PedsCases Podcast Scripts

This is a text version of a podcast from Pedscases.com on an "**Approach to Recurrent Fevers.**" These podcasts are designed to give medical students an overview of key topics in pediatrics. The audio versions are accessible on iTunes or at www.pedcases.com/podcasts.

Approach to Recurrent Fevers

Developed by Josh Koegler and Dr. Dax Rumsey for PedsCases.com.
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Introduction

Hi, welcome to Pedscases. My name is Josh Koegler and I am a second year medical student at the University of Alberta working with Dr. Dax Rumsey, a Paediatric Rheumatologist at the Stollery Children's Hospital in Edmonton, Alberta. The topic for today is an approach to recurrent fevers in children, with a focus on rheumatologic causes thereof. Dr. Rumsey and I have worked together to bring you this podcast and we hope you will find it useful.

By the end of this podcast, you should be able to:

- List the broad categories that should be included in a differential diagnosis for recurrent fevers in children
- Describe key points on history for a child presenting with recurrent fevers
- Demonstrate a focused physical exam on a child presenting recurrent fevers
- Review 3 key rheumatologic diagnoses that include recurrent fever

Differential Diagnosis

The top 3 causes of recurrent fever are:

1. Infection,
2. Infection, and
3. Infection.

The other main categories are:

4. Rheumatologic/inflammatory and
5. Oncologic causes[1].

When building your differential diagnosis, it's important to remember that rheumatologic causes are rare and that infection and oncologic causes must be ruled out first, with multiple (or back to back) infections being the most common cause of recurrent fever[1].

Case

Let's move onto the case:

You are a medical student on a pediatric rheumatology rotation. You are asked to see a 5 year-old boy presenting with "recurrent fevers".

Take a moment to consider what questions you would ask this boy and his family on history.

History

Let's go through some important questions, focused on recurrent fevers, to add to your basic history.

A. History of Presenting Illness

1. Fever
First you want to identify if it is a true fever by asking: How was it measured? And what was the temperature? You also want to identify the characteristics of the fever. Ask about: Any patterns? Does the fever spike once per day (also known as quotidian)? Or is the fever persistent? You would also want to identify how many days the fever episodes last, what the time interval is between episodes, and how long they have been happening. Ask: Are there any obvious triggers for the episodes? How are they treating the fever? Does anything alleviate the fever? As well as: How is the child between episodes? In some conditions, patients may continue to suffer symptoms even after the fever has left or, in contrast, patients can be completely well between fever episodes. To help rule out infectious causes of the fevers: Ask about sick contacts, daycare attendance, travel, and the health of other family members during episodes.

2. Associated symptoms
It's also important to identify symptoms associated with the fever. Inquire about: Any rashes, oral ulcers, redness of the eyes, swelling of the lymph glands, sore throat, chest pain or shortness of breath, abdominal pain, as well as joint pain or swelling.
Keep in mind a potential oncologic cause of recurrent fevers and ask about:
Any changes in appetite or weight loss, changes in energy, night sweats, or nighttime pain.

B. Past Medical History
When discussing past medical history, remember to ask about any previous investigations during febrile episodes, including blood or urine cultures, throat swabs, and any other investigations. Cultures and swabs may identify infectious causes, but keep in mind that children with recurrent fevers can have infections overlapping with a rheumatologic condition, so one positive swab, does not rule out a rheumatologic cause.

C. Family History
When discussing the child's family history, two important things to ask about are consanguinity (as in, are the parents related in any way other than by marriage?) and ethnicity. Ask about anyone with autoimmune disease in the family, for example, juvenile arthritis, rheumatoid arthritis, psoriasis, inflammatory bowel disease, etc. Also ask about a family history of kidney disease.

Case

Let's get back to our case. You take a thorough fever history and discover that your patient has had these fevers since he was two years old. The interval between the fevers has been quite variable, with no obvious pattern, but the fevers usually last around two days. He often gets a bright red rash on his foot/ankle, severe stomach pain, and diarrhea when he has these fevers. He was born in Canada, but both parents are from Armenia and are first cousins. The patient has a grandfather currently on dialysis due to 'chronic kidney disease'.

