Outcome following onset of juvenile idiopathic inflammatory arthritis: II. Predictors of outcome in juvenile arthritis

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Objective. To assess the relative contributions of demographic, clinical and laboratory variables in predicting outcome in juvenile idiopathic inflammatory arthritis (JIA), based on a review of the existing literature.

Methods. Electronic reference database searches for the previous 10 yr were conducted and studies examining the role of major potential predictors of main outcomes were identified. Where possible, subjects were grouped by JIA disease subtype. In addition to demographic variables, the following disease-related predictors were assessed: nature of joint involvement, acute-phase response, and presence of autoantibodies. These were then analysed for three main outcomes of interest: remission as assessed by disease activity; functional impairment; and structural damage as assessed by radiological joint erosions.

Results. In general, female gender, polyarticular and symmetrical joint involvement, elevated inflammatory markers and rheumatoid factor positivity were the most consistent predictors of a poor outcome, although the studies were frequently inconsistent in both the direction and the magnitude of the effects.

Conclusions. These data are too variable to accurately identify those predictors associated with poor outcome following the onset of JIA. Although some of this variation may be the result of true differences between study populations, the vast majority of inconsistencies are explainable by the absence of standardized classification systems, outcome definitions, therapeutic approach and research tools. More comprehensive prospective evaluation is required before robust prediction models can be generated.

KEY WORDS: Juvenile arthritis, Outcome, Predictors, Remission, Function, Bone erosion.

Juvenile idiopathic arthritis (JIA) is a heterogeneous disorder comprising several disease subtypes [1–3]. These subtypes vary in their demographic characteristics, the pattern and severity of joint involvement and extra-articular manifestations, as well as the production of autoantibodies such as rheumatoid factor (RF) and antinuclear antibody (ANA). In an accompanying paper [4] we have reviewed the available published literature from the relatively small number of well-conducted outcome studies in JIA in an attempt to quantify the likelihood of key outcomes, namely remission, important levels of disability, and development of joint erosions. Specifically, we compared the frequency of these outcomes between the different recognized subtypes. There was a broadly consistent finding that children with oligoarthritis had a substantially better outcome than those with either systemic or polyarticular disease in relation to the main outcomes considered (remission, disability and radiological damage) [5–9]. Overall, however, there was little consistency in the results found, which could be explained by both random variation, given the small size of most of the studies, and a considerable number of methodological differences. These inconsistencies are also at least partly the result of the subtype classification being based on arbitrary combinations of clinical and laboratory features. Thus, in considering a prognosis following the onset of JIA it is important to consider the predictive role of the individual disease features rather than relying on disease subtype alone.

We have therefore undertaken a systematic review of the available published studies to consider the relative contributions of the following predictors: demographic factors, age and gender, as well as disease-related aspects, including the pattern and severity of joint involvement at presentation, level of inflammatory markers, and the presence of autoantibodies. As with our companion paper [4], we have focused attention on three outcomes: remission, functional limitation and structural damage, particularly radiographic erosions.

Methods

The material analysed was based on a systematic review of published outcome studies in the past 10 yr in cohorts of children with JIA. The rationale for choosing this time frame was to reduce the differences between studies in terms of their drug treatment strategies by considering only those from more recent years, although in some of the studies with longer duration of
follow-up there were still patients who had received treatment before the 1980s. In order to minimize the effect of inherent differences in the definitions, only studies reporting on juvenile chronic arthritis (JCA; ULAR classification), juvenile rheumatoid arthritis (JRA; ACR classification) and JIA [International League of Associations for Rheumatology (ILAR) classification] were included. Furthermore, only subtypes present in all three classification schemes were included, i.e. systemic, persistent oligoarticular, extended oligoarticular, RF− and RF+ polyarthritis. Details of the strategy for selecting studies are provided elsewhere [4]. Data were extracted on the following predictors: (i) age at onset and gender; (ii) disease-related apart from onset subtype: disease course, duration and persistence; (iii) specific nature of joint involvement in terms of involvement of specific joints and joint groups, joint count and symmetry; (iv) acute-phase response based on ESR and CRP; and (v) autoantibodies, including RF and ANA. The studies selected for this overview are listed in Table 1, including the number of subjects studied, together with the outcomes considered.

