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Review article

Insight into gastrointestinal manifestations of some pediatric autoinflammatory disorders

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List of abbreviations

AIFEC	Autoinflammation and infantile enterocolitis
CTLA 4	Cytotoxic T-Lymphocyte Associated Protein 4
DMARDs	Disease modifying antirheumatic drugs
GIT	Gastrointestinal tract
HA20	Haploinsufficiency of A20
IEI	Inborn errors of immunity
LRBA	LPS Responsive Beige-Like Anchor Protein
MKD	Mevalonate kinase deficiency
NLRC4	NLR-family CARD domain-containing protein 4
PEDBD	Paediatric Bechet's disease
SAIS	Systemic autoinflammatory syndromes
SJIA	Systemic juvenile idiopathic arthritis

Introduction

Human immune system's main function is the protection of the human body from invading pathogenic organisms and elimination of toxins and allergens (defence mechanism). Another function, of no less importance, is the ability of the immune system to discriminate between self and non-self-antigens. This ability of the immune response to avoid damaging self-tissues is referred to as self-tolerance. The immune system uses two main arms to perform these functions, the adaptive immune response, and the innate immune response. Both arms of the immune system work in an integrated manner linked together by a network of intracellular and extracellular cytokines.[1]

Gastrointestinal tract is a front-line organ inface of antigens, organisms, and parasites. It is an important organ in the first line immune response. The components of the innate and adaptive immune responses are well expressed throughout the GIT including innate immune cells, physical barriers, mucosal associated lymphoid tissue, secondary mesenteric lymphoid organs, proteins, secretory IgA, and intestinal microbiota. For these reasons, GIT is a common target to express disease in primary immune deficiency disorders, autoimmune disorders and autoinflammatory disorders. [2,3]

Systemic autoinflammatory syndromes (SAIS) are a heterogeneous group of rare hereditary diseases characterized by seemingly unprovoked antigen-independent pathologic inflammation. These disorders result from a genetic defect in the innate arm of the immune response. [4,5] Unlike autoimmune diseases, which result from defects in the adaptive component of the immune system, autoinflammatory syndromes usually lack the tissue-specific autoantibodies and the autoreactive T lymphocytes but possess other local tissue factors that induce the inflammatory response; this is a central differentiating point between autoinflammatory and autoimmune diseases. [6]

Systemic autoinflammatory syndromes present with diverse symptoms of unexplained pathological inflammation affecting almost all body organs mainly; fever, musculoskeletal manifestations, serositis, lymphadenopathy, skin, CNS involvement and gastrointestinal manifestations. This diverse clinical presentation makes the diagnosis of SAIS challenging and requires extensive clinical and laboratory workup to exclude other causes that can present with systemic inflammation as malignancy, acute and chronic infections, or rheumatic diseases. [6]

Gut involvement in systemic autoinflammation has been in the earliest descriptions of the autoinflammatory diseases. It may be either primary being a cardinal feature of the disease or as secondary feature related to medications or as just an association. Paediatric Bechet's disease, Very Early Onset Inflammatory bowel disease (VEOIBD), Haploinsufficiency of A20, NLRC4 and Mevalonate kinase deficiency, and DAD2 deficiency are examples of SAIS with GIT manifestations (Table 1). A wide range of symptoms may present in different disorders ranging from mild abdominal pain, oral ulcers, diarrhoea, bloody diarrhoea, malabsorption, polyps, granuloma formation or failure to thrive. Symptoms may present initially or develop gradually during disease course.

1. Paediatric Bechet's disease

Bechet's disease (BD) was first described in 1937 by the Turkish dermatologist Hulusi Bechet as a disease causing recurrent oral and genital ulcers.[7] It is a multisystem vasculitis that affect all types and sizes of blood vessels and can affect all body organs especially gastrointestinal, cardiovascular, ocular, and nervous system.

The exact pathogenic mechanism of Bechet's disease is still not fully understood; However, multifactorial inflammatory response had been described including infectious and environmental triggers in a genetically susceptible individual. Human Leucocyte Antigen B51 (HLA B51) is a known genetic predisposition to BD.[8]

A wide range of clinical manifestations in Bechet's disease including recurrent oral and genital ulcers, cutaneous lesions as erythema nodosum, acneiform lesions, papulopustular lesions. Ocular manifestations; posterior and anterior uveitis, retinal vasculitis, vitreous haemorrhage. Vascular involvement of both venous and arterial type as deep venous thrombosis and pulmonary artery aneurysm. [9]

Gastrointestinal manifestations in BD are more common in children than adults and include abdominal pain, diarrhoea, gastrointestinal bleeding. Mucosal ulcers tend to affect the ileocecal junction and can be differentiated from inflammatory bowel disease by the more specific morphology including round ulcers, number of less than 6, single or multiple distribution and absence of cobblestone appearance.[10]

