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Approach to Systemic Juvenile Idiopathic Arthritis

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Introduction:

This is Rebecca Quilty, a third-year pediatrics resident at Memorial University of Newfoundland. I developed this podcast with the help of Dr. Ronald Laxer, a pediatric rheumatologist at the University of Toronto.

Objectives

1. To discuss the classification criteria and the clinical features of systemic juvenile idiopathic arthritis (JIA)
2. To describe a broad differential diagnosis for a patient presenting with systemic JIA
3. To discuss macrophage activation syndrome (MAS) as a severe complication which may be associated with systemic JIA
4. To delineate the role of the general pediatrician in the management of children with systemic JIA

Case

You are a fourth year medical student doing a rotation on the general pediatric ward and you get called to see a consult in the ED regarding Anna, a 5 year old girl with a two-week history of fever. On history, you gather that she was previously well until the onset of her fever and the fever occurs daily, spiking as high as 39°C every evening. Her parents show pictures of an erythematous rash present on her trunk and extremities accompanying the fever. The last few days she has had pain in her wrists and knees and her mother feels her knees are a bit swollen. She has no other symptoms of infection, has had no sick contacts. She has had no recent weight loss and feels well between the fever episodes. She has taken ibuprofen as needed for her joint pain but does not take any other medications.

On review of her vitals, her temperature is 37.6 °C tympanic (Mom states that it is almost the time that her fever spikes). On exam, you note that she appears well. You palpate a 1cm cervical lymph node and an inguinal lymph node slightly smaller than 1 cm. The cardiac, respiratory, and abdominal exams are unremarkable. You note a faint

erythematous macular rash on her proximal thighs. You can appreciate bilateral knee effusions and there is limitation in the range of motion in her wrists bilaterally.

While keeping an open mind and a broad differential, you consider whether this could be a case of systemic JIA?

Definition and Classification Criteria

Systemic JIA is one of the subtypes of JIA, the most common rheumatic disease in children. Like many rheumatic diseases, JIA and systemic JIA have classification criteria which were originally designed to classify relatively similar groups of patients for research purposes. While these classification criteria identify homogeneous groups of patients with a specific disease, they do not always capture the whole spectrum of presentations for a disease. Despite this limitation, they are often used in the clinical setting to aid in diagnosis.

Before delving into the classification criteria, let's briefly review making a diagnosis of arthritis. Arthritis is diagnosed when there is a swollen joint (effusion) OR if two or more of the following features are present: limited range of movement of a joint, tenderness on palpation of the joint line, or pain during range of movement, also known as stress pain.

The International League of Associations for Rheumatology has developed the current classification criteria for JIA. The criteria state that it is arthritis of unknown etiology, occurring before the age of 16, lasting for at least six weeks, and other causes of arthritis are excluded (e.g. infection, other systemic diseases like SLE or IBD). The classification criteria for systemic JIA are based upon the above criteria. To meet the criteria, there must be arthritis with or preceded by fever lasting at least 2 weeks that is daily for at least 3 days and accompanied by at least one of: nonfixed erythematous rash, generalized lymphadenopathy, hepatomegaly and/or splenomegaly, and serositis.

It is important to mention that there may soon be changes in the classification criteria for JIA. A revision of the classification of JIA was proposed in 2019 by the Pediatric Rheumatology International Trial Organization, but it has not yet been validated or formally adopted. Goals of this change are to create more homogenous groups of patients with arthritis as there is a better understanding of JIA since the previous criteria were adopted. They have proposed to define JIA as a group of disorders, not a single disease, occurring in children < 18 years of age. As well, types of JIA will no longer be classified based on number of joints involved, and one aspect will involve differentiating types of arthritis representing the childhood counterpart of adult arthritis (ex: enthesitis-related arthritis and ankylosing spondylitis) from chronic arthritis that is observed only in children. It will also allow for the classification of patients with systemic JIA without the requirement for six weeks of arthritis.

Presentation

Typically, patients with systemic JIA will present with a fever and a constellation of other systemic symptoms. The fever pattern is usually distinct in that it will spike to greater than 38.5 degrees once or twice daily and then fall to baseline or even slightly lower than baseline. Children will often feel and look very unwell during the fever spike and will feel

well in between. In many cases, a rash will accompany the fever spikes. The classical rash for systemic JIA is a salmon-colored macular or maculopapular rash that is transient. A clinical pearl regarding the rash is that it will often resolve when the fever subsides, distinguishing it from typical viral exanthems or drug rashes. A clinical sign that may be elicited is the Koebner phenomenon, the development of rash in areas of minor trauma, where gently brushing the skin can cause the development of linear maculopapular lesions.

