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Enthesitis-Related Arthritis (ERA)

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Introduction:

Hi everyone, my name is Vivian Szeto and I am a medical student at the University of Alberta in Edmonton, Canada. In conjunction with Dr. Rumsey, a Pediatric Rheumatologist at the University of Alberta and Stollery Children's Hospital in Edmonton, Canada, I have created this podcast to provide you with an approach to Enthesitis-Related Arthritis or simply ERA.

Today's objectives for the ERA PedsCase will include:

1. Define and classify ERA
2. Review the epidemiology of ERA
3. Review the etiology and pathogenesis of ERA
4. Recognize the clinical presentation of ERA and potential differential diagnoses
5. Discuss pertinent investigations
6. Discuss management of patients with ERA
7. Discuss the course and prognosis of ERA

The Case

Let's start with a case! A 12-year-old boy presents to the family clinic with his mother, complaining of pain. You are currently working at this clinic and have been asked to take a history. The patient tells you that he has been having intermittent musculoskeletal pain and stiffness for the past 3 months. He has been experiencing pain in both knees and his right heel. He reports fatigue and difficulty participating in gym class as the small joints of his toes are swollen and stiff, which makes running difficult. Based on the history, you suspect this patient may be presenting with Enthesitis-Related Arthritis. What do you do next?

ERA Definition

Enthesitis-related arthritis, or ERA, is a type of Juvenile Idiopathic Arthritis (JIA) that typically involves inflammation and swelling of joints and entheses of the lower extremities. Entheses are the sites of attachment of ligament, tendon, or fascia to bone. It is characterized by the presence of human leukocyte antigen-B27 (HLA-B27) and absence of rheumatoid factor (RF).

A certain percentage of ERA cases will eventually go on to develop axial involvement. Once axial involvement occurs, the classification of this presentation is still debatable; as some

rheumatologists will refer to this disease as Juvenile Ankylosing Spondylitis (JAS), while others consider JAS as a subclass of ERA.

The International League of Associations for Rheumatology (ILAR) Classification of ERA defines ERA as:
A form of JIA that is characterized by:
A) The presence of arthritis and enthesitis
OR
B) Arthritis or enthesitis with 2 or more of the following:

1. Sacroiliac joint tenderness and/or inflammatory lumbosacral pain
2. Presence of HLA-B27
3. Family history of HLA-B27-associated disease (AS, ERA, sacroiliitis with IBD, reactive arthritis, acute anterior uveitis) in a 1st degree relative
4. Acute symptomatic anterior uveitis
5. Onset of arthritis in a boy after 6 years of age

Exclusion criteria for the diagnosis for ERA include:
Psoriasis in a patient or 1st degree relative, IgM RF positivity, systemic JIA, arthritis fulfilling two JIA categories.

Epidemiology of ERA

ERA accounts for approximately 10-19% of children classified with JIA, with males being diagnosed more commonly than females. In Canada, 1 female for every 3.4 to 4.1 males is diagnosed with ERA. The mean age at diagnosis is reported to be 10-13 years old. In terms of racial distribution, in Canada, ERA is two times more common in children of European origin than those who are not. Among those of non-European ancestry, children of Asian descent are more likely to be diagnosed with ERA than any other form of JIA.

Etiology and Pathogenesis of ERA

The exact cause of ERA has yet to be fully elucidated. It has been postulated that there may be an infectious etiology, but none has been proven to date. It is recognized that there is a familial pattern with patients positive for HLA-B27, but the exact mechanism(s) by which this relates to the development of ERA has yet to be established.

Clinical Presentation and Differential Diagnosis

ERA onset is typically insidious with the presence of intermittent peripheral joint stiffness with limited range of motion of the lower extremities and musculoskeletal pain. Patients with ERA typically suffer from oligoarticular arthritis (4 or less joints affected). The joints of the lower extremity are more frequently affected than those of the upper extremity and the involvement is often asymmetric. Common sites of arthritis include the hip, knees, small joints of the foot and toes, and ankles. Small joints of the hands are less commonly involved and shoulders are also uncommonly affected.

In addition to arthritis, ERA patients often have enthesitis around the knee, foot/ankle, or both. Other sites of enthesitis include: pelvis, spine, upper extremity, and chest. Axial involvement, as previously mentioned, typically presents later in the course of the disease with symptoms showing roughly 5-10 years from disease onset, if at all.

Up to one third of children with ERA also suffer from tarsitis, which is inflammation of the intertarsal joints of the foot. Tarsitis causes tenderness, pain, and restriction of range of motion of the midfoot.