Bechet's disease in adults and children is different in many clinical and etiological aspect. Arthritis and arthralgia and gastrointestinal system involvement, neurological findings, arthralgia and positive family history are more common in children. This is while genital lesions and vascular lesions are more common in adult patients. Several classification criteria for Paediatric Bechet's Disease (PBD) have been proposed, the widely accepted ones are proposed by the International Study Group. The new sets of classification criteria which is the only one for paediatric BD were also developed for paediatric cases by the PEDBD group. [11,12]

The primary goal for the treatment is preventing the organ damages by suppressing the ongoing inflammation and forestalling the disease flares. Lines of treatment include topical and systemic corticosteroids for oral ulcers. Colchicine is used as anti-inflammatory drug for the mucocutaneous manifestations. Methotrexate is useful in ocular and mucocutaneous manifestations, azathioprine is used in gastrointestinal, venous thrombotic manifestations, and gastrointestinal manifestations. Biologic agents namely anti TNF (Infliximab and adalimumab) are used as first line agents in neurologic involvement. Also in ocular, arterial and venous thrombotic manifestations. [10]

2. Very Early Onset Inflammatory bowel disease (VEOIBD)

Inflammatory bowel disease (IBD) comprises a group of autoimmune diseases with primarily gut inflammation. The underlying etiopathogenesis of IBD is not fully understood and it encompasses multifactorial environmental and genetic factors. Very early onset inflammatory bowel disease is a subgroup of IBD with onset present early before the age of 6. It can be further subdivided into infantile onset (before age of 2 years) and neonatal onset during the first month of life. [13]

Unlike IBD, VEOIBD has been linked to underlying genetic defects in genes of inborn errors of immunity. More than 70 candidate genes have been described. This underlying molecular defect can be detected in 15 to 20 % of VEOIBD cases. Underlying genetic disorders may include epithelial barrier defects, phagocytic disorders, Cellular defects, T regulatory cell defects, and autoinflammatory conditions. [14]

Interleukin-10 (IL-10) limits the secretion of proinflammatory cytokines, such as tumor necrosis factor α and interleukin-12, so it restricts the inflammatory response. Two types of IL10 receptors are present, IL-10 R1 and IL-10 R2. Autosomal recessive loss of function mutations in IL-10R and/or IL-10 encoding genes is one of the molecular bases of early-onset inflammatory bowel disease (EO-IBD). [15]

Patients may present with severe enterocolitis (bloody diarrhea, colonic abscesses, perianal fistula, and oral ulcers) associated with recurrent fever and failure to thrive. Skin and musculoskeletal manifestations include acute recurrent arthritis of large joints and recurrent folliculitis. Recurrent infections may indicate a defect in the immune responses in those patients. Evaluation of patients with VEOIBD requires high index of suspicion and multidisciplinary team of paediatrician, immunologist and gastroenterologist. Consanguinity or family history of similar immune disorders, history of recurrent infection, associated autoimmune of hyper inflammatory or immune dysregulation manifestations should be taken in consideration. Laboratory evaluation include flowcytometry of T and B cells, NK cells, immunoglobulin assay, vaccine response and

neutrophil exudative function. Flow cytometry assay of intracellular proteins as FOXp3, CTLA4, LRBA may be needed. Cytokine assay as IL1, IL18, TNF, IL 10 may be also useful. Finally molecular testing may give the underlying responsible mutation. [14]

VEO-IBD is refractory to standard immunosuppressants, and usually requires more therapeutic options according to the underlying identified or suspected IEI. Anti TNF agents (infliximab and adalimumab), anti IL1, Abatacept are possible therapeutic options based on the underlying genetic disorder, while hematopoietic stem cell transplantation (HSCT) has resulted in complete clinical remission in most transplanted patients with IL10 R defects. [15, 16]

3. Mevalonate kinase deficiency (MVKD)

Mevalonate kinase (MVK) associated periodic fever syndromes (OMIM #260920), also called hyper immunoglobulin D syndrome (HIDS), and it was formerly called "Dutch fever", was first described in 1984 by Van der Meer et al.[17] Defect in the MVK gene on chromosome 12q24 that encodes for the enzyme mevalonate kinase has been linked to HIDS in 1999. Mevalonate kinase enzyme acts on the mevalonic acid as a substrate and is the second enzyme of mevalonate pathway of cholesterol and nonsterol-isoprenoids biosynthesis.[18] The exact underlying pathogenesis of HIDS is not well understood, in one hypothesis, the shortage of mevalonate-derived intermediates, and in particular of geranylgeranyl pyrophosphate (GGPP), has been linked with the activation of caspase-1 and thereby with the production of the pro inflammatory cytokine IL-1β.[19]

Partial deficiency of MVK which results in hyper IgD syndrome. Fever attacks in HIDS are longer than in FMF but shorter than in TRAPS lasting around 7 days and recur every 4–8 weeks. Other symptoms that may accompany fever include abdominal pain, diarrhea, vomiting, arthritis, skin rash, mouth ulcers, splenomegaly and painful cervical lymphadenopathy. [20]

