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Toward an understanding of the long-term outcome of juvenile idiopathic arthritis

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ABSTRACT

Over the past four decades, a number of studies have evaluated the long-term outcome of juvenile idiopathic arthritis (JIA) and some of them have also attempted to identify early prognostic factors. This editorial addresses, by reviewing the surveys that have analyzed the outcome of JIA in term of clinical remission, physical disability, and radiographic damage, the clinical questions that are most relevant in this area of study. Altogether, the available data indicate that JIA is not a benign disease because a considerable number of patients still enter adulthood with persistently active disease and a significant proportion of them may develop severe physical disability.

Among the different onset forms, the long-term outcome is best in persistent oligoarthritis and worst in RF-positive polyarthritis; the outcome of systemic arthritis is widely variable, perhaps reflecting the heterogeneity of this JIA subtype. The comparison of earlier studies with those published in the last decade shows a decline in the frequency of patients with severe physical disability over the years; however, the proportion of patients who enter adulthood with active disease does not seem to be diminished.

Although there is considerable data on prognostic factors in JIA, prediction of long-term outcome early after disease presentation is still difficult because comparisons among studies are hindered for a variety of reasons. Thus, while a considerable body of data is accumulating, the definition of the long-term outcome of JIA remains imperfect. To increase the comparability of future analyses and to obtain generalizable information on the prognosis of JIA and its prediction, a great deal of effort should be directed toward standardizing the study design and the measurement of predictors and outcomes.

Introduction

Over the last 40 years, there has been a growing interest in the investigation of the long-term outcome of juvenile idiopathic arthritis (JIA) and in the search for early prognostic factors (1, 2). Most of the published studies have focused on the traditional disease-centered outcomes, which include clinical remission, physical disability, and radiographic damage. In recent years, increasing attention has been paid to broader outcomes such as physical and psychosocial well-being, pain perception, and socioeconomic attainments, and to other potential problems resulting from the disease or its treatment such as osteoporosis, growth, surgery, and ocular sequelae. The purpose of this editorial is to address, by reviewing the existing literature, the questions that are most relevant in this area of study. Only surveys that examined the outcome in terms of clinical remission, physical disability, and radiographic damage will be discussed.

Is JIAa benign disease?

In the past, a central paradigm in pediatric rheumatology was that 80% of children with JIAcould expect to be rid of inflammation when they reached adulthood (3). This optimistic view is not, however, supported by the earlier outcome studies, which showed much less encouraging figures in terms of the probability of long-term disease remission (3-14). Looking at the analyses published in the last 10 years, which are likely to reflect the positive impact of recent therapeutic advances, the percentage of patients with clinical remission or inactive disease at follow-up ranges from 40% to 60%, which is much lower than the 80% claimed in the paradigm (15-23) (Table I). Furthermore, the percentage of patients who have severe functional impairment (Stenbrocker functional class III or IV) at their last observation is, on average, around 10% (15, 17-20, 24, 25) (Table I). Taken together, these data indicate that JIAis not a benign disease because a considerable number of patients still enter adulthood with persistently active disease and a significant proportion of them may develop severe physical disability.

Does the outcome of the different JIAsubtypes differ?

JIA is a heterogeneous disease entity, which includes conditions that are clinically distinct and have different natural histories (27, 28). It is therefore likely that the prognosis of the diverse subtypes is not uniform. Unfortunately, the majority of previous studies have not separated the disease subsets. Those investigators who have stratified patients by onset category have, however, found that the outcome is different. Examining the studies published in the last 10 years (15, 17, 18, 20-22, 24, 26, 29-32), the percentage of patients in clinical remission, in Steinbrocker class III or IV, and with evidence of radiographic joint damage at their last follow-up ranged from 33% to 80%, from 0 to 65%, and from 14% to 75%, respectively, for systemic arthritis; from 0 to 15%, from 5% to 38%, and from 75% to 77%, respectively, for rheumatoid factor (RF)-positive polyarthritis; from 23% to 46%, from 3% to 41%, and from 40 to 43%, respectively, for RF-negative polyarthritis; from 12 to 35%, from 36% to 43%, and from 25% to 33% respectively, for extended oligoarthritis; and from 43% to 73%, from 0 to 7%, and from 5% to 27%, respectively, for persistent oligoarthritis. These findings indicate that the long-term outcome is best in persistent oligoarthritis and worst in RF-positive polyarthritis, and that the outcome of systemic arthritis is widely variable, perhaps reflecting the heterogeneity of this JIAsubtype.

Table I. Percentage of JIA patients with clinical remission/inactive disease and in Steinbrocker functional class III or IVat follow-up in the outcome studies published after 1994.

Author, year	No. of patients	Mean/median disease duration (years)	% of patients with remission/inactive disease	% of patients in Steinbrocker class III or IV
David, 1994	43	19.7	-	14
Andersson-Gare, 1995	124	7.1	60	5
Flato, 1998	72	9.7	-	8
Koivuniemi, 1999	30	7.8	60	-
Zak, 2000	65	26.4	63	11
Minden, 2002	215	16.5	45	10
Oen, 2002	392	10.5	56	2.5
Packham, 2002	246	28.3	57	37
Fantini, 2003	683	8.8	58	-
Flato, 2003	268	14.9	50	-
Foster, 2003	82	21	61	-

Table II. Comparison of the percentage of JIA patients with continuing active disease and in Steinbrocker functional class III or IV at follow-up between the outcome studies published before and after 1991.

