 (1987)

4. Laaksonen, A.L: A prognostic study of juvenile rheumatoid arthritis. *Acta Paed Scand* 166 (Suppl), 1-163 (1966)

5. Rennebohm, R & J.K. Correll: Comprehensive management of juvenile rheumatoid arthritis. *Nurs Clin North Am* 19, 647-662 (1984)

6. Fink, C.W: Proposal for the development of classification criteria for idiopathic arthritides of childhood. *J Rheumatol* 22 (issue 8), 1566-1569 (1995)

7. Anderson Gare, B & A. Fasth: The natural history of juvenile chronic arthritis: a population based cohort study: I: onset and disease process. *J Rheumatol* 22, 295-307 (1995)

8. Steinbrocker, O, C.H. Traeger & R.C. Batterman: Therapeutic criteria in rheumatoid arthritis. *JAMA* 140 (issue 8) 659-662 (1949)

9. Duffy, C..M & K.N. Watanabe Duffy: Health assessment in the rheumatic diseases of childhood. *Curr opin Rheumatol* 9, 440-447 (1997)

10. Singh, G, B.H. Athreya, J.F. Fries & D.P. Goldsmith: Measurement of health status in children with juvenile rheumatoid arthritis. *Arthritis Rheum* 37(issue 12),1761-1769 (1994)

11. Lovell, D.J, S. Howe, E. Shear, S. Hartner, G. McGirr, M. Schulte, & J.E. Levinson: Development of a disability measurement tool for juvenile rheumatoid arthritis. The juvenile arthritis functional assessment scale. *Arthritis Rheum* 32 (issue 11), 1390-1395 (1989)

12. Isomaki, H: Long-term outcome of rheumatoid arthritis. *Scand J Rheum* 95(S), 3-8 (1992)

13. Jeremy, R, J. Schaller, R. Arkless, R.L. Wedgwood & L.A. Healey: Juvenile rheumatoid arthritis persisting into adulthood. *Am J Med* 45, 419-434 (1968)

14. Ansell, B.M & P.H.N. Wood: Prognosis in juvenile chronic polyarthritis. *Clin Rheum Dis* 2, 397-412 (1979)

15. Hanson, V, H. Kornreich, B. Bernstein, K. Koster-King & B. Singsen: Prognosis of juvenile rheumatoid arthritis. *Arthritis Rheum* 20, 279-284, (1977)

16. Stoeber, E: Prognosis in juvenile chronic arthritis: Follow up of 433 chronic rheumatic children. *Eur J Pediatr* 135, 225-228 (1981)

17. David, J, C. Cooper, L. Hickey, J. Lloyd, C. Dove, C. McCullough & P. Woo: The functional and psychological outcome of juvenile chronic arthritis in young adulthood. *Br J Rheum* 33, 876-881 (1994)

18. van der Net, J, A.B.J. Prakken, P.J.M. Helders, M.T. Berge, M.V. Herwaarden, G. Sinnema, E.J. deWilde & W. Kuis: Correlates of disablement in polyarticular juvenile chronic arthritis- a cross-sectional study. *Br J Rheum* 35, 91-100 (1996)

19. Anderson Gare, B & A. Fasth: The natural history of juvenile chronic arthritis: a population based cohort study: II: Outcome. *J Rheumatol* 22, 308-319 (1995)

20. Anderson Gare, B & A. Fasth: Epidemiology of juvenile chronic arthritis in southwestern Sweden: a 5-year prospective population study. *Pediatrics* 90, 950-958 (1992)

21. Ruperto, N, A. Ravelli, J.E. Levinson, E.S. Shear, K. Murray, B.L. Tague, A. Martini, D.N. Glass & E.H. Giannini: Long-term health outcomes and quality of life in American and Italian inception cohorts of patients with juvenile rheumatoid arthritis. I. Outcome status. *J Rheumatol* 24, 945-951 (1997)

