Early predictors of outcome in juvenile idiopathic arthritis

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ABSTRACT

The definition and management of "early arthritis" in children differ from those in adults because juvenile idiopathic arthritis (JIA) is markedly different from adult rheumatoid arthritis. Since a significant proportion of patients with JIA develop articular damage and enter adult life with persistently active disease, it is important to predict early in the disease course the long-term outcome in order to tailor treatment to the risk of disability.

Over the past 3 decades a number of studies have evaluated the long-term outcome of cohorts of patients with JIA and some of them have also attempted to identify early prognostic factors. In summary, greater severity/extension of arthritis at onset, symmetric disease, precocious hip/wrist involvement, the presence of rheumatoid factor, and prolonged active disease were the best predictors of a poor outcome. Specific correlates for systemic JIA were persistent systemic features and thrombocytosis at 6 months following presentation, whereas joint symmetry and a higher erythrocyte sedimentation rate at onset were associated with a more severe course in oligoarticular JIA.

However, although data is accumulating on prognostic factors in JIA, prediction of long-term outcome in the first few months remains difficult. To better define prognostic factors in future analyses, a considerable effort should be made to increase standardization among studies. Furthermore, a radiographic scoring system and a set of remission criteria specific for JIA should be developed.

Introduction

Problems related to the definition and management of "early arthritis" in children differ from those in adults because juvenile idiopathic arthritis (JIA) itself markedly differs from adult rheumatoid arthritis (RA). JIA is a term that encompasses any form of arthritis which lasts for more than 6 weeks, is of unknown origin and has its onset before 16 years of age. This very heterogeneous condition has been classified into different subsets according to the symptoms present during the first 6 months of disease. A number of classification systems have been developed over the years (Table I). The most recent is that proposed by the International League of Associations for Rheumatology (ILAR) (1).

Oligoarticular JIA, which accounts for about 50% of all JIA cases, is not observed in adults, while systemic JIA (15% of all JIA cases) is of rare occurrence in adulthood (adult onset Still's

Table I. Comparison of classification criteria for chronic arthritis in childhood.

ACR JRA (4)	EULAR JCA (5)	ILAR JIA (1)
Systemic arthritis	Systemic arthritis	Systemic arthritis
Pauciarticular arthritis	Pauciarticular arthritis	Oligoarthritis Persistent Extended
Polyarticular arthritis	Polyarticular arthritis JRA (RF-positive) Spondyloarthropathies	Polyarthritis (RF-negative) Polyarthritis (RF-positive) Psoriatic arthritis Enthesitis related arthritis Undifferentiated arthritis

See text for abbreviations.
Note: Spondyloarthropathies include juvenile ankylosing spondylitis, juvenile psoriatic arthritis, Reiter's syndrome and the arthropathies of inflammatory bowel disease. Children with spondyloarthropathies are excluded from the ACR classification. RF positivity is not a differentiating criterion in the ACR classification while it is in the EULAR classification.

disease). On the other hand, polyarticular rheumatoid factor (RF)-positive JIA, which is on clinical, genetic and prognostic grounds identical to adult RF-positive RA, is very rare in childhood (3% of all JIA cases). JIA associated with enthesitis shares many similarities with spondyloarthropathies and indeed a certain proportion of patients develop sacroileitis over time. Polyarticular RF-negative and psoriatic JIA appear to be less clearly defined conditions (2).

JIA is not a benign disease since it has been shown that a sizable proportion of patients develop articular damage and enter adult life with active disease (3). It would therefore be of great importance to predict early in the disease course the ultimate outcome in order to tailor treatment to the risk of disability. However, although most children can be categorized in one of the various JIA subsets after the first 6 months of disease, this does not allow a reliable prediction of the potential outcome, since the evolution can differ greatly among patients belonging to the same onset type. This variability in outcome has stimulated many studies aimed at identifying early predictors of poor outcome.

Problems with outcome studies in JIA

Over the past 3 decades, a number of studies have evaluated the long-term outcome of cohorts of patients with JIA and some of them have also attempted to identify early prognostic factors (3). In general, most studies have focused on physical disability, whereas radiographic progression, health-related quality of life, and socioeconomic outcomes have received less attention. Regardless of the outcome assessed, comparisons among existing studies are hindered for a number of reasons.

First, the diagnostic criteria differ: some studies have adhered to the American College of Rheumatology (ACR) classification for juvenile rheumatoid arthritis (JRA) (4), whereas others have adopted the European League Against Rheumatism (EULAR) system for juvenile chronic arthritis (JCA) (5); in the most recent analyses, the ILAR revised criteria (1) for JIA have been chosen most frequently. Differences between these criteria (Table I) may have led to the inclusion of different patient populations (i.e. the juvenile spondyloarthropathies are incorporated in the EULAR and ILAR criteria, but not in the ACR classification) and may have, therefore, affected the estimates of outcome.

