Enthesitis Related Arthritis; a New Era of Understanding

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Abstract

Enthesitis related arthritis (ERA) is one of the most poorly understood and under-researched forms of childhood arthritis. Emerging evidence suggests that inflammatory spinal arthritis occurs earlier than previously thought and that there may be 2 distinct clinical phenotypes of disease - those with predominantly axial ERA and those with peripheral arthritis and enthesitis, who never develop spinal disease. This has important implications for management and warrants further study. This review will highlight the existing evidence for the diagnosis and treatment of ERA and discuss future research directions.

Key words: Spondyloarthropathy, sacroiliitis, enthesitis, juvenile idiopathic arthritis, HLA B27

Introduction

Enthesitis related arthritis (ERA), a subtype of juvenile idiopathic arthritis (JIA) associated with human leukocyte antigen (HLA) B27, shares some similarities with adult spondyloarthropathy. However, the clinical features are often different and little is known about the natural history of ERA with no long-term observational studies. The rationale for current treatment is largely based on extrapolation of evidence from other conditions, such as other forms of JIA and adult spondyloarthropathy which may not be appropriate.

The paucity of evidence in ERA is accounted for by historical problems with disease classification, lack of a validated disease activity score and the challenges posed in imaging the musculoskeletal system within the developing child and adolescent. This is compounded by a dearth of knowledge of the pathophysiological mechanisms underpinning disease.

This review aims to provide an update on the latest understanding and management of ERA and highlight the unmet research needs for this important condition.

Background

The presence of axial arthritis in the paediatric population has long been acknowledged with terms such as juvenile spondyloarthritis and juvenile spondyloarthropathy. However, the lack of accepted diagnostic criteria hampered the development of collaborative research in this field. In addition, such terms
failed to acknowledge the perceived typical juvenile presentation of the disease, with peripheral arthritis and enthesitis, until 1982 and the description of the SEA syndrome (seronegative enthesopathy and arthropathy) [1].

Following from this, the definition of ERA in the International League of Associations for Rheumatology (ILAR) classification criteria for JIA [2] gave greater importance to arthritis and enthesopathy over inflammatory back pain for diagnosis (Table 1). There are still some problems with the classification criteria for the ERA category, in particular the exclusion of patients with a family history of psoriasis, despite typical features of ERA.

Table 1. ILAR classification criteria for ERA [2]

<table>
<thead>
<tr>
<th>ILAR classification criteria for ERA:</th>
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<tr>
<td>1. arthritis and enthesitis OR</td>
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<td>2. arthritis or enthesitis with 2 of</td>
</tr>
<tr>
<td>- sacroiliac joint tenderness, inflammatory spinal pain or both</td>
</tr>
<tr>
<td>- HLA B27</td>
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<tr>
<td>- family history in 1st degree relative of medically confirmed HLA B27 associated disease</td>
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<tr>
<td>- acute anterior uveitis</td>
</tr>
<tr>
<td>- onset of arthritis in a boy after the age of 6 years</td>
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<tr>
<td>Patients with psoriasis or with psoriasis in a 1st degree relative are also excluded.</td>
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</table>

Epidemiology

Given that ERA is a relatively new term, there are a lack of studies reporting the incidence, prevalence and clinical outcomes of this condition. Epidemiology has been inferred from previous studies of juvenile spondyloarthritides utilizing differing classification systems and in patients from different ethnic backgrounds, perhaps explaining the wide range of values that have been reported [3].

The proportion of adults who developed AS in childhood is reported as being between 8.6 and 11%. Some studies have tried to extrapolate the prevalence from this giving a figure of 11-86 per 100,000 children [4]. This seems high considering the prevalence of JIA is probably around 57-220 per 100,000 [5] but may reflect that spondyloarthropathy often takes many years to diagnose. In data from studies evaluating the ILAR criteria, around 11-16% of patients with JIA were found to have ERA [6, 7].

The variation observed between different racial and ethnic groups mirrors the differences in the frequency of HLA B27 positivity. In healthy individuals in the UK this is around 8% but in some populations may be as high as 50% [8].