Systemic symptoms are rarely present in children with ERA. However, fatigue, sleep disturbances, and low-grade fever may occur. Patients with ERA are also at risk of acute, symptomatic inflammation of the eyes called uveitis. This presents as an acutely red, painful, photophobic eye. Uveitis normally does not precede the onset of musculoskeletal complaints and often presents unilaterally with frequent reoccurrence that may leave ocular sequelae. Gastrointestinal symptoms may be present in those with ERA. However, those symptoms, if present, should prompt consideration of the diagnosis of inflammatory bowel disease (IBD). Should a patient present with abdominal pain and diarrhea, then this may be more suggestive of arthritis related to inflammatory bowel disease (IBD). Renal, cardiopulmonary, and central nervous system disease are also rare in children with ERA.

Lastly, differential diagnoses to consider that may have similar physical exam findings as those with enthesitis include: Osgood-Schlatter disease (apophysitis of the tibial tubercle), Sinding-Larsen-Johansson syndrome (traction apophysitis of the lower pole of the patella) and Sever's disease (calcaneal apophysitis). Excessive running and jogging will also mimic inflammatory enthesitis. As well, pressures over sites of entheses in children with leukemia or bone tumours may produce pain similar to enthesitis. However, the pain resulting from inflammatory entheses is more discreet and less severe than that found in children with cancer. Finally, fibromyalgia or amplified MSK pain syndrome can present with similar findings on physical exam as ERA.

Examination and Investigations

To start, a careful and detailed history is very important to help with narrowing the differential. Next, it is important to perform a thorough physical examination. We will focus on the MSK exam here. There are several ways to approach the MSK exam. One method is the "Look, Move, Feel" approach. For "Look", begin with observing the patient standing. Using the acronym SEADS, look for any obvious signs of: Swelling, Erythema, Atrophy (muscle), Deformity, or Skin changes. This is followed by examining the patient's gait by asking the patient to walk, run, toe-walk, and heel-walk. Make sure to look for any changes in the patient's stance and swing phases while walking and also look for any signs of antalgic gait that may be suggestive of enthesitis or arthritis of the hips, knees, or ankles.

Next, check the patient's range of motion in "Move". Examine the patient's active range of motion followed by passive range of motion, making note of any limitation or voiced pain.

For "Feel," begin by examining and palpating for evidence of arthritis (joint effusion). This is followed by a thorough enthesitis exam. This consists of applying pressure to various insertion sites of tendons/ligaments/fascia into bone. Examples of commonly involved areas include: the Achilles tendon attachment into the calcaneus and the patellar and quadriceps tendon attachments into the patella (at the tibial tuberosity, and 6, 10, and 2 o'clock positions around the patella).

Special tests for axial skeletal involvement should be considered. To check for SI joint involvement, a FABER test can be performed (this is an acronym that stands for Flexion ABduction, and External Rotation of the hip). A positive test is indicated by tenderness in the contralateral SI joint. To test flexion of the patient's lower back, a modified Schober's exam should be performed. This exam begins by asking the child to stand with their knees and back straight and land marking for the dimples of Venus. The examiner should make a mark there, one 5 cm below (point A) and another 10 cm above (point B). Then ask the patient to keep their knees straight and lean forward to touch their toes. The increase in distance between points A and B is used as an indicator of spinal mobility. Normal range would include a measurement of change of greater or equal to 6 cm.

In terms of laboratory examination, there are a few distinguishing features. Anemia may present due to chronic disease. ESR and CRP values may be elevated, but could also be normal. HLA-B27 has been shown to be present in 60-80% of ERA patients. This, however, is not a diagnostic test, but rather a risk indicator.

As for radiographic examination, x-rays of affected areas may be ordered in patients with ERA. Possible radiological characteristics include the following:

-In the enthesitis regions such as the calcaneus, tibial tuberosity: soft tissue swelling and erosions or spur formation at insertions.

-At the peripheral joints: soft tissue swelling, accelerated ossification, and epiphyseal overgrowth, periostitis, joint-space narrowing, erosions, and ankylosis.

-Sacroiliac disease: diffuse osteoporosis of the pelvis, blurring of subchondral margins, erosions (iliac side first), reactive sclerosis, joint-space narrowing, fusion (late).

-In the vertebral column: vertebral epiphysitis with anterior vertebral squaring, anterior ligament calcification, "bamboo spine" (rare in children).

-An MRI would be helpful to detect early changes in the SI joints and the spine.

