What are Autoinflammatory Diseases?

Sagar Bhattad

Abstract

Autoinflammatory diseases/syndromes are a new group of heterogeneous diseases characterized by "spontaneous onset of inflammation with no evidence of infection, autoimmunity or allergy and occur due to a defect in the innate immune system." With the advancement of molecular genetics and next-generation sequencing technologies, new diseases are being added to this list every year. In this review, a brief description of a few autoinflammatory diseases would be provided along with a clinical approach. Salient clinical features have been highlighted.

Keywords: Autoinflammatory diseases, Blau syndrome, Innate immunity, Periodic fevers.

Pediatric Infectious Disease (2020): 10.5005/jp-journals-10081-1275

Introduction

Autoinflammatory diseases/syndromes are a new group of heterogeneous diseases characterized by "spontaneous onset of inflammation with no evidence of infection, autoimmunity or allergy and occur due to a defect in the innate immune system."

Differential Diagnosis in a Febrile Patient

Conventionally, the list of differential diagnosis in a febrile patient would include

- Infection
- Autoimmunity
- Malignancy
- Allergy (though patients with allergic diseases, often, may not have fever)

One must add "Autoinflammation" as a differential diagnosis to this list!

Autoimmune vs Autoinflammatory: What is the Difference?

In order to understand this difference, one must be familiar with innate and adaptive immune systems (Table 1).

Autoimmune diseases are characterized by attack on self-antigen and tissues by autoreactive T and B cells—*a defect in the adaptive immune system*.

Autoinflammatory diseases are characterized by damage to one's own tissues by spontaneous inflammation caused by abnormally active innate immune cells (neutrophils, macrophages, etc)—*a defect in the innate immune system* (Table 2).

Table 1: Key features of innate and adaptive immune system

	Innate immune system	*Adaptive immune system*
Key players	Neutrophils, macrophages, dendritic cells	T cells and B cells
Key mediators	Cytokines	Antibodies
Line of defence	First line	Second line

Division of Pediatric Immunology and Rheumatology, Department of Pediatrics, Aster CMI Hospital, Bengaluru, Karnataka, India

Corresponding Author: Sagar Bhattad, Division of Pediatric Immunology and Rheumatology, Department of Pediatrics, Aster CMI Hospital, Bengaluru, Karnataka, India, Phone: +91 9779433934, e-mail: drsagarbhattad@gmail.com

How to cite this article: Bhattad S. What are Autoinflammatory Diseases? Pediatr Inf Dis 2020;2(3):122–124.

Source of support: Nil

Conflict of interest: None

More than 35 monogenic systemic autoinflammatory diseases (SAIDs) have been described to date.[1] With the advancement of molecular genetics and next-generation sequencing technologies, new diseases are being added to this list every year. In the next section of this review, a brief description of a few autoinflammatory diseases would be provided. Salient clinical features have been highlighted.

Periodic Fever Syndromes

The hereditary periodic fever syndromes are a group of monogenic diseases that present with recurrent bouts of fever and associated pleural and/or peritoneal inflammation, arthritis, and various types of skin rash (Table 3).

Table 2: Differences between autoimmune and autoinflammatory diseases

	Autoimmune diseases	*Autoinflammatory diseases*
Key system involved	Dysfunction of the adaptive immune system	Dysfunction of the innate immune system
Key players	Autoreactive T and B cells	Abnormally active innate immune cells
Damage caused by	Autoantibodies	Excess cytokines (IL-1, IL-6 etc.)
Examples	Lupus, rheumatoid arthritis, scleroderma etc.	Periodic fever syndromes etc.

Table 3: Periodic fever syndromes—A quick review

	PFAPA	*FMF*	*TRAPS*	*NOMID*	*MWS*	*HIDS*
Duration of each attack	4–6 days	< 2 days	Weeks (usually > 14 days)	Continuous	1–2 days	4–6 days
Age at onset	2–5 years	Childhood	Childhood	Neonatal	Childhood	Less than one
Mode of inheritance	Unknown	AR	AD	AD	AD	AR
Gene involved	Not known	*MEFV*	*TNFRSF1A*	*NLRP3*	*NLRP3*	*MVK*
Key clinical features	Oral ulcers, cervical adenopathy	Erythematous rash, pain abdomen	Migratory rash, pain abdomen, periorbital edema	Neonatal/ infantile onset fevers, deforming polyarthritis (epiphyseal bone formation, urticarial rashes)	Urticarial skin rashes, myalgia, arthralgia	Cervical lymphadenopathy, maculopapular rash
Complications	None (good prognosis)	Amyloidosis	Amyloidosis	SNHL, Aseptic meningitis, amyloidosis	SNHL	

PFAPA, periodic fever, aphthous stomatitis, pharyngitis and adenitis; FMF, familial mediterranean fever; TRAPS, TNF receptor-associated periodic fever syndrome; NOMID, neonatal onset multisystem inflammatory disease; MWS, Muckle-Wells syndrome; HIDS, hyper-IgD syndrome; AR, autosomal recessive; AD, autosomal dominant; SNHL, sensorineural hearing loss

Recurrent Fevers and Pharyngitis—Periodic Fever, Aphthous Stomatitis, Pharyngitis, and Adenitis Syndrome

Periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) usually presents between the age of 2 and 5.

Recurrent fevers, each episode lasting from 4 to 6 days, recurs at a fixed regular interval of 3–6 weeks. Fevers are associated with oral ulcers, tonsillitis, pharyngitis, and enlarged cervical nodes. Throat cultures are sterile. Inflammatory parameters are high during febrile periods.