Second, the assessment tools and the predictor variables used are widely variable and poorly standardized, thus further contributing to the production of diverging or even contradictory results. Regarding this issue, the refinement of the clinical instruments over the years should be taken into account. To give an example, the assessment of physical disability in the past has generally been made through the Steinbrocker classification (6) which, however, is an adult-oriented measure, and furthermore is relatively insensitive and lacks discriminative power, whereas the more recent studies have used the Childhood Health Assessment Questionnaire (CHAQ) (7), which is a much more comprehensive and flexible tool that has been specifically validated for use in the pediatric patients.

Further sources of disparity among studies are the differences in the length of follow-up, the fact that some analyses have included all JIA subgroups whereas others have been stratified by onset subtype, the varying degree of completeness of patient retrieval, and the use, particularly in older studies, of univariate rather than multivariate analyses. The major difficulty, however, that arises when the past studies are compared with more recent ones is the fact that up until the late 1980s there were virtually no drugs of proven benefit for JIA, whereas in the last decade there have been major therapeutic advances in the treatment of this disease, including the widespread use of methotrexate and intra-articular corticosteroids, the aggressive early introduction of these drugs and/or other disease modifying anti-rheumatic medications and, in the recent years, the availability of the newer biologic agents. This progress in therapy is likely to have led to a considerable improvement in the prognosis of the disease. Recently the declining use of long-term steroid treatment may have also influenced the outcome.

To minimize the impact of these limitations, this review will be restricted to studies published after 1990. Furthermore, only those analyses that investigated outcome in terms of clinical remission, physical disability, and radiographic damage will be discussed. To overcome the differences in terminology, the term JIA will be used to refer collectively to JRA, JCA and JIA.

Clinical remission

Remission is a fundamental aspect of long-term oucome studies, as active disease persisting into adulthood is one of the greatest problems JIA patients may face. Furthermore, it is well known that the more persistent the synovitis, the greater the risk of joint destruction, especially as the skeletal system becomes mature (8). In evaluating the reported rates of remission, differences in the definition of remission are an additional source of variation which must be considered. Remission rates vary widely among studies and JIA subtypes. Using a standardized method such as the Kaplan-Meyer survival curves, the reported projected rates at 10 years were 37% and 38% for systemic (9, 10), 54%, 47% and 36% for oligoarticular (9-11), 15% for polyarticular JIA as a whole (10), 23% for RF-negative polyarticular (9), 6% for RF-positive polyarticular (9), and 17% for juvenile spondyloarthropathies (10). These figures indicate that JIA patients often enter adulthood with persistently active disease.

Minden *et al*. (10) found that age at onset and laboratory indicators of inflammation at onset had no effect on the probability of remission, whereas HLA-B27 positive patients with oligoarthritis and late disease onset (age > 6 years) had a statistically significant lower likelihood of remission. They suggested that these patients may have juvenile spondyloarthropathy, despite their not fulfilling the criteria for spondyloarthropathy. Fantini *et al*. (12) found no differences in the rate of remission by sex or age at onset, while patients who were referred early (<1 year

from disease onset) had a significantly higher remission rate at the last visit. Flato *et al*. (13) reported that young age at onset, DRB1*08, positive IgM RF, long duration of an elevated erythrocyte sedimentation rate (ESR), and a large number of affected joints within the first 6 months were risk factors for the absence of remission at follow-up. Among patients with systemic disease, the frequency of remission was found to be 100% in those with a monocyclic course, 37% in those with intermittent course, and 23% in those with persistently active course (14). Joint symmetry and ESR ≥ 20/hr in the first 6 months were significantly associated with a lesser likelihood of entering clinical remission in patients with oligoarticular-onset JIA (15).

Physical disability

Over the years, a general trend towards improvement in functional outcome has been documented in JIA (3). After 1995, studies of long-term disability have used the newer functional measures, particularly the CHAQ. For this instrument, the following categorization of the degree of physical disability has been proposed: 0 = none; 0.1 – 0.5 = mild; 0.6 – 1.5 = moderate; >1.5= severe (16). Using this scheme, the median CHAQ scores for patients with systemic JIA were in the mild range in 2 studies, but higher scores (1.0) were obtained in others (16-18). For oligoarticular-onset disease, median scores were generally in the none and mild ranges (16,19,20). Greater variations have been observed for polyarticular patients, with median scores from the mild to severe ranges (16,19-21). Recently, Oen *et al.* (9) found that 44%, 57%, 36%, and 8% patients with systemic, oligoarticular, RF-negative and RF-positive oligoarticular JIA, respectively, reported no disability (CHAQ = 0), while frequencies in the worst outcome group (CHAQ > 1.5) were 15%, 1%, 8%, and 18%, respectively. Taken together, these findings suggest that a significant proportion of JIA patients may develop an appreciable degree of disability over the years.