Now that we are satisfied with the history, let's move on to the physical exam:
Before we discuss the physical exam, think of what you would look for in a patient with recurrent fevers.

Physical Exam

It's important to record the patient's vital signs, as well as their height and weight, and to plot these, noting any changes in growth over time. Look for conjunctivitis, lymphadenopathy, oropharyngeal erythema/exudate and oral ulcers (also known as apthous stomatitis). When performing the chest exam, make sure to look for signs of pleuritis, including friction rubs. In the abdominal exam, look for hepatosplenomegaly or peritoneal signs, including rebound tenderness. Complete a joint exam noting any joint effusions, tenderness, or limitation in range of motion, and a thorough skin exam for rashes.

Case

Back to our case: You perform a physical exam, but it is unremarkable. This is not unusual and it is important for the listener to take note that if the patient is not being examined during an episode, the physical exam can be completely normal.

So, now that you have an approach to the history and physical, let's take a moment to consider some of the main causes of recurrent fever in rheumatology.

Auto-inflammatory Conditions

In rheumatology, recurrent fevers can be associated with auto-inflammatory diseases. Let's start by defining what this means.

The innate immune system is the body's first line of defense against pathogens and includes cells such as macrophages and neutrophils. In contrast, the adaptive immune system is responsible for defense against specific pathogens. The adaptive immune system includes cells such as T cells and B cells, and antibodies.

The term auto-inflammatory is used to describe conditions where there is a dysfunctional innate immune system, which leads to seemingly unprovoked inflammation[2]. This is in contrast to autoimmune conditions, where we see dysfunction of the adaptive immune system, including self-reactive T cells and autoantibodies[3]. Although there is often overlap between autoimmune and auto-inflammatory conditions, when you hear auto-inflammatory, think about the innate immune system.
We will now talk about three of these auto-inflammatory conditions. Two of the conditions that we will discuss are known as periodic fever syndromes and one is a type of juvenile idiopathic arthritis (JIA). The first periodic fever syndrome we will discuss is PFAPA:

1. PFAPA:
    - Stands for Periodic Fevers with Aphthous Stomatitis, Pharyngitis, and (Cervical) Adenitis
    - It is the most common Periodic Fever Syndrome[4]
    - The typical length of the febrile episodes of PFAPA is 3-6 days[5] and
    - The interval between fevers is approximately 3-8 weeks[5]. For a given patient, these intervals are usually quite consistent and are described as "clockwork," with parents even being able to predict their child's next episode[6].
    - The typical features associated with the fevers are defined in the name. That is, aphthous stomatitis, pharyngitis, and cervical adenitis[6]. A child need not have all the features to get this diagnosis, however. Children with PFAPA are usually quite well in between fevers.
    - To date, there is no known genetic mutation that causes PFAPA[4] and
    - The condition is usually benign and outgrown. However, it can be quite disruptive to the life of the patient and their parents for many years if not successfully treated[6].

The second Periodic Fever Syndrome we will discuss is:

2. Familial Mediterranean Fever (or FMF)
    - FMF is an autosomal recessive single gene disorder and is the most common Periodic Fever Syndrome with a known genetic mutation[7].
    - FMF is most common in Mediterranean populations, especially Arabs, Armenians and Sephardic and Ashkenazi Jewish people.[8]
    - The length of the febrile episodes of FMF are usually 12-72 hours[6] and
    - The interval between fevers is variable[9]
    - Typical associated features include serositis (especially peritonitis), monoarthritis, and rarely an erysipelas-like rash (bright red rash, resembling a rash associated with streptococcal infection) on the lower extremities[6].

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- A serious potential complication of untreated FMF is amyloidosis, which is a build-up of amyloid in end organs, most commonly the kidney[9]. That's why, in the history section, we asked about a family history of kidney disease, as undiagnosed FMF can present as kidney disease. Despite the autosomal recessive inheritance pattern, it can show up in multiple generations, especially in cultures where consanguinity is common.