These children are often misdiagnosed to have recurrent tonsillo-pharyngitis and given antibiotics with no relief. In all children with recurrent fever and pharyngitis, one must keep PFAPA as a possibility. A single dose of prednisolone (1 mg/kg) causes immediate defervescence and is diagnostic.[2]

Recurrent Fevers and Rashes: Hyper-IgD Syndrome

Hyper-IgD Syndrome (HIDS)

Onset <6 months of age.

Recurrent fevers, each episode lasting for 3 to 7 days.

Fevers associated with abdominal pain, diarrhea, nausea, vomiting, and macular rashes.

Diagnosis:

- Elevated mevalonate in urine during acute attacks
- Mutation in *MVK* gene (autosomal recessive inheritance)

Recurrent Fevers and Pain Abdomen: TRAPS

TNF Receptor-associated Periodic Fever Syndrome (TRAPS)

Onset in the first decade.

Recurrent fevers–each episode lasts for weeks.

Associated with severe pain abdomen (sterile peritonitis), periorbital edema, conjunctivitis, and erythematous macular rash.

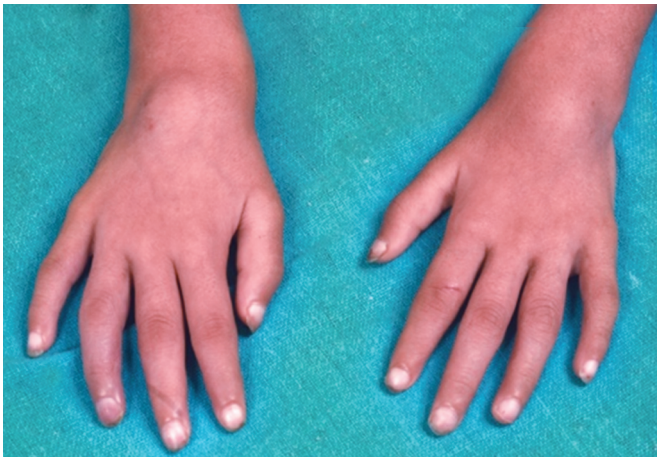

Fig. 1: Boggy swelling of the wrists in a child with Blau syndrome

Diagnosis–high inflammatory parameters, thrombocytosis.

Genetic studies—mutation in TNF receptor gene - *TNFRSF1A*.

Boggy Symmetric Arthritis and Granulomatous Uveitis—Blau Syndrome

Blau syndrome–early onset sarcoidosis

In children with symmetric polyarthritis, features that may point towards Blau syndrome are:

- Boggy swelling of synovium (Fig. 1)
- Granulomatous uveitis
- Rash–micropapular (skin biopsy: non caseating granuloma)
- Family history suggestive of arthritis and/or uveitis in either of the parents (autosomal dominant inheritance).

Blau syndrome is caused by mutation in *NOD2* gene.[3] Aggressive and timely treatment is warranted to prevent serious complications (blindness and permanent deformities).

Osteomyelitis as a Presentation

Chronic Recurrent Multifocal Osteomyelitis

Onset in childhood.

Children with chronic recurrent multifocal (CRMO) present with fever, bone pain, soft tissue swelling, and increased inflammatory markers. They are often misdiagnosed to have bacterial osteomyelitis. The features that must make one think of CRMO is involvement of multiple bones. Cultures are sterile. Bone scan or whole-body MRI would often pick up sites of bone inflammation with no clinical signs. In any child presenting with second episode of osteomyelitis OR multi-focal osteomyelitis, osteomyelitis affecting clavicle, one must think of CRMO. While there is no role of antibiotics, these children can be treated with NSAIDs and disease modifying anti-rheumatic drugs.[4]

Neurological Presentation

Aicardi–Goutieres' Syndrome

Infants presenting with developmental delay and intracranial calcification are often thought to have intrauterine CMV infection (the acronym TORCH syndrome is well known). In children presenting with developmental delay or regression and intracranial calcification, one must keep Aicardi–Goutieres' syndrome (AGS) as a differential diagnosis. These children often have skin rashes and raised inflammatory markers (features that distinguish AGS from congenital CMV disease).

AGS is a group of disease that belongs to type I interferonopathy. These children can be treated with JAK inhibitors and antivirals (reverse transcriptase inhibitors).[5]

Conclusion

- Every fever is not due to an infection!
- Autoinflammatory diseases are characterized by spontaneous onset of inflammation and occur due to a defect in innate immune system.
- Pattern recognition is the clue in making a timely diagnosis.

References

1. Havnaer A, Han G. Autoinflammatory disorders: a review and update on pathogenesis and treatment. Am J Clin Dermatol 2019;20(4):539–564. DOI: 10.1007/s40257-019-00440-y.
2. Vanoni F, Theodoropoulou K, Hofer M. PFAPA syndrome: a review on treatment and outcome. Pediatr Rheumatol 2016;14(1):38. DOI: 10.1186/s12969-016-0101-9.
3. Caso F, Galozzi P, Costa L, et al. Autoinflammatory granulomatous diseases: from Blau syndrome and early-onset sarcoidosis to NOD2-mediated disease and Crohn's disease. RMD Open 2015;1(1):e000097. DOI: 10.1136/rmdopen-2015-000097.
4. Buch K, Thuesen ACB, Brøns C, et al. Chronic non-bacterial osteomyelitis: a review. Calcif Tissue Int 2019;104(5):544–553. DOI: 10.1007/s00223-018-0495-0.
5. Vanderver A, Adang L, Gavazzi F, et al. Janus kinase inhibition in the Aicardi-Goutières syndrome. N Engl J Med 2020;383(10):986–989. DOI: 10.1056/NEJMc2001362.