Several reports have examined variables that may affect long-term functional outcome, as measured by the CHAQ. Female sex and articular severity (but not the active joint count) were associated with a CHAQ > 0.5 in two studies (16, 20). In the former study, the second strongest determinant for disability was IgM RF, whereas in the latter antinuclear antibody positivity predicted a good outcome (CHAQ < 0.5), perhaps because of its association with oligoarticular JIA. However, onset subtype, age at onset and immunogenetic analyses (HLA-B5, 8, 35; DR1,3, 5; and DQ3) did not correlate with CHAQ scores. The correlation of active disease duration with greater disability was confirmed by other studies (19, 22). Using the adult counterpart of the CHAQ (i.e. the HAQ), Flato *et al*. found that predictors of physical disability (HAQ score >0) were female sex, symmetric arthritis, early hip involvement, long duration of elevated ESR, and positive IgM RF (13), whereas Minden *et al.* failed to observe any relationship with sex, age at onset or ILAR subgroup (23).

Specific analyses in patients with oligoarticular-onset JIA showed that arthritis in more that one joint, involvement of the upper limbs and/or cervical spine, and an ESR ≥ 20 at onset increased the odds of a polyarticular course of the disease (11). In the same JIA subtype, Al-Matar *et al.* (15) found that symmetric disease in the first 6 months was predictive of disability (CHAQ score >0.12). Among patients with systemic disease, a polyarticular pattern with hip involvement at 6 months predicted a high articular index at 3 years after onset (24). Persistent fever or requirement for corticosteroids and thrombocytosis at 6 months folowing presentation correlated with a high CHAQ score (> 0.75) at a minimum of 2 years after onset (17). A recent Canadian study also showed that predictive factors differ among onset subtypes (25). In systemic patients, male sex predicted worse disability, whereas adult rheumatoid arthritis-associated shared epitope was highly protective. Early joint space narrowing and residence on a reserve (rather than urban, suburban, or rural) was predictive of worse disability in patients with oligoarticular JIA. Male sex and rural residence predicted a better functional outcome for RF-negative polyarticular patients. No predictive variables for worse disability, including shared epitope, were identified among patients with RF-positive disease. In general, active disease duration was highly correlated with disability, whereas no correlations of HLA alleles with longterm outcome for most subsets of JIA were observed.

In the recent years, a new area of research has emerged that is aimed at correlating specific genetic polymorphisms with the risk for the development of severe, destructive arthritis. Concerning JIA, De Benedetti *et al.* (26) have shown that in patients with systemic disease, carriage of the -173 single-nucleotide G-to-C polymorphism of the macrophage migration inhibitory factor (MIF) gene is associated with an insufficient response to corticosteroid therapy, continued active disease and poorer functional outcome. Notably, the same authors previously found evidence that MIF may play a significant role in the pathogenesis of systemic JIA (27).

Radiographic damage

Radiographic evidence of joint damage is an important outcome measure that is infrequently discussed in prognostic studies. Furthermore, the severity of radiographic changes has rarely been assessed through a standardized method, reflecting of the lack of established, validated radiographic scoring systems for use in the pediatric age. The frequency of joint destruction varies considerably among the diverse subtypes of JIA. In long-term studies in which patients have been followed for median intervals of 5 to 9 years, the frequencies of destructive changes range from 63% to 75% for the systemic form, 8% to 27% for the oligoarticular form, 35% to 67% for RF-negative and RF-positive polyarthritis combined, to 39% for RF-negative patients alone, and 79% for RF-positive polyarthritis (20, 25, 28).

There are few correlations of JIA features with radiographic joint destruction. Long duration of an elevated ESR, late admission, late start of disease-mo-

Table II. Early predictors of outcome of juvenile idiopathic arthritis in studies published after 1990.