The age of onset of ERA is relatively homogeneous and tends to be late childhood and adolescence although there are case reports of much younger children being affected [9].

The male to female ratio is 6-7:1. In adult spondyloarthropathy, the ratio is 2.7:1. The fact that male sex forms part of the classification criteria for ERA explains this in part. In addition, it is thought that manifestations in females may be less severe or may affect predominantly the peripheral joints leading to their classification as other forms of JIA [4].

Pathophysiology

The etiology of ERA is unknown. The strong association with HLA B27 suggests a genetic mechanism. HLA B27 is positive in between 76 and 85% of patients with ERA [10, 11]. A study in children with JIA found that, in boys, HLA B27 was associated with older age at disease onset, higher number of active joints within the first 3 years of disease, involvement of the small joints of the lower limbs and enthesitis. There was an association with inflammatory back pain in both sexes [12].

24 different subtypes of HLA B27 have been identified, each differing by a few amino acids. The most widespread subtype in adult spondyloarthropathy is B2705 but certain subtypes of HLA B27 predispose to early disease [13]. A recent study of Latvian HLA B27 positive JIA patients demonstrated that B2705 was also the most common subtype present in patients with ERA [14].

In adults, it is well recognized that other genetic factors play a role and recent genome-wide association studies have identified several susceptibility genes, including endoplasmic reticulum aminopeptidase 1 (ERAP1), interleukin (IL)-23 receptor (R), anthrax toxin receptor 2 (ANTXR2) and IL-1R2 [15]. Thus explaining the strong familial association noted in addition to that conveyed by HLA B27. In ERA, a recent study demonstrated a strong association with ERAP1 and a possible association with IL23R [16]. Further larger studies are needed to confirm this association.

Clinical Features

The historical view of ERA as a peripheral arthritis and enthesitis at disease onset, with axial features only developing after many years is now out-dated.
The use of magnetic resonance imaging (MRI) and increased clinical suspicion is identifying inflammatory spinal disease much earlier than previously reported.

Pagnini et al published data on their cohort of 59 ERA patients finding 30.9% had MRI-confirmed axial disease at a median of 1 year 3 months after diagnosis [17]. From our own cohort of nearly 80 patients, around a third have inflammatory spinal symptoms at disease onset [18]. Axial disease does not occur in all patients but can be expected in over half of those diagnosed with ERA after around 2-3 years. It may be present on MRI without any clinical symptoms in around 10% of these patients. It is therefore imperative that where there is clinical suspicion of ERA, patients are questioned and examined thoroughly to identify the presence of spinal disease.

These findings have lead to the suggestion that there are in fact 2 distinct clinical phenotypes of disease (Table 2): those with early axial disease often associated with hip arthritis [19] in addition to peripheral arthritis and those who follow a more peripheral disease course with arthritis and enthesitis and do not develop axial disease [17,18]. These two distinctive disease patterns imply underlying differences in mechanisms of disease at a molecular level. This may have implications in terms of future treatment strategies for ERA and warrants further scientific study.

Table 2. Two clinical phenotypes of ERA

<table>
<thead>
<tr>
<th>Axial ERA</th>
<th>Peripheral ERA</th>
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<tr>
<td>• older age at disease onset</td>
<td>• younger age at disease onset</td>
</tr>
<tr>
<td>• higher rate of HLA B27</td>
<td>• lower rate of HLA B27</td>
</tr>
<tr>
<td>• more hip arthritis</td>
<td>• more ankle arthritis</td>
</tr>
<tr>
<td>• more extra-articular manifestations</td>
<td>• more enthesitis</td>
</tr>
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</table>

There is frequently a delay in diagnosis as the initial symptoms can be vague and difficult for the child to localize, for example alternating buttock, groin, thigh and heel pain. There may be several episodes of pain which spontaneously resolve.

Typically arthritis is found in around 4 joints although this can vary widely between patients and the peripheral arthritis predominantly affects the lower limbs in an asymmetrical distribution. The most commonly affected joints are listed in Table 3 with approximate percentage of patients affected from our cohort (unpublished observation). Isolated hip joint arthritis may be the presenting feature and predicts early axial disease. Involvement of the small toe joints is common in ERA but rare in other forms of JIA. Tarsitis causing pain and restriction of the midfoot, although uncommon is very characteristic of ERA.