Author, year	% of patients with active disease	% of patients in Steinbrocker class III or IV	Author, year	% of patients with active disease	% of patients in Steinbrocker class III or IV
Bunim, 1959	-	31	David, 1994	-	14
Laaksonen, 1966	41	48	Andersson-Gare, 1995	49	5
Jeremy, 1968	-	24	Flato, 1998	40	8
Ansell, 1976	31	23	Koivuniemi, 1999	40	-
Calabro, 1976	35	-	Zak, 2000	37	11
Hill, 1976	-	33	Minden, 2002	55	10
Hanson, 1977	55	28	Oen, 2002	41	2.5
Stoeber, 1981	-	41	Packham, 2002	43	37
Rennebohm, 1984	33	9	Fantini, 2003	42	-
Pedersen, 1987	37	3	Flato, 2003	50	-
Calabro, 1989	43	15	Foster, 2003	39	-
Levinson, 1991	45	17			

Has the prognosis of JIAimproved over the years?

The answer to this question is still unclear, although it is likely that the recent therapeutic advances, primarily the introduction of methotrexate (33) and earlier treatment with disease-modifying antirheumatic drugs (DMARDs) (it is too early to judge the impact of the newer biologic agents, such as the tumor necrosis factor inhibitors) have markedly improved the prognosis of the disease. Useful insights regarding this question can be obtained by comparing the percentage of patients with persistently active disease and in Steinbrocker class III or IV at follow-up between the studies published before 1991 (3-14) and those published after 1991 (15-25), as illustrated in Table II. This comparison shows a clear decline in the frequency of patients with severe physical disability over the years. However, the proportion of patients who enter adulthood with active disease seems not be diminished.

Is the long-term outcome of JIA predictable?

A reliable outcome prediction is important because in routine clinical practice these is the need for prognostic criteria that can 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 administering unnecessary and expensive treatments to patients with early JIA whose disease is unlikely to progress.

Problems relating to the prediction of outcome in early JIAare different from those in adults (34, 35) because JIAdiffers markedly from adult rheumatoid arthritis (RA). Several studies have sought prognostic information on JIA based on factors at disease onset (reviewed in 2). In summary, a greater severity/extension of arthritis at onset, symmetric joint disease, precocious wrist/hip involvement, the presence of RF, prolonged active disease, and early radiographic changes were the best predictors of a poor outcome. Specific correlations for systemic JIAwere persistent systemic features and thrombocytosis at 6 months following presentation, whereas joint symmetry and a higher erythrocyte sedimentation rate (ESR) at onset were associated with a more severe course in oligoarticular

JIA. However, although considerable data are accumulating on prognostic factors in JIA, prediction of the long-term outcome early after disease presentation remains difficult.

What are the problems with the outcome studies performed so far?

Studies on outcome in JIA are difficult to compare and interpret for several reasons. First, the diagnostic criteria differ; some studies have adhered to the American College of Rheumatology (ACR) classification (36), whereas others have adopted the European League Against Rheumatism (EULAR) system (37). In the more recent analyses, the International League of Associations for Rheumatology (ILAR) revised criteria (38) has been chosen most frequently. Differences between these criteria may have led to the inclusion of different patient populations (i.e. the juvenile spondiloarthropathies are incorporated in the EULAR and ILAR criteria, but not in the ACR classification) and may, therefore, affect the estimates of outcome.

Second, the assessment tools and the predictor variables used are widely variable and poorly standardized, thus further contributing to the generation of divergent or even contradictory results. Further sources of disparities among studies are the differences in the length of follow-up, the fact that some analyses have included all JIA subgroups whereas others were stratified by onset subtype, the variable completeness of patient retrieval, the refinement of clinical instruments over the years (e.g. the replacement of the Steinbrocker functional classification with the Childhood Health Assessment Questionnaire for the assessment of physical disability), and the fact that some studies are population-based (and thus less affected by a selection bias), whereas the large majority have analyzed referral center-based populations (and thus are at risk of a selection bias toward more severe cases).

The major problem, however, that arises when the past studies are compared with the more recent ones is due to the fact that until the end of the 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 intraarticular corticosteroids, the earlier introduction of these drugs and, in the recent years, the availability of the newer biologic agents. Recent use of less long-term steroid treatment may have also influenced the outcome.

How future studies can be improved?

To increase the comparability of future analyses and obtain generalizable information on the long-term outcome of JIA and its prediction, considerable effort should be directed toward standardizing the study design and the clinical measurements (Table III). Above all, the uniform definition and assessment of disease outcomes is necessary. However, with regard to disease remission validated, widely accepted criteria for JIA do not currently exist and consequently the term is used inconsistently in clinical studies, making comparisons of remission rates difficult. With the aim of developing validated, evidence-based criteria, a consensus conference was held on Marco Island, Florida, USA in May 2003, which led to the development of draft criteria for inactive disease, clinical remission on medication and clinical remission off medication (39). These criteria showed face, construct, and comprehensive (content) validity. In this work in progress, they are being examined for predictive, criterion (accuracy), and discriminative validity across existing clinical databases and will then be validated in a prospective fashion.