As described previously, the majority of these studies was not truly prospective, and only one study collected standardized clinical information at study entry for prospective evaluation [10]. The follow-up period differed greatly not only within studies but also from one study to another, with a wide range of 4.1–26.4 yr. There were also differences in the approaches used to measure the different outcomes and the nature of the analysis method used. As a consequence a formal meta-analysis was not possible.

The data are presented by different groups of predictors and their influence on the three outcomes considered. Clearly, not all studies evaluated all the outcomes or all the predictors. We were interested in assessing the strength of the associations between the predictors investigated and the outcomes considered. In presenting these data, as a guide we have identified studies where no statistically significant associations were found for specific predictors. We have also attempted to categorize the strength of any reported associations in a somewhat crude manner. Thus, for predictors and outcomes that were both dichotomous we have distinguished those results which suggest an odds ratio (OR) or risk ratio (i) between 1.0 and 2.0, (ii) between 2.1 and 5.0, and (iii) greater than 5.0. Some studies only undertook univariate analyses, whereas others presented the results of multivariate modelling, and such difference has been distinguished in our analysis. There are obvious limitations in such an arbitrary approach. Firstly, the lack of statistical significance may be a consequence of low power. Secondly, the size of any observed effect is a consequence in part of the stratification used for both predictor and outcome. However, the evaluation of the relative role of the predictors within a study is more robust.

Results

Predictors of disease remission

Data on the predictors of disease remission or continued disease activity are summarized in Table 2. Most of the reported predictors are from the ‘disease-related’ category. Systemic onset disease consistently predicted continuing disease activity. Polyarticular onset was a strong predictor of continued disease activity, especially in females [11], although in another study [9] this was not significant. Furthermore, polyarticular course was not significant in predicting remission when compared with oligoarticular course in one study [8] but reached significance in another study [12]. There was only one study which did not find course subtype a significant predictor for persistent disease activity [11], although monoarthritis and persistent pauciarticular cases were not compared with the extended ones as a group. Oligo- or pauciarticular course was consistently reported to be associated with a more favourable outcome when compared with other subtypes [8, 10, 12].

Details of the nature of joint involvement were only reported in three studies [9–11] and some aspects strongly predicted continued disease activity, but these varied between studies (Table 2). Laboratory markers showed some correlation with disease activity. Both ESR and CRP were significantly (P<0.0001 and P=0.009, respectively) associated with persistent disease activity based on EULAR remission criteria at follow-up [11]; however, 48% of the patients classified as having active or stable disease had normal levels of these markers. In another report [13] CRP was significantly elevated in those with active disease at follow-up (P<0.001). RF was also found a strong predictor, although only in one study [9], whilst either not reported in others [8, 12] or not found to be significant [10, 11].

ANA was only reported in one publication as a predictor of continued disease activity; this from univariate analysis [9]. Most studies either provided no report on the influence of gender or found no differences. In one study female gender was an
important predictor of poor outcome, especially in those with polyarticular disease [7].

Predictors of functional loss

The details on the predictors of functional loss or disability are summarized in Table 3. Presence of active disease, as defined by EULAR or ACR [14] remission criteria at follow-up [4], consistently predicted a poor functional outcome [7, 8, 15], and a polyarticular disease course also demonstrated a similar relationship [7, 8]. Gare and Fasth [7], using EULAR remission criteria, reported the strongest determinant of disability at follow-up to be continuing disease activity with OR = 299.6 (P = 0.0001) compared with those with ‘inactive disease’ (no evidence of drug therapy) had an OR of 14.4 (P = 0.015) when compared with inactive disease or remission. In terms of disease duration as a predictor for this outcome, however, two extremely opposite observations were made. Whilst Gare and Fasth [7] found an inverse relationship between disease duration and disability, others [13] reported a direct effect. The reason for this difference is not clear. The former study, with median follow-up time of 7.1 yr, dichotomized the Childhood Health Assessment Questionnaire (CHAQ) disability index (DI) as ≥0.5 or <0.5, whilst the latter, with much longer follow-up time (26.4 yr), used disability indices of 0 or >0. The study populations were different in terms of case mix, and left censorship (loss of cases to follow-up) existed in the latter study. Other studies did not report any relationship between disability and the duration of follow-up. Female gender independently was found to predict disability by Flato et al. [9]. As with remission, the combination of female gender and polyarticular onset predicted a more profound functional impairment. Other factors from a multiple logistic regression model which predicted disability in this study were symmetrical arthritis, early hip joint involvement, long duration of elevated ESR, and positive immunoglobulin M RF. The highest measured CRP within the first 5 yr after disease onset was significantly higher (P < 0.01) in patients with disability measured by CHAQ [8], whilst highest ESR values were not significantly different (P = 0.07). Others found both ESR and CRP at follow-up to be significantly associated (P < 0.0001 for both) with abnormal Health Assessment Questionnaire (HAQ) scores [5]. RF+ polyarticular subjects were more likely to be functionally impaired [7, 9], the former study suggesting a 44 times greater likelihood of having a CHAQ score above 0.5. This observation is not a consistent one, however. In another study, and only on univariate analysis, was there a significant association between RF+ polyarticular cases with higher HAQ scores (1.5–3.0). Interestingly, this was not reaching significance for RF+ cases in spite of a higher proportion with disability in the above range [5]. The numbers in the RF+ and RF- polyarthritis groups in that study were 37 and 41, and the proportions with HAQ disability index above 1.5 were 53 and 50%, respectively. Others, however [8], found no association in any direction. There are few data on ANA and disability, though this antibody had a protective effect in predicting disability in one report [16].

Predictors of structural damage

Five studies reported on the predictors of joint erosions, the findings of which are presented in Table 4. RF status was a powerful predictor in those with polyarticular disease and those with a polyarticular onset who were of the RF– subtype had no greater risk of erosions compared with either those with a pauciarticular onset [17] or all other onset subtypes [11]. The presence of RF was also strongly predictive of joint erosions in one study [9], with OR of 15.6 (95% confidence interval 2.2–112), but was not significant in another [8].

Disease duration was found to be a significant predictor of the development of joint erosions in two studies [11, 17], whilst others with longer follow-up ranges [8, 9, 18] did not report any significant findings. Acute-phase response was consistent in predicting joint erosions, the maintenance of a high ESR showing the greatest influence on this [8, 9]. The height of this elevation of ESR is also important. Thus, an initial ESR over 100 mm/h in oligoarticular onset disease was associated with a 4.4 times greater chance of developing polyarticular course and a six-fold increased risk of erosions [18].

In general, demographic predictors were not significant. Whilst older age at onset was protective in pauciarticular onset, it predicted erosions in other subtypes [9]. In only one study was female gender protective against ‘yearly radiographic progression’ in polyarticular JIA [19].

Discussion

Our aim was to consider whether the published data available would permit any valid conclusions as to which, and to what
extent, clinical and laboratory variables might be used to predict the outcome following presentation with JIA. As discussed above, there is a considerable body of evidence, which has been reviewed in a companion paper [4], that the disease subtype in broad terms is a guide to outcome. Specifically, children with an oligoarticular onset have a better prognosis than those with either a polyarticular or a systemic onset. However, these categories cover a broad spectrum of disease severity and the goals of the present analysis were to determine whether there were specific clinical or laboratory variables that might better predict outcome.