22. Ruperto, N, A. Ravelli, J.E. Levinson, E.S. Shear, K. Murray, B.L. Tague, A. Martini, D.N. Glass & E.H. Giannini: Long-term health outcomes and quality of life in American and Italian inception cohorts of patients with juvenile rheumatoid arthritis. II. Early predictors of outcome. *J Rheumatol* 24, 952-958 (1997)

23. Baum, J& G. Gutowska: Death in juvenile rheumatoid arthritis. *Arthritis Rheum* 20, 253-255 (1977)

24. Woo, P: Amyloidosis in pediatric rheumatic diseases. *J Rheumatol* 19, S(35) 10-16 (1992)

25. Savolainen, H.A & H.A. Isomaki: Decrease in the number of deaths from secondary amyloidosis in patients with juvenile rheumatoid arthritis. *J Rheumatol* 20, 1201-1203 (1993)

26. Kanski, J.J: Uveitis in juvenile chronic arthritis: Incidence, clinical features and prognosis. *Eye* 2, 641-645 (1988)

27. Sherry, D.D, E.D. Mellins & R.J. Wedgwood: Decreasing severity of chronic uveitis in children with pauciarticular arthritis. *Am J Dis Child* 145, 1026-1028 (1991)

28. Rosenberg, A.M: Uveitis associated with juvenile rheumatoid arthritis. *Semin Arthritis Rheum* 16, 158-173 (1987)

29. Cimaz, R.G & C.W. Fink: The articular prognosis of pauciarticular onset juvenile arthritis is not influenced by the presence of uveitis. *J Rheumatol* 23, 357-359 (1996)

30. Wolf, M.D, P.R. Lichter & C.G. Ragsdale: Prognostic factors in the uveitis of juvenile rheumatoid arthritis. *Ophthalmology* 94, 1242-1248 (1987)

31. Cabral, D.A, R.E. Petty, P.N. Malleson, S. Ensworth, A.O. McCormick & M.L. Schroeder: Visual prognosis in children with chronic anterior uveitis and arthritis. *J Rheumatol* 21, 2370-2375 (1994)

32. Dana, M.R, J. Merayo-Lloves, D.A. Schaumberg & C.S. Foster: Visual outcomes prognosticators in juvenile rheumatoid arthritis associated uveitis. *Ophthalmology* 104, 236-244 (1997)

33. Chalom, E.C, D.P. Goldsmith, M.A. Koehler, B. Bittar, C.D. Rose, B.E. Ostrov & G.F. Keenan: Prevalence and outcome of uveitis in a regional cohort of patients with juvenile rheumatoid arthritis. *J Rheumatol* 24, 2031-2034 (1997)

34. Hill, R.H, A. Hersterin & K. Walters: Juvenile rheumatoid arthritis: Follow-up into adulthood – medical, sexual and social status. *Can Med Assoc Journal* 11424, 790-795 (1976)

35. Baildam, E.M, P.J. Holt, S.C. Conway & M.J.S. Morton: The association between function and psychological problems in children with juvenile chronic arthritis. *British J Rheum* 34, 470-477 (1995)

36. Miller III, J.J: Psychosocial factors related to rheumatic diseases in childhood. *J Rheumatol* 20 S(38), 1-11 (1993)

37. Peterson, L.S, T. Mason, A.M. Nelson, W.M. O'Fallan & S.E. Gabriel: Psychosocial outcomes and health status of adults who have had juvenile rheumatoid arthritis. *Arthritis Rheum* 40 (issue 12), 2235-2240 (1997)

38. Lovell, D.L, B. Athreya, H.M. Emery, D.L. Gibbas, J.E. Levinson, C.B. Lindsley, C.H. Spencer & P.H. White: School attendance and patterns, special services and special needs in pediatric patients with rheumatic diseases. *Arthritis Care Res* 3 (issue 4), 196-203 (1990)

39. White, P.H & E.S. Shear: Transition and job readiness for adolescents with juvenile arthritis and other chronic illness. *J Rheumatol* 19, S (33) 23-27 (1992)