In contrast, considerable uniformity exists in the assessment of physical functioning and disability, which are currently measured in most studies by means of the Childhood Health Assessment Questionnaire (40, 41). Although the CHAQ certainly represents the gold standard for the measurement of physical disability in JIA, there are nevertheless some problems with its use in outcome studies that should be kept in mind. First, the CHAQ has shown significant ceiling effects and skewing of the scales (i.e., the tendency of a large proportion of the subjects to score at the lower end of the 0-3 scale, with a score of 0 for no disability and 3 for severe disability), particularly those patients with fewer joints involved (42, 43). Second, the estimation of physical disability in patients with ongoing disease activity can be markedly inflated by inflammatory joint symptoms, particularly by the degree of pain (44, 45). Third, the parents' observation of their children's physical function has frequently been found to be inaccurate, generally being overestimated as the severity of arthritis increased and underestimated as the level of pain increased (46).

A further, as yet under-recognized shortcoming of the use of the CHAQ in prognostic studies in JIA is that it may not capture all the possible forms of articular or extra-articular damage that may develop over time. Examples of damage that may not be adequately assessed by the CHAQ include, in the articular domain, micrognathia, prosthetic joint replacement, and valgus deformity and, in the extra-articular do-

Table III. Suggestions for the improvement of future studies on the long-term outcome of JIA.

Better standardization of the study design
- use of consistent classification criteria
- stratification of patients by JIAcategory
- assessment of predictors early enough after disease presentation (e.g. within 6 to 12 months)
- assessment of outcomes at precise time points (e.g. at 5, 10, 15 years after disease presentation)

Better standardization of clinical assessments
- use of uniform predictors and outcome parameters
- use of instruments validated for the pediatric age (or for the adult age if > 18 years old)
- consideration of the different therapeutic regimens

main, height retardation, impaired vision resulting from uveitis, localized growth defects, vertebral scoliosis, and osteoporotic fractures. With the aim of covering and scoring all forms of long-term articular and extra-articular morbidity in patients with JIA, we have recently created a damage assessment tool – the Juvenile Arthritis Damage Index (JADI) – which is currently being validated. Preliminary analyses of 102 patients with a disease duration ≥5 years seen consecutively at our department over a one-year period have shown that the instrument is feasible, reliable, and has good construct validity (unpublished observations).

Although the assessment of radiographic joint damage has been included in several prognostic studies, the severity of radiographic changes has rarely been examined using a standardized method because – unlike such assessments in adult RA (47, 48) – there is a lack of established, validated scoring systems for use in the pediatric age. In recent years, some investigators have explored the reliability, feasibility, and clinical correlations of different methods for the assessment of radiographic progression in JIA. Van Rossum *et al*. (49) scored all entry radiographs from a placebo-controlled trial of sulfasalazine for the presence of swelling, osteopenia, joint space narrowing, growth abnormalities, subchondral bone cysts, erosions, and malalignment. They found that erosions, joint space narrowing, and malalignment were readily and reproducibly identified, whereas soft-tissue swelling, osteopenia, and growth disturbances posed more difficulty. Although univariate analysis showed a good correlation between the overall clinical severity and the presence of radiographic abnormalities, this relationship was largely unpredictable in specific joints.

Magni-Manzoni *et al.* (50) investigated the rate of radiographic progression, as assessed by measuring the carpo-metacarpal length (Poznanski method), in 94 patients with polyarticular JIA. On average patients experienced significant radiographic progression over time, which was more pronounced during the first year of observation. The early Poznanski score change was consistently predictive of yearly radiographic progression and long-term joint damage and physical disability. The authors concluded that the Poznanski score is a meaningful outcome measure in JIA and that its measurement early in the disease course can help to identify those patients who are at greater risk for joint destruction and poor functional outcome. Altogether, these studies indicate that standardized scoring systems can be developed and used to assess the progression of radiographic joint damage in JIA.

Conclusion

Knowledge of the disease course and outcome for JIA is essential both in order to provide counseling and to present appropriate treatment options to patients and their families. Continuing evaluation of current treatment strategies is necessary in order to obtain up-to-date information regarding the outcome achievable. However, although a considerable body of data is accumulating, the definition of the long-term outcome of JIA remains imperfect. To increase the comparability of future analyses and obtain generalizable information on the prognosis of JIA and its prediction, a great deal of effort should be directed toward standardizing study designs and the measurement of predictors and outcomes. Because population-based studies are very difficult to perform in most countries, future insights will be predominantly sought through the analysis of referral center-based populations. An optimal referral center-based study might be conducted in a prospective fashion through a multi-center, multi-national collaborative project. Such a study should include all newly diagnosed JIA patients seen consecutively in each center over a defined time period. The patients enrolled should be assessed at study entry and then over time, at standardized time points and according to a uniform and comprehensive study protocol.

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