Focus

Juvenile idiopathic arthritis and its long term outcome

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Introduction

KEY POINTS

- Up to 50 per cent of children still have active disease 25 years after the onset of their symptoms
- Joint damage occurs in up to 45 per cent of children with juvenile arthritis within two years of onset
- It is vital to classify JIA accurately, tailor treatment to individual needs and start effective treatment early
- There is a relatively limited window of opportunity to use antirheumatic medication to influence the outcome of JIA
- Referral for expert assessment and a multidisciplinary approach should be instituted early to prevent adverse social and employment outcomes

Juvenile idiopathic arthritis is a heterogeneous group of diseases in which the common factor is persistent arthritis in one or more joints starting under the age of 16 years. It has recently been reclassified to reflect this heterogeneity (see box 1).

As this suggests, childhood arthritis encompasses many different diseases, some of which are quite unlike those found in adults. Systemic arthritis (previously referred to as Still's disease) has no real adult equivalent. It most commonly affects children under the age of five years and presents with a high remittent fever accompanied by a maculopapular rash.

Other systemic features include lymphadenopathy, hepatosplenomegaly and pericarditis. Laboratory investigations reveal a leucocytosis and thrombocytosis, a high ESR and negative tests for rheumatoid factor. Similarly, the oligoarthritis occurring in young girls accompanied by a positive ANA and a high risk of anterior uveitis has no adult equivalent. Only 10 per cent of children presenting with arthritis have a rheumatoid factor positive disease resembling adult rheumatoid arthritis.

Despite the diversity of diseases encompassed by the term juvenile idiopathic arthritis (JIA), there is a widely held belief among both physicians and parents that, unlike arthritis in adults, the prognosis of childhood-onset disease is very good. This is encouraged by publications such as the American Arthritis Society booklet which recently stated "that 80 per cent of children with JIA can expect to be rid of inflammation when they reach adulthood" and "80 per cent of children with JIA will grow up without deformity".

Not surprisingly, many parents interpret these statements as implying that something magical will happen at puberty to resolve the child's arthritis. This article looks at the evidence on which the statements are based and attempts to give a balanced view of the long term outcome in juvenile arthritis.

Measuring outcome

There are a number of different outcome measures that can be looked at to assess the full impact of the disease on the child's later life. These include measures of disease activity, x-rays studies of joint destruction, measures of functional ability, educational and employment status and, ultimately, mortality.

In terms of disease activity, studies from as early as 1966 show that, contrary to popular opinion, up to 50 per cent of children still have active disease 25 years after the onset of their symptoms.1 These earlier studies have been criticised as being hospital based, and only following seriously affected children, but a recent study from the UK following all children presenting to a district general hospital showed almost identical results.2 In addition, it revealed that joint damage, as shown by erosions on x-ray, also occurs in up to 45 per cent of children affected by juvenile arthritis starting within two years of the onset of their disease.

Functional capacity in arthritis is traditionally assessed in terms of the Steinbocker index, Class 3 or 4 denoting severe disability (see box 2).

Studies using this index show that the longer children are followed, the more progress to severe disability. Levinson showed that 45 per cent of patients followed for over 25 years reached the Stein-bocker class 3 or 4 categories implying severe disability.3 Therefore, in terms of disease activity and functional status, it is probably nearer the truth that between 30 and 50 per cent of patients with JIA will begin their adult lives with active arthritis and have significant functional limitation at follow-up.

TABLE: MORTALITY RATES IN CHILDREN WITH JIA

	Number	Deaths	age %
Europe	2100	18	0.9
United States	11287	22	0.8
Pacific Area	459	8	0.7
US standardised mortality figure (Levinson 1992) 0.08			0.08

Psychological morbidity

The psychological outcomes of JIA also give cause for concern. In a UK study of 43 patients with polyarticular JIA with a disease duration of 19 years, 21 per cent were clinically depressed and 32 per cent felt that arthritis had a severe effect on their personal relationships.4

When educational outcome and employment status were examined in two UK centres, it was found that academic achievements were at least equal to those of controls, but unemployment rates of patients with JIA were three times higher than the national average.5 Thus, patients with JIA demonstrate poor employment outcomes in adult life despite good educational attainment at school.