40. Miller III, J.J, P.W. Spitz, U. Simpson & G.F. Williams: The social function of young adults who had arthritis in childhood. *J Pediatr* 100 (issue 3), 378-382 (1982)

41. Still, G.F: On a form of chronic joint disease in children. Reprinted in *Clin orthop* 259, 4-10 (1990)

42. Ansell, B.M & E.G Bywaters: Growth in Still's disease. *Ann Rheum Dis* 15, 295-318 (1956)

43. Bernstein, B.H, D. Stobie, B.H. Singsen, K. Koster-King, H.K. Kornreich & V. Hanson: Growth retardation in juvenile rheumatoid arthritis. *Arthritis Rheum* 20(S), 212-216 (1977)

44. Lovell, D.J & P.H. White: Growth and nutrition in juvenile rheumatoid arthritis.
In: *Pediatric Rheumatology Update*. Eds: P. Woo, P. White and B. Ansell. Oxford University Press: Oxford, England. 47-56 (1990)

45. Fraser, P.A, S. Hoch, D. Erlandson, R. Partridge & J.M. Jackson: The timing of menarche in juvenile rheumatoid arthritis. *J Adolesc Health Care* 9, 483-487 (1988)

46. Ostensen, M: Pregnancy in patients with a history of juvenile rheumatoid arthritis. *Arthritis Rheum* 34 (issue 7), 881-887 (1991)

47. Poznanski, A.K: Radiological approaches to pediatric joint disease. *J Rheumatol* 19, S (33): 78-93 (1992)

48. Senac, M.O, D. Deutsch, B.H. Bernstein, P. Stanley, J.V. Crues III, D.W. Stoller & J. Mink: MRI in juvenile rheumatoid arthritis. *Am J Roentgenol* 150, 873-878 (1988)

49. Yulish, B.S, J.M. Lieberman, A.J. Jewman, P.J. Bryan, G.P. Mulopulos & M.T. Modic: Juvenile rheumatoid arthritis: Assessment with MR imaging. *Radiology* 165, 149-152 (1987)

50. Brown, D.G, N.L. Edwards. J.M. Greer, S. Longley, T. Gillespy III & R.S. Panush: Magnetic resonance imaging in patients with inflammatory arthritis of the knee. *Clin Rheumatol* 9, 73-83 (1990)

51. Dequeker, J & A. Mardjuadi: Prognostic factors in juvenile chronic arthritis. *J Rheumatol* 9, 909-915 (1982)

52. Giannini, E.H & E.J. Brewer: Poor correlation between the ESR and clinical activity of juvenile rheumatoid arthritis. *Clin Rheumatol* 6, 197-201 (1987)

53. Hall, P.J, S.J. Burman, M.R. Laurent, D.C. Briggs, H.E. Venning, A. M. Leak, P.A. Bedford & B.M.Ansell: Genetic susceptibility to early onset pauciarticular juvenile rheumatoid arthritis: a study of HLA and complement markers in 158 British patients. *Ann Rheum Dis* 45, 464-474 (1986)

54. Morling, N, J. Friis, C. Heilmann, C. Hellesen, B.K. Jacobsen, B. Jorgensen, F. Karup Pedersen, A. Svejgaard & K. Thomsen: HLA antigen frequencies in juvenile chronic arthritis. *Scand J Rheumatol* 14, 209-216 (1985)

55. Sheerin, K.A, E. H. Giannini, E.J. Brewer Jr, & K.S. Barron: HLA B 27 associated arthropathy in childhood: Long-term clinical and diagnostic outcome. *Arthritis Rheum* 31 (issue 9), 1165-1170 (1988)

56. Ravelli, A, S. Viola, B. Ramenghi, N. Ruperto, L. Zonta & A. Martini: Radiographic progress in juvenile rheumatoid arthritis patients treated with methotrexate: *Arthritis Rheum* 39, S59 (1996)

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