In HIDS, the diagnosis is made, as in all periodic fever, after exclusion of all other causes that may lead to recurrent febrile episodes. Increased levels of immunoglobulin D (IgD) (more than 100 IU/ml) is noticed in patients with HIDS, however, the IgD level may be normal to the age of three years and was found normal in some patients with genetically confirmed HIDS.[21] Moreover, IgD may be elevated in other periodic fever syndromes as FMF and TRAPS, so it is not specific for the HIDS. In most patients (80%) immunoglobulin A (IgA) is elevated to high levels. [22] The elevated IgA and IgD are of polyclonal origin, a matter that can exclude other causes of elevated IgA as multiple myeloma and other hematological malignancies. Enhanced excretion of mevalonic acid provide strong evidence for HIDS, however, level of excretion is markedly less than that is found in mevalonic aciduria (MVA) and may be only detected during the attacks with a lot of technical difficulties. The diagnosis is confirmed by low activity of mevalonate kinase or by demonstration of disease-causing mutations in the MVK gene.

Treatment options of MVA are limited and didn't result in complete improvement nor stopped the progression of neurological deficit. Administration of cholesterol in diet showed some improvement and stabilization of the clinical condition. Corticosteroids during the attacks resulted in suppression of the attacks and improvement within 24 hours. [23] For HIDS, colchicine and NSAIDs are not useful neither in the acute attack nor in the long-term treatment. Anti-IL-1 (anakinra, canakinumab) showed a favourable response in some patients recently and they can be given continuously in severe cases or as on demand treatment in some cases. Also, anti-TNF showed a good response in another group of patients, however, anti-IL-1 are to be considered as the first-line treatment.[23, 24]

4. Familial Mediterranean fever

Familial Mediterranean fever (FMF) (OMIM#249100) is the prototype of systemic autoinflammatory syndromes. It is the oldest and most common form of monogenic periodic fever syndromes, characterized by recurrent and self-limited episodes of fever and serositis. The earliest descriptions of FMF go back to first half of the 20th century when an episodic fever attacks with late fatal renal involvement were described, at this time it was called "Benign paroxysmal peritonitis"[25,26] and "periodic disease".[27] In 1958, Heller et al,[28] gave the current nomenclature "familial Mediterranean fever" to this fever syndrome that happens exclusively in persons from Mediterranean area. In 1997, the candidate gene for FMF, **ME**diterranean **FE**ver (**MEFV** gene), was concomitantly and independently identified by the French consortium and international consortium for familial Mediterranean fever.[29,30]

MEFV gene is a ten-exons gene located on chromosome 16 (16p13.3). It encodes for Pyrin, also called marenostrin (from the Latin mare nostrum "our sea"), which is a 781 amino acid protein.[29,30] Pyrin is expressed predominantly in the cytoplasm of cells of myeloid lineage; neutrophils

and macrophages, as well as synovial fibroblasts and dendritic cells. It is a major regulatory component of the inflammasome. Activation of the inflammasome by the mutated pyrin in FMF patients activates the caspase-1 leading to cleavage and activation of the proinflammatory cytokine interleukin-1β which is responsible for the inflammatory manifestations in FMF.[31] Additionally, pyrin takes part in the regulation of nuclear factor β (NF-β) activation and in regulation of apoptosis.[31] Dysregulation of the inflammasome due to mutated components underlies autoinflammatory diseases other than FMF including CAPS.

Clinically, FMF is characterized by self-limited short episodes of fever associated with peritonitis like abdominal pain, pleuritic chest pain, arthritis and erysipelas like rash. Not all the symptoms are present in each attack but either a single symptom or a different combination of them. The duration of the fever attack is short ranging from one to three days, it is the shortest duration among the periodic fever syndromes and may be as short as six hours. Gastrointestinal involvement commonly present in patient with FMF, severe peritonitis like abdominal pain is the classic feature of FMF. Other GIT manifestations include constipation or diarrhoea and vomiting during the attacks. Mucosal inflammation, ulceration and defects especially were detected on a good number of patients on endoscopic examination. Complications including amyloidosis and vasculitis can also affect the GIT. [32,33] Additionally, other inflammatory GIT disorders as IBD may be associated simultaneously with FMF in the same patient. Moreover; mutations in the MEFV gene were found in other inflammatory diseases including inflammatory bowel disease and rheumatoid arthritis without clinical FMF. [34]

Colchicine is the mainstay for treatment of FMF.[35] It was first introduced in 1972.[36] It is mainly absorbed in the jejunum and ileum, and it is metabolized by the liver and only small amounts are excreted unchanged in the urine. The exact mechanism of action by which colchicine prevents the attacks of FMF and suppresses the inflammation is not well understood. Colchicine related gastrointestinal disturbances and diarrhoea are quiet common side effects.[34]

5. Haploinsufficiency of A20

A recently described autosomal dominant disorder is caused by a heterozygous loss of function mutation in tumour necrosis factor (TNF)-α-induced protein 3 gene (TNFAIP3 gene) leading to haploinsufficiency of A20 (HA20). These mutations cause insufficient deubiquitinase (