Treatment Approach

A child presenting with suspected ERA should be referred to a pediatric rheumatologist who will work alongside a team of specialists (physiotherapists, occupational therapists, dieticians, etc.) to diagnose, treat, and monitor the child over time. For non-drug-therapy interventions, the patient will work with physiotherapy, who will help them maintain good range of motion in their joints and strength in their muscles, and occupational therapy, who will teach them modified maneuvers to help complete their activities of daily living. In patients suffering from foot enthesitis, custom orthotics and heel cups may help relieve pain. Exercise and maintenance of good posture to minimize loss of range of motion is also recommended.

In terms of medications, a stepwise approach is followed, starting with Non-Steroidal Anti-Inflammatory Drugs (NSAIDs). This initial pharmacological management helps to provide

symptomatic relief of pain and treats the inflammation when properly dosed. Common options include Naproxen, Indomethacin, and Celebrex.

Another treatment option at various times in the disease course is glucocorticoid therapy. This can be in topical form (for uveitis) or intra-articular form (injected into an active joint(s), either at disease onset or later in the disease course). Entheses can be injected with steroid, but this is rarely done due to the risk of tendon/ligament rupture.

The next treatment option would be starting the patient on disease modifying anti-rheumatic drugs (DMARDs). These drugs are useful for the treatment of peripheral disease activity, which is the predominant disease manifestation in children with ERA. Examples include Sulfasalazine and Methotrexate.

The top step in this ladder approach is biological agents. The most commonly used biologics are the TNF inhibitors, which are effective and safe for the treatment of ERA. Biologics are indicated in patients whose disease is refractory to DMARDs. Also, those with with axial disease are often started on biologics earlier in their course, as axial disease does not typically respond to treatment with DMARDs. Examples of TNF inhibitors include: Etanercept, Infliximab, and Adalimumab.

There is a very limited role for surgical management of ERA.

Course of Disease and Prognosis

The presentation and progression of ERA is highly variable from child to child. The majority of studies show worse prognosis with poorer physical function, higher pain scores, and ongoing disease activity in children with ERA compared with children with other categories of JIA. Children with all categories of JIA, including ERA, are encouraged to participate in recreational activities and exercise.

Studies have shown that up to 44% of patients with ERA will go into disease remission. Overall, the assessment of outcomes in ERA is currently limited.

Case Summary

Now back to the case! After your history and physical, you suspect that the young man in your clinic has ERA. Thus, you decide to refer him to a pediatric rheumatologist.

Two months later, you receive a letter from the pediatric rheumatologist who confirms the diagnosis of ERA in your patient. The patient was started on Naproxen. The rheumatologist suspects SI joint involvement and will send the patient for an MRI. He also recommends physiotherapy and occupational therapy treatment to help with activities of daily living. As well, he recommends an annual eye check with an ophthalmologist to screen for uveitis (or more frequently, if symptomatic). He thanks you for your astute recognition of the problem and appropriate and timely referral.

Key Take Home Points

To summarize, here are some key take home points:

1) ERA is a type of juvenile idiopathic arthritis which involves inflammation and swelling of joints and entheses, typically of the lower extremities.
2) ERA is most commonly diagnosed in adolescent males.
3) Clinical presentation of ERA typically includes an insidious onset of oligoarticular arthritis (4 or less joints affected) and entheseal tenderness around the knee, hip, foot, and ankle.
4) A differential diagnosis would include: excessive running and jogging, which will mimic inflammatory enthesitis, fibromyalgia, or one or more apophysitis syndromes (Osgood-Schlatter disease, Sinding-Larsen-Johansson syndrome and Sever's disease).
5) Important aspects of an approach to these patients include: taking a thorough history, performing a thorough exam of all the joints and enthesis points (Look, Move, Feel), consideration of blood work (e.g. CBCd, ESR, CRP), and radiographic investigations (X-rays and/or MRI). Discussion with and early referral to a pediatric rheumatologist is highly recommended.
6) Management of ERA would include using a step-wise approach: non-pharmacologic treatment (physiotherapy, occupational therapy) for all, Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), disease modifying anti-rheumatic drugs (DMARDs), and finally biologics. Potential glucocorticoid treatment can also be considered. There is a very limited role for surgical intervention in the management of ERA. Also, regular lab work, eye exams, and clinical appointments are key.
7) The prognosis of ERA is highly variable from child to child but tends to be worse than in other categories of JIA.

Thank you for listening to the podcast on ERA. Stay tuned for more podcasts to come!

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