Author (ref.), year	No. of patients	Outcomes investigated	Predictors identified
Schneider *et al.* (29), 1992§	38	Radiographic damage	Persistent systemic symptoms and platelet count ≥ 600 x 10^9/l at 6 months
Andersson Gare *et al.* (20), 1995	124	Physical disability	Female sex, IgM RF
Ruperto *et al.* (16), 1997	227	Physical disability	Articular severity score
Flato *et al.* (19), 1998	72	Radiographic damage	Long duration of active disease, late admission, late start of DMARD, IgM RF
Spiegel *et al.* (17), 2000§	111	Physical disability	Active systemic disease and platelet count ≥ 600 x 10^9/l at 6 mos.
Minden *et al.*(10), 2000	171	Clinical remission (lack of)	HLA-B27, onset age > 6 yrs
Guillaume *et al.* (11), 2000#	207	Radiographic damage	ESR ≥ 100 mm/h
Lomater *et al.* (14), 2000§	80	Clinical remission	Monocyclic course
Al-Matar *et al.* (15), 2002#	205	Clinical remission (lack of), physical disability, radiographic damage	ESR ≥ 20 mm/h, Symmetric disease, ankle and/or wrist disease
Modesto *et al.* (24), 2001§	91	Articular outcome	Polyarthritis, hip involvement
Oen *et al.* (25), 2003	393	Physical disability	Male sex§, residence on a reserve#,joint space narrowing within 2 years#
Fantini *et al.* (12), 2003	683	Clinical remission	Early referral to tertiary care center
Flato *et al.* (13), 2003	268	Clinical remission (lack of), physical disability, radiographic damage	Young onset age, large number of affected joints, long duration of elevated ESR, IgM, RF, symmetric arthritis, female sex, hip involvement, DRB1*01, DRB1*08 + HLA-B27
Van Rossum *et al.* (30), 2003	67	Radiographic damage	IgM RF, HLA-B27
Magni-Manzoni *et al.* (31), 2003	94	Physical disability, radiographic damage	Early Poznanski score change
De Benedetti *et al.* (26), 2003§	136	Physical disability	MIF-173*C allele

#Only oligoarticular-onset JIA; §only systemic-onset JIA; RF: rheumatoid factor; ESR: erythrocyte sedimentation rate; DMARD: disease modifying antirheumatic drugs.

difying antirheumatic (DMARD) therapy, and IgM RF had a positive relationship with joint erosions (19), and for patients with oligoarticular JIA specifically, an ESR > 100 was associated with radiographic joint destruction (joint space narrowing or erosions) (11). Al-Matar *et al.* (15) found that symmetric disease and ankle and/or wrist involvement were predictive of erosive disease in patients with oligoarticular-onset disease. For patients with systemic JIA, the development of destructive changes by 2 years after disease onset was associated with persistent systemic symptoms and thrombocytosis at 6 months (29). By reviewing the radiographs obtained at entry of a placebo-controlled study of sulfasalazine in patients with oligoarticular or polyarticular JIA, Van Rossum *et al.* (30) found increased odd ratios for the presence of radiographic changes and IgM-RF or HLA-B27 positivity. In another study, the odds of joint space narrowing and erosions on late radiographs were both increased by longer active disease duration and systemic and polyarticular onset (regardless of RF status) relative to oligoarticular onset (25). The development of joint erosions was found to be associated with early onset, a large number of clinically affected joints,positive IgM RF, long duration of elevated ESR, symmetric arthritis, and absence of DPB1*02 by Flato *et al.* (13). In the same study, the presence of HLA-B27 and DR8B1*08 in combination increased the risk of joint erosions. Recently, Magni-Manzoni *et al.* (31) determined the rate of radiographic progression in the wrists, as measured by the Poznanski score, in patients with polyarticular JIA. They found that patients experienced on average a significant radiographic progression over time, which was more pronounced in the first year of observation. The early Poznanski score change was predictive of yearly radiographic progression, long-term joint damage and physical disability.

Conclusion

Although considerable data are accumulating on prognostic factors in JIA (Table II), prediction of long-term outcome in the early months remains difficult. In summary, greater severity/extension of arthritis at onset, symmetric disease, precocious hip/wrist involvement, presence of RF, prolonged active disease, and early radiographic changes

were the best predictors of poor outcome. The findings regarding the contribution of sex, age at onset and HLA-B27 are less consistent,probably due to the confounding effects of onset subtype. Specific correlates for systemic JIA were persistent systemic features and thrombocytosis at 6 months following presentation, whereas joint symmetry and a higher ESR at onset were associated with a more severe course in oligoarticular JIA.

To further define prognostic factors and increase the comparability of patient cohorts in future analyses, a considerable effort should be made to improve standardization in the areas of study design and clinical assessment. Better standardization of study design can be pursued by: (a) making the classification criteria among studies consistent, thus ensuring homogeneity of the JIA categories enrolled; (b) analyzing the outcome data according to the different JIA categories; (c) assessing the predictor variables early enough after disease presentation (i.e., within 6 to 12 months); and (d) assessing the long-term outcome at precise time points (i.e., at 5,10, 15 years after disease presentation). Improvement of clinical assessment would require the use of uniform predictor and outcome parameters and of instruments validated for the pediatric patient. Further refinements in outcome measurement can be achieved through the development of radiographic scoring systems and remission criteria specific for JIA. Finally, since the therapeutic regimen may affect outcome, the contribution of the different drug therapies should be taken into account.

Reliable outcome prediction is important because in routine clinical practice these is a need for prognostic criteria that will help to differentiate early in the course of JIA those patients who are likely to have progressive destructive disease from those with self-limiting or non-erosive disease. The recent availability of high-cost therapies makes it important to utilize such prognostic criteria to avoid giving unnecessary and expensive treatments to patients with early JIA whose disease is unlikely to progress.

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