Enthesitis is estimated to be present in 80-90% of patients at onset [9], although this may be difficult to detect clinically. This most commonly affects the patellar tendon insertion at the inferior pole of the patella, plantar fascial insertion at the calcaneus as well as metatarsal heads and the Achilles tendon insertion [20]. Enthesitis does not only occur in ERA, but also in psoriatic and undifferentiated forms of JIA. Mechanical enthesopathy is also common in children and teenagers and may be difficult to distinguish from inflammatory enthesitis.

Table 3. Commonly affected joints in ERA (unpublished observation from University College Hospital, London cohort of ERA patients)

<table>
<thead>
<tr>
<th>Commonly affected joints</th>
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<tbody>
<tr>
<td>• Knee (65%)</td>
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<tr>
<td>• Hip (60%)</td>
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<tr>
<td>• Ankle (50%)</td>
</tr>
<tr>
<td>• Lumbar spine (50%)</td>
</tr>
<tr>
<td>• Sacroiliac joints (50%)</td>
</tr>
<tr>
<td>• Metatarsal phalangeal joints (25%)</td>
</tr>
<tr>
<td>• Tarsal joints (15%)</td>
</tr>
</tbody>
</table>

Systemic symptoms are uncommon. Inflammatory markers can be raised or normal and there may be mild anaemia, raised leukocytes and platelets. Anaemia may also alert the clinician to the presence of sub-clinical inflammatory bowel disease.

Clinical assessment and assessment tools

The core outcome variables for JIA do not capture axial disease well and do not specifically assess enthesitis and are therefore likely to underestimate disease activity in ERA. Although they have been validated in JIA, there has been no assessment of their use specifically in ERA.

Adaptation of assessment tools already in use for adult spondyloarthropathy summarized in Table 4 may provide the answer.
Table 4. Examples of disease activity scores for ankylosing spondylitis

<table>
<thead>
<tr>
<th>Assessment tool</th>
<th>Questionnaire assessing</th>
</tr>
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</table>
| Bath ankylosing spondylitis disease activity index (BASDAI) [21] | - fatigue  
- pain in the spine and peripheral joints  
- localized tenderness  
- severity and duration of morning stiffness |
| Bath ankylosing spondylitis functional index (BASFI) [22] | - spine and peripheral joint function                                                   |
| Ankylosing spondylitis disease activity score (ASDAS) [23] | Composite score of:  
- questions from the BASDAI, including  
- those concerning back pain, morning stiffness,  
- peripheral joint pain and swelling  
- patient global assessment  
- CRP or ESR |

The development and validation of a disease activity tool specifically for ERA is now crucial for collaborative research and to effectively measure response to treatment. With the inclusion of an enthesitis score, the ‘juvenile ASDAS’ or ‘ERA-DAI’ may provide a more useful assessment tool in ERA.

Natural History

As ERA is relatively recently defined, there is little data on clinical outcomes in ERA and the natural history of the disease is poorly understood. Follow up studies were published for patients diagnosed with SEA syndrome. Sacroiliitis was found to develop in most patients within 10 years [24]. Burgos-Vargas and Clark reported 75% of patients with an initial diagnosis of SEA syndrome progressed to axial disease in 5 years.

There are no such longitudinal studies yet in ERA. However, it is clear that axial disease occurs much earlier than previously thought and this has important implications for treatment.

It is known that in comparison with other forms of JIA, ERA has one of the lowest remission rates at 17% (oligo 54%, systemic 38%, poly 15%) [25]. There are few quality of life studies but general fitness rates are low in ERA patients, years after diagnosis and even in remission [26]. In a study by Flato et al, patients with ERA had higher levels of physical disability, more bodily pain and poorer physical health compared to patients with oligoarticular and polyarticular JIA after 15 years of follow up [11]. Poor prognostic indicators were a family history of ankylosing spondylitis (AS), the presence of HLA DRB1*08, the absence of HLA DRB1*02, a persistently raised ESR, early hip or ankle involvement and a high number of affected joints within the first 6 months.