Arthritis is another key clinical feature of systemic JIA, and it is currently necessary to meet the classification criteria. Notably, arthritis is not always present initially and may develop weeks to months later. It is often polyarticular and can affect any joint, but the knees, wrists, and ankles are most often involved.

Other clinical features of systemic JIA include generalized lymphadenopathy that is usually non-tender, hepatosplenomegaly, and serositis. With respect to serositis, pericarditis occurs more commonly than pleuritis. While symptoms such as chest pain with worsening upon lying flat may be suggestive of pericarditis, serositis may be asymptomatic and only detected by chest x-ray or echocardiogram.

Differential Diagnoses

The presentation of a fever with systemic symptoms leads to a broad differential diagnosis and it is important to first consider more common causes than systemic JIA that can lead to negative consequences if they are missed. We can categorically classify these other causes into several big groups: infectious, malignant, and autoimmune or other inflammatory conditions.

In terms of infectious causes, it will be important to consider viral and bacterial infections. Features that may suggest an infectious cause would include less predictable fever patterns, persistent rash, sick contacts, or other signs or symptoms of infection. An important infectious cause to consider on the differential is acute rheumatic fever, while a post-infectious causes to consider is reactive arthritis. The workup for a presentation suggestive of systemic JIA will typically include an infectious workup which, depending on the clinical picture, will likely include cultures, viral serologies, and other tests such as antistreptolysin O titres.

Important malignant causes to consider include leukemia and lymphoma. Clinical features that would be more in keeping with a malignant cause would include bone pain and tenderness not isolated to the joint, night-time pain, severe constitutional symptoms (e.g., night sweats, weight loss), or abnormalities in the CBC (e.g., low or high white blood cell count, low platelet count). Owing to the similarities in presentation with children with systemic JIA, there is usually a discussion as to whether a bone marrow biopsy is warranted to rule out leukemia or lymphoma. This is especially important when considering using corticosteroid therapy as treating patients with hematological malignancies with corticosteroids prior to diagnosis can make the diagnosis difficult, negatively affect their course, and risk a later diagnosis and lowered response to chemotherapy.

While there are many autoimmune or autoinflammatory conditions to consider on the differential diagnosis as well, some key conditions to think about include systemic lupus

erythematosus (SLE), inflammatory bowel disease (IBD, especially Crohn disease), and serum sickness. In SLE, there may be more characteristic skin features such as a malar or discoid rash, photosensitivity, abnormal urinalysis or autoantibodies present (e.g. anti-dsDNA). In IBD, there are typically more significant gastrointestinal symptoms, weight loss, oral ulcers. In serum sickness, there will be a causative agent, such as a medication, the rash is often more urticarial, and the fevers are continuous.

Workup

With this differential diagnosis in mind, investigations will be ordered based on the initial assessment. Laboratory features suggestive of systemic JIA include an elevated white blood cell count, an elevated platelet count (due to inflammation), and an anemia that is microcytic. Other inflammatory markers, including CRP and ESR, are elevated. Ferritin should also be checked and is typically elevated. Autoantibodies, including ANA and rheumatoid factor, do not help in making the diagnosis of systemic JIA and are usually negative, but they can be helpful when considering other differential diagnoses. Measuring ANA may be helpful if heavily suspecting a diagnosis of SLE as a negative ANA effectively rules out SLE.

Complications

Back to the case:

Anna was admitted from the ED to the General Pediatrics ward. You are now the first year resident on call that night and you get a call from the nurse the following morning asking you to come and reassess Anna. She has been febrile since she was admitted, and she seems more drowsy. When you go to see her, she is tachycardic and febrile but her other vital signs are stable. She is confused when you speak with her and on exam you now feel a splenic edge 2-3cm below the costal margin. Her repeat bloodwork scheduled for this morning shows a low white blood cell and platelet count.

What do you think is going on?

