When to Suspect Autoinflammatory/ Recurrent Fever Syndromes

James W. Verbsky, MD, PhD

KEYWORDS

• Fever • Autoinflammatory • IL-1beta • TNF-α • Innate immunity

KEY POINTS

- Autoinflammatory disorders result in persistent or recurrent episodes of inflammation due to mutations in innate immune system sensors.
- Autoinflammatory disorders should be considered only after a workup for autoimmune disorders, malignancy, or immune deficiency.
- Once an autoinflammatory disorder is diagnosed, targeted therapies are often available.

BACKGROUND AND PATHOPHYSIOLOGY OF AUTOINFLAMMATORY DISORDERS

Inflammation, the classic quadrad of "rubor (redness), tumor (swelling), calor (heat), and dolor (pain)", is a fundamental concept of immunology and a common observation in clinical medicine. One could add "fever" as a fifth marker of inflammation, although it is not unusual to have inflammation without fever.

Inflammation is central to the function of the innate immune system that has evolved to recognize pathogens of all types, including fungi, bacteria, virus, protozoa, and helminths. This system is highly diverse, with multiple related and unrelated protein family members, likely due to the evolution driven by diverse pathogens. These protein families are often referred to pathogen recognition receptors (PRR) and they have evolved to recognize conserved microbial products, known as pathogen-associated molecular patterns (PAMPs). PAMPs are equally diverse, and include molecules unique to microbes, such as lipopolysaccharide (LPS), lipoteichoic acid (LTA), flagellin, and viral nucleic acids, among others. Because humans do not make these molecules, they are natural targets for recognition by the immune system.

This recognition of pathogens is the first line of defense of the immune system, and recognition by PRRs leads to rapid induction of inflammation. Inflammation by these different pathways is scripted, and thus consistent each time that pathogen is

Pediatric Rheumatology, Medical College of Wisconsin, Children's Corporate Center, Suite C465, 9000 West Wisconsin Avenue, PO Box 1997, Milwaukee, WI 53201-1997, USA
E-mail address: jverbsky@mcw.edu

Pediatr Clin N Am 64 (2017) 111–125
http://dx.doi.org/10.1016/j.pcl.2016.08.008 **pediatric.theclinics.com**

recognized. The response to subsequent challenges is no faster or of greater magnitude than the initial response; that is, the innate immune system does not "learn," but is essential to activate the adaptive immune system (ie, T and B lymphocytes) that does learn, and through the acquisition of memory is much more effective at clearing pathogens than the innate immune system.

Not all inflammation is alike, however, and different PRRs are activated by different PAMPs, resulting in differing responses. For example, antiviral PRRs activate the production of interferons that induce inflammation but also induce changes in stromal cells to help slow viral replication until the adaptive immune system can be activated. PRRs specific for LPS or other bacterial products lead to nuclear factor (NF)-κB activation and the generation of number inflammatory proteins. These pathways promote immune cell recruitment, production of stromal cell factors that aid in slowing microbial infiltration, and activate systemic pathways that help protect the host, such as the acute phase response.

Autoinflammatory syndromes are defined as disorders characterized by persistent or recurrent bouts of inflammation without features of autoimmunity (ie, autoantibodies or autoreactive T cells). These disorders are also referred to as periodic fever syndromes, although this nomenclature is falling out of favor as we learn more about these disorders. Many of these disorders exhibit inflammation without fever, and the inflammation can be persistent rather than episodic. Autoinflammatory disorders typical involve activating mutations in PRRs, or loss of regulatory proteins that regulate signaling of PRRs. Because the innate immune system does not exhibit memory and thus each inflammatory episode is of similar magnitude to past episodes, these bouts of inflammation can persist or recur for years before pathology occurs. In contrast, autoimmune disorders do exhibit memory, and thus autoimmune responses can ramp up quickly leading to serious illness in a relatively short period of time (Fig. 1).

When to Consider Autoinflammatory Disorders

When considering the diagnosis of an autoinflammatory syndrome in a child with recurrent fevers or inflammation, it is important to realize that fevers are a part of childhood and are overwhelmingly caused by innocuous infections. Autoinflammatory disorders should not be the first consideration of a child with recurrent fevers, as these are rare disorders. The initial workup of a child with recurrent infections should focus on ruling out more serious conditions, such as autoimmune disease, malignancy, or

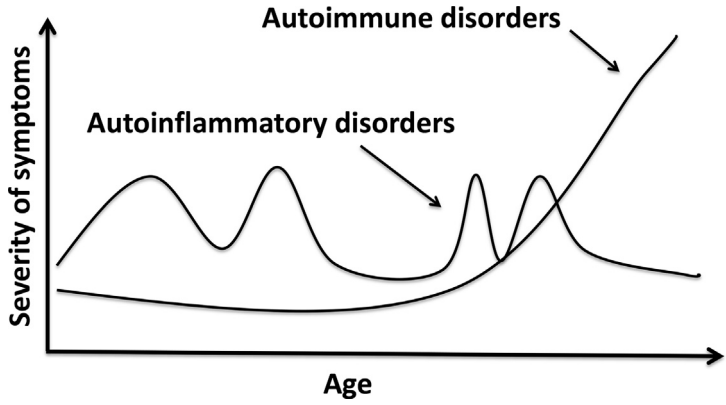

Fig. 1. Graphic representation of symptoms over time of autoinflammatory disorders and autoimmune disorders.