The third auto-inflammatory condition we will discuss is:

3. Systemic Juvenile Idiopathic Arthritis or sJIA
   - sJIA is one of the 7 types of Juvenile idiopathic arthritis and was formerly known as Still's Disease.
   - The fever associated with sJIA is described as lasting at least 2 weeks in duration with at least 3 days of quotidian (or daily spiking) fever, which classically reaches sub-normal temperatures in between spikes[10].
   - The fever is often persistent until treated. Once treated, patients can have flares of fever and associated symptoms over time.
   - Besides the fever, to be diagnosed with sJIA, a child must have arthritis and at least one other feature out of: typical rash [which is salmon-colored, often appears on the proximal extremities, and is evanescent[10] (meaning that it comes and goes, rather than being persistent)], generalized lymphadenopathy, enlargement of liver or spleen, or serositis.
   - Macrophage Activating Syndrome (or MAS) is a potentially life-threatening complication of sJIA[10].

Case

Now that we've learned about some rheumatologic causes of recurrent fever, what do we think was the cause of our patient's periodic fevers? …Yes, FMF. The patient had short fevers, erysipelas-like rash on the foot/ankle, and severe abdominal pain, was of Armenian descent, and his parents were consanguineous. We also noted a history of kidney disease in the family, may have been due to undiagnosed FMF. This diagnosis can often be made clinically, but it is useful to send genetic testing to confirm the diagnosis and prognosticate, depending on the mutation(s) found.

Fever Diary

In this case, we were lucky to obtain a lot of fever information on the history. However, many patients are not readily able to recall such information. A useful tool is to have families keep a fever diary with details about the frequency and patterns of fever, temperatures reached, potential triggers, associated symptoms, and dates of the episodes.

Take-Home Points

Well, we've reached the end of the podcast. Before we close, let's review some key points.

1. It's important to create a wide differential when dealing with recurrent fevers in children.
2. History is key. Identify if the episodes are truly fevers, the patterns of the fevers, and any associated symptoms.
3. Physical exam can be normal if you are not seeing the child during an episode.
4. Three major rheumatologic causes of recurrent fever are the autoinflammatory diseases PFAPA, FMF, and sJIA.
5. Although rare, it is important to diagnosis these conditions, as they can be disruptive to life, cause chronic complications, and even be life-threatening.Finally, remember to ask patients to keep a fever diary

Thanks for listening!

References

1. Torreggiani S, Filocamo G, and Esposito S. (2016). Recurrent Fever in Children. *International Journal of Molecular Sciences* 17(4):448.
2. Rigante D, Frediani B, and Cantarini L. (2016). A Comprehensive Overview of the Hereditary Periodic Fever Syndromes. *Clinical Reviews in Allergy & Immunology*. doi:10.1007/s12016-016-8537-8
3. Aksentijevich I and Kastner DL. (2011). Genetics of monogenic autoinflammatory diseases: past successes, future challenges. *Nature Reviews Rheumatology* 7(8):469–478.
4. Vanoni F, Theodoropoulou K, and Hofer, M. (2016). PFAPA syndrome: a review on treatment and outcome. *Pediatric Rheumatology Online Journal*. 14:38.
5. Thomas KT, Feder Jr HM, Lawton AR, and Edwards KM. (1999). Periodic fever syndrome in children. J Pediatr. 135(1):15–21.
6. Wekell P, Karlsson A, Berg S, and Fasth A. (2016). Review of autoinflammatory diseases, with a special focus on periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis syndrome. *Acta Paediatrica.* 105(10): 1140-1151.
7. Ozen S and Bilginer Y. (2014). A clinical guide to autoinflammatory diseases: familial Mediterranean Fever and next-of-kin. *Nature Reviews Rheumatology* 10:135–47.
8. Sohar E, Gafni J, Pras M, and Heller H. (1967) Familial Mediterranean fever: a survey of 470 cases and review of the literature. *The American Journal of Medicine* 43:227–253.
9. Padeh S and Berkun Y. (2016). Familial Mediterranean fever. *Current Opinion in Rheumatology*, 28(5):523–529.
10. Shenoi, S., & Wallace, C. (2016) Diagnosis and Treatment of Systemic Juvenile Idiopathic Arthritis. *The Journal of Pediatrics*. 177:19-26.

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