Systemic JIA is distinct from the other subtypes of JIA in many ways, one of which being that patients may have more severe symptoms at presentation with higher risk of morbidities associated with their disease. An important cause of morbidity is macrophage activation syndrome (MAS), a complication that can accompany systemic JIA, along with some other rheumatic and malignant disorders. MAS is a “ramped up” inflammatory process where there is an explosion in production of inflammatory cytokines from activated T cells and macrophages that can infiltrate organ systems.

Associated clinical features may include a fever that is now persistent, increasing hepatosplenomegaly, new encephalopathy, bruising or mucosal bleeding. Laboratory features may include pancytopenia, high serum transaminases, high triglyceride, low fibrinogen, elevated D-dimer, and high serum ferritin (often > 10 000 µg/L). Patients with MAS may rapidly deteriorate to multiorgan failure and may need hemodynamic support in the ICU setting; therefore, they must be managed promptly.

It is important to note that MAS may present similarly to sepsis, and there may be infectious causes of MAS, therefore an infectious workup including cultures and viral serologies along with antibiotic therapy may be warranted.

Treatment

Overarching treatment goals in systemic JIA include to reduce symptoms, control inflammation, and prevent complications. In children newly-diagnosed with systemic JIA who are stable, a course of NSAIDs may be used as initial therapy, as in other types of JIA. If there is not a rapid improvement or there is a worsening in symptoms, systemic corticosteroids and/or a biologic agent (anti-interleukin-1 or 6) are the next steps. Systemic corticosteroid treatment is associated with significant side effects, so effort is taken to limit the duration of steroid therapy in favor of biologics.

In children that are newly-diagnosed with systemic JIA who have severe symptoms or who have presented in MAS, the mainstay of treatment is prompt IV corticosteroid therapy. IVIg may be used prior to steroid therapy if children are stable and the diagnostic work-up is still ongoing with malignancy still not ruled out.

General Pediatrics Pearls

Systemic JIA is a rare disease, and it is important to be aware of it to hasten the diagnosis and reduce the risk of morbidities.

While the management of children with systemic JIA is usually overseen by a pediatric rheumatologist, this is in conjunction with their general pediatrician who will coordinate many aspects of their care. One important element of general pediatric management involves monitoring growth. Children with persistent disease and chronic inflammation may experience growth limitations and pubertal delay. Those treated with systemic corticosteroid treatment are at risk of weight gain and of delayed growth, thus should be monitored with regular discussions regarding healthy living practices such as healthy food choices and regular physical activity.

Monitoring for side effects of medications such as systemic corticosteroids is another key feature of long-term management. Regular blood pressure checks to monitor for hypertension, surveillance for steroid-induced diabetes, encouraging calcium and vitamin D intake for bone health, and coordinating annual eye examinations to assess for glaucoma or cataracts are all important elements of chronic management for patients on long-term systemic corticosteroids. As well, in these cases, there is also a risk of adrenal suppression with chronic supraphysiologic doses of corticosteroids, and stress dosing may be a consideration when children are unwell. Children may also experience immunosuppression when on chronic corticosteroids or biologics, therefore a plan should be arranged for prompt medical assessment in the event of a fever or infection.

General pediatrics providers can also provide support to patients and their families as they navigate the challenges of living with this chronic disease. Pediatricians may be able to arrange for any needed accommodations at school due to missed time and can coordinate further support for families by connecting them with local or national arthritis organizations.

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Summary

Here are some main takeaway points of this podcast episode:

1. The classification criteria of systemic JIA include arthritis, with or preceded by fever lasting at least 2 weeks that is daily for at least 3 days and accompanied by at least one of: nonfixed erythematous rash, generalized lymphadenopathy, hepatomegaly and/or splenomegaly, and serositis.

2. It's important to keep a broad differential diagnosis for a patient presenting with fever and systemic symptoms that includes infectious, malignant, autoimmune, and inflammatory causes.

3. MAS is a severe complication of certain rheumatic conditions such as systemic JIA that requires prompt recognition and management to prevent morbidity. It includes features such as persistent fever, worsening hepatosplenomegaly, new encephalopathy, bruising or mucosal bleeding, pancytopenia, high transaminases, and high ferritin.

4. The optimal management of patients with systemic JIA include both a pediatric rheumatologist overseeing management along with a general pediatrician who can provide longitudinal care monitoring growth, for medication side effects, and providing psychosocial support to patients and their families.

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