The major findings were very modest. Female gender is possibly a marker of poorer outcome, but mainly in polyarticular disease. The differences between the studies in their assessment of gender may be a function of the case-mix, in that in studies with low proportions with polyarticular disease girls did not appear to have a worse outcome [8, 12, 20]. Age at onset was too inconsistent as a predictor of outcome for any useful conclusion.

Several studies analysed the impact of the number, site and pattern (e.g. symmetry) of joint involvement at presentation and during the early course of the disease on outcome. The number of joints involved is a key factor in determining subtype, e.g. oligoarticular vs polyarticular disease. Thus, the observation that the number of affected joints is associated with an increased likelihood of persistent arthritis [9] is consistent with the overall poorer outcome in those with polyarticular disease [4]. However, there are other aspects of joint involvement that influence disease outcome, though an explanation for these very diverse findings is elusive. Thus, ankle involvement at onset has been reported in one study to be a bad prognostic sign, indicating greater likelihood of higher joint count at follow-up [11], whereas in another study there was an almost identically increased risk of the same outcome with upper limb involvement [18]. Furthermore, hand involvement [16] and hip arthritis [9] have been shown to predict disability and cervical spine involvement to predict joint erosions, whilst knee arthritis appears to be protective against erosive disease in pauciarticular onset [9]. These differences lack an easily plausible biological explanation but the pattern of joint involvement may have a more powerful influence on the outcome, in this case erosive disease. Symmetrical involvement at onset also predicted significant disability and was associated with a much greater risk of erosions [9]. As this study also showed an influence of joint

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### Table 3. Predictors of disability in juvenile inflammatory arthritis

<table>
<thead>
<tr>
<th>Reference</th>
<th>AAO</th>
<th>Gender</th>
<th>Onset</th>
<th>Course</th>
<th>Duration</th>
<th>Active disease</th>
<th>Nature of joint involvement</th>
<th>Acute-phase response</th>
<th>Autoantibodies</th>
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<tbody>
<tr>
<td>7</td>
<td>7</td>
<td>7</td>
<td>NS</td>
<td>Poly++</td>
<td>&lt;5yr++a</td>
<td>5–10yr++b</td>
<td>Joint</td>
<td>ESR</td>
<td>CRP</td>
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<td>16</td>
<td>≥6yr**</td>
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<td>Hand++</td>
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<td>NS</td>
<td>Poly++</td>
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### Table 4. Predictors of joint erosions in juvenile inflammatory arthritis

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<th>Reference</th>
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<th>Onset</th>
<th>Course</th>
<th>Duration</th>
<th>Active disease</th>
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<th>Acute-phase response</th>
<th>Autoantibodies</th>
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<td>+</td>
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<td>17</td>
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<td>System+++g</td>
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<td>RF= Poly+++g</td>
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+, ++, ++++, OR/RR 1.0–2.0, 2.1–5.0, >5.0, respectively (from multivariate analysis). Relative risks not available. *, **, ***, OR/RR with similar ranges to above, but from univariate analysis. Relative risks not available. NS, not significant. aCompared with intermediate duration (5–10yr). bCompared with long duration (>10yr). cNegatively correlated. dOther onset compared with pauciarticular. eOnly in systemic subtype.
count, another explanation is that the greater number of affected joints the more likely it is that symmetry will be observed. In addition, symmetry was not reported to have any influence on disease persistence. The pattern of joint involvement is consistent with the not surprising conclusion that the more joints involved early on the worse the prognosis, but the question as to whether involvement of specific joints (e.g. large joints) or whether the involvement is symmetrical remains largely unanswered.

Consistent with the number of joints is the level of inflammatory markers, both in terms of the height and persistence of the acute-phase response. A number of studies reported on the relationship between elevations of either ESR or CRP at baseline and poor outcome. Interestingly, the maintenance of a high ESR showed the greatest influence on all the three outcomes concerned here in one study [9], whilst others found this relationship limited to prediction of joint erosions [8]. The height of the elevation of ESR is also important. Thus, an initial ESR over 100 mm/h in oligoarticular-onset disease is a particularly bad prognostic sign [18]. Other indirect measures of inflammation were used in some studies. An example was measuring platelet count as a predictor of disability amongst cases with systemic disease, where for each 100 × 10⁹/l of platelets above the normal range, a 1.45-fold increase in the likelihood of D1 ≥ 0.75 was observed [15]. Again, these are not surprising findings but raise the hypothesis that treatment aimed at maximal suppression of disease activity has the possibility of improving outcome.

In the polyarticular subgroup, the presence of RF was shown in several studies to be a predictor of poor outcome, including increased disability and increased radiographic damage [7, 9, 16]. Interestingly, in all of the above studies the role of RF has been considered only in the context of polyarticular-onset subtypes, consistent with the rules of the main classification schemes. Perhaps it would be interesting to investigate the role of RF in other types of arthritis (currently unclassifiable in the ILAR scheme), and find out if similar relationship exists.

Some of the main methodological issues in relation to the lack of any uniform criteria for measuring clinical remission, physical disability, radiographic damage or any other outcome of interest are outlined in the companion paper to this review [4]. In addition, there are several other major technical issues, which render any conclusions drawn so far provisional at best. Only one of the studies was truly prospective [10], which has two consequences. Firstly, if an inception cohort were not recruited then the subjects captured in the cohorts studied would selectively exclude those lost to follow-up for whatever reasons (left censorship), who might have shown a different relationship between predictors and outcome. Secondly, the quality of information gathered retrospectively from clinical records is likely to be inferior and subject both to errors and omissions compared with the standardized approach adopted in prospective studies. The variables themselves were recorded differently and subject to different stratifications that render comparison between studies difficult if not impossible, though this is less important for variables such as age, gender or presenting joint(s). By contrast, the variability in the outcome assessment is even greater (as described previously [4]). It is reasonable to assume that the HAQ, CHAQ and Steinbrocker functional class, for example, will identify similar children as being severely disabled but the definitions of remission and disease persistence vary too much for useful comment. The duration of follow-up also varies considerably between studies and it is unlikely that baseline ESR, for example, would have a similar influence on outcome at 3yr as it would at 15yr.

One key question, which is barely touched on by some of the studies, is whether the relationships found are primary or secondary. Specifically, only a few studies undertook multivariate analysis, so the independent contribution of the different factors could not be easily assessed. Further, the presentation of results as ORs or equivalent gives no insight as to how much of the outcomes investigated can be explained by the variables identified. Statistical significance is an arbitrary phenomenon, related in large part to sample size, but knowledge is needed on how these various risk factors act in concert and whether the level of prediction is sufficiently useful for offering accurate prognosis and informed treatment decisions.

There are also several potential factors that might influence outcome that have not been examined. There is a large literature on the role of genetic factors, particularly HLA, on explaining susceptibility to JIA and its various subtypes [21, 22] but there are virtually no data on whether any of the susceptibility alleles, or indeed other polymorphisms, predict outcome.

The published data have considered themselves as natural history studies, but of course they in all cases include children treated with the disease-modification drugs deemed appropriate at the time. It would be important to be able to adjust for the treatment effect to gain a better insight into the true impact of RF status, for example. Early response to treatment may be an important predictor of outcomes, but only one study used standardized core set criteria to measure this [19]. This study did not find the treatment response significant in predicting their outcomes of interest, including radiological damage and function. There are also likely to be several other factors that might influence outcome which are harder to measure, such as psychological aspects and levels of physical activity or inactivity.

In summary, there is a remarkable dearth of evidence regarding the ability to accurately identify those children who, following the onset of arthritis, will have a good or poor outcome, but subgroup classification alone is unlikely to suffice. It is of paramount importance to be able to offer such prognosis in terms of both therapy planning and providing information for the children and their respective families. As mentioned previously [4], large multicentre and prospective studies with predefined and standardized assessment of predictors are required to enable clinicians to offer accurate prognosis.

The authors have declared no conflicts of interest.

References