Extra-articular manifestations

The incidence of extra-articular manifestations is difficult to quantify because of the previous problems with classification criteria. However, we have observed that extra-articular manifestations appear to be associated with axial disease and HLA B27 [18].

Data on extra-articular manifestations from studies published over 3 decades ago is summarized in Table 5. In 1993 Mielants et al reported evidence of gut inflammation in 75% patients with late onset pauciarticular JCA, progressing to adult spondyloarthropathy [27].

Table 5. Extra-articular manifestations in juvenile spondyloarthropathy

<table>
<thead>
<tr>
<th>Extra-articular manifestations</th>
<th>Percentage affected</th>
</tr>
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<tbody>
<tr>
<td>Acute anterior uveitis</td>
<td>27% [28]</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>up to 75% [27]</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>Case reports only</td>
</tr>
<tr>
<td>Restrictive lung function defects</td>
<td>up to 1/3 [30]</td>
</tr>
<tr>
<td>IgA nephropathy</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

The data in Table 5 is based on studies that pre-date the use of biologics in the treatment of ERA. As tumour necrosis factor (TNF)-α blockers appear to significantly reduce disease activity, it is likely that some of the above figures will have improved. Up to date studies are needed.

Imaging

In the adolescent patient, interpretation of images can be difficult and unreliable. Mechanical back pain is common and the features of an immature skeleton, such as the apparent widening of the sacroiliac joints seen on plain radiographs may mimic appearances seen in the presence of inflammation. X-rays are not sensitive to acute inflammatory changes and will only show advanced disease in the sacroiliac joints. For these reasons plain radiographs are not useful in the adolescent patient.

Ultrasound and Doppler ultrasound have been shown to be better than clinical examination in the detection of enthesitis in patients with JIA [31] and may provide a useful adjunct to a future ERA disease activity score.

MRI has become the gold standard imaging modality for detecting arthritis and enthesitis, improving the assessment of disease activity and response to treatment. In the
sacroiliac joints, MRI can show features of both acute inflammation (bone marrow oedema/osteitis, enthesitis and capsulitis) and structural damage (erosions, subchondral sclerosis, subchondral fatty change and bony ankylosis). Structural changes without bone marrow oedema are not considered as diagnostic of active disease. There is some evidence in adults that inflammatory changes on MRI pre-date the development of structural changes indicating that MRI does show early disease [32]. In children and adolescents there is no gold standard MRI technique therefore it is difficult to be certain whether changes seen in the sacroiliac joints truly represent active disease or are perhaps related to changes of skeletal immaturity.

MRI has, however, been shown to detect changes consistent with early and sub-clinical sacroiliitis in children. A study by Bollow et al showed that contrast-enhanced MRI detected sacroiliitis in significantly more children than plain radiographs [33]. A further study by the same author using dynamic MRI showed that this was an effective discriminator of acute and chronic inflammation. The detection of sacroiliitis seemed to be associated with disease duration and high inflammatory markers [34]. The advantages of MRI over other imaging modalities are the lack of ionizing radiation, ability to detect sub-clinical disease, to monitor treatment efficacy and differentiate between acute and chronic inflammation. However, at present the use of intravenous contrast is still necessary and images remain difficult to interpret in the context of the immature adolescent skeleton.

Future advances in diffusion and perfusion MRI techniques that quantify the physiological behaviour of tissue will enhance disease assessment, monitoring and may even be useful in predicting response to therapy. Further studies of these physiologically based imaging techniques are required in larger numbers of patients with ERA to establish their efficacy for early diagnosis and monitoring of therapy. The development of quantitative imaging may help develop and validate a disease activity score.

Management

As with all chronic childhood diseases, ERA should be managed by a multidisciplinary team. Physiotherapy and rehabilitation are an essential part of treatment and effective transition to adult services is important.

A summary of commonly used non-biologic treatment can be found in Table 6. Clinical trial data for these treatments is lacking but it is widely accepted that disease modifying anti-rheumatic drugs (DMARDs) can be useful for peripheral arthritis but may not be as effective for enthesitis and axial inflammation. In our cohort however, we have observed that patients with axial ERA treated with methotrexate or sulfasalazine do sometimes show radiographic improvement on MRI. It is impossible to say without prospective controlled trials whether this is a true effect of the medication or part of the natural history of the disease. It is therefore our policy to start all patients on methotrexate or sulfasalazine prior to the introduction of biologic therapy. In addition, we have observed that there may be a synergistic effect when these drugs are co-prescribed with anti-TNF therapy. All of these observations need further study and appropriate validation.

### Table 6. Non-biologic treatment in ERA

<table>
<thead>
<tr>
<th>Drug Use</th>
<th>Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-steroidal anti-inflammatory (NSAIDs)</td>
<td>For symptomatic relief</td>
</tr>
<tr>
<td>Intra-articular steroid</td>
<td>For peripheral arthritis but not enthesitis because of the risk of tendon rupture</td>
</tr>
<tr>
<td>Systemic corticosteroid</td>
<td>For severe inflammation only but use with caution because of side effects</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>For peripheral arthritis but less effective for enthesitis and axial disease</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>For peripheral arthritis and possibly axial disease but no proven benefit in clinical trials in ERA</td>
</tr>
</tbody>
</table>

The efficacy of anti-TNF treatment has been shown to be effective and well tolerated in children with polyarticular JIA [37] and in adult AS in large randomized controlled trials [38]. However, in ERA the evidence for anti-TNF treatment is limited to small open label observational studies (Table 7) and a case report demonstrating radiographical improvement [39].

From the data in (Table 7), anti-TNF therapy certainly appears to be effective in ERA but prospective controlled studies are currently lacking. Validated disease activity measures are a pre-requisite for future trials, as is correlation with MRI findings. At present, each study defines its own outcome measures making collaborative research difficult.

Interestingly, in established adult AS it is well recognized that although anti-TNF treatment reduces the signs and symptoms of disease, it does not prevent further radiological
In light of the uncertainty regarding the treatment of ERA, we have designed a suggested management protocol to rationalize treatment and enable further study (Figure 1).

**Table 7. Evidence for anti-TNF treatment in ERA.**

<table>
<thead>
<tr>
<th>Study published</th>
<th>Patients</th>
<th>Treatment</th>
<th>Evidence</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004 [40]</td>
<td>8</td>
<td>Etanercept</td>
<td>Open label, pilot study</td>
<td>Significant improvement in all patients over 2 year trial</td>
</tr>
<tr>
<td>2005 [41]</td>
<td>10</td>
<td>Infliximab or Etanercept</td>
<td>Open label pilot study</td>
<td>Significant improvement in all patients over 1 year follow up</td>
</tr>
<tr>
<td>2009 [42]</td>
<td>20</td>
<td>Infliximab, etanercept or adalimumab</td>
<td>Retrospective case review</td>
<td>‘Remission rate’ of 70% at 6 months. Treatment cessation followed by relapse after 2.5-3 months</td>
</tr>
<tr>
<td>2011 [43]</td>
<td>22</td>
<td>Infliximab, etanercept or adalimumab</td>
<td>Observational data from registry</td>
<td>Effective and safe treatment but inactive disease in 32% only at 6 months and sustained ‘disease free state’ could not be achieved</td>
</tr>
</tbody>
</table>

The way that ERA is thought of is changing. From being a childhood disease of arthritis and enthesitis and only progressing to involve the axial skeleton in late adolescence or adulthood, it is now evident that in a large subgroup of patients axial disease occurs early, often within the first 2-3 years. Further studies are needed to look at the natural history of ERA and in particular to identify those features- clinical or...
molecular-which may predict the axial ERA phenotype. This has important implications for treatment as, if identified early, there may be a unique opportunity to halt radiological progression of disease in the spine, in contrast with the adult form of the disease where it is already too late.

The development of a disease activity tool, as well as a gold standard MRI technique for the axial skeleton in children and adolescents is now essential for future trials. This will enable a greater understanding of this important disease and confirm the efficacy of treatment in large clinical studies.

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**References**