Finally, in terms of mortality, studies from around the world have shown that death rates in JIA are considerably in excess of the standardised norm (see table).

It is difficult, therefore, to avoid Packham's conclusion that "no significant reduction in morbidity in JIA has occurred over the past 30 years".

Individualise treatment

How, therefore, can we manage our children with JIA more effectively?

Firstly, we must recognise that the term JIA includes diversely different diseases, as shown in box 1. A young girl with systemic onset disease who presents with rash, fever, lymphadenopathy, pericarditis and hepatosplenomegaly represents a completely different disease from the 12-year-old boy who presents with a single swollen knee. Both have forms of childhood arthritis, but will require completely different approaches to their management.

Treatment programmes in the past have grouped these children as having a single disease and attempted to treat them with identical drug regimens, which may explain the poor outcome of individual patients. Therefore, it is vital to classify children's disease accurately and tailor treatment to their individual needs.

Identify risk factors

Secondly, we need to identify the risk factors for aggressive disease and for those children who are going to develop disability in later life. New tools are being developed for this, particularly in terms of HLA typing, but we already know that female patients who are IgM rheumatoid factor positive and have a polyarticular onset with continuing disease activity do particularly badly in later years.

Start treatment early

Thirdly, we need to start effective treatment early in the course of disease. We know that 65 per cent of patients with polyarticular disease onset develop bony erosions in their joints within 2.6 years of disease onset. We also know that only 85 per cent of patients will begin second line antirheumatic medication within 2.5 years of the onset of the disease. Thus in the majority of these children irreversible bone damage has occurred before treatment has even begun.

These findings are based on plain x-rays, but MRI studies have shown that these x-rays underestimate actual joint damage and major damage may occur within a few months of the onset of disease. Therefore, it appears there is a relatively limited window of opportunity in which we may use anti-rheumatic medication to influence the outcome of these diseases.

Current treatment

Do we possess effective medication to prevent the destruction of children's joints? Modern management depends upon the early use of methotrexate plus other immunosuppressive drugs such as cyclosporin.

Methotrexate has been shown to be effective both in terms of disease activity, radiological progression and functional improvement in systemic polyarticular and oligoarticular disease.6 It is particularly well tolerated in children, with doses of 20mg per week leading to no reported cases of long term problems in terms of liver toxicity, quite unlike the studies in adults. Even better results have been obtained by combinations such as methotrexate and cyclosporin or intravenous cyclophosphomide.

Future treatments

Exciting new forms of therapy are on the horizon, including the new TNF-alpha blocker, etanercept, which is currently available in both the US and Australia but is not yet registered or funded here.

A study from the US in 1999 of 69 children with polyarticular JIA, who had failed

therapy with methotrexate and cyclosporin, showed that 74 per cent had an excellent response to etanercept. When these responders were subsequently randomised to placebo or continuing etanercept only 28 per cent of the active treatment group "flared" after six months compared with 81 per cent of the placebo group "flaring" within one month.7

The drug is given by subcutaneous injection twice-weekly and so far very few treatment-associated adverse reactions have been reported. It represents an enormous advance in the treatment of children with JIA, but this comes at a cost, approximately $20,000 annually.

Perhaps more experimentally, a brief report last year described four patients with severe JIA who had progressive disease despite prednisone, methotrexate and cyclosporin, who responded well to autologous stem cell transplantation, with drug-free disease remissions of between six and 18 months.8 However, later in the same year at an international conference, when the worldwide experience of bone marrow transplantation was discussed, it became apparent that of 23 patients undergoing the procedure, there had been five deaths, several due to overwhelming toxoplasmosis infection. It was generally agreed that such a mortality rate was not acceptable in a non-fatal disease and very strict limitations have been put on further such studies.

Conclusion

The prognosis of JIA has in the past been substantially worse than was generally believed. Recent advances in the recognition of the diversity of the diseases involved, the risk factors for progressive disease and the introduction of new, effective tools for halting disease progression should all lead to a much better prognosis in the future. It is, however, clear that early recognition and referral for expert assessment are essential before irreversible joint damage occurs, and that a multidisciplinary approach to management should be instituted early to prevent adverse social and employment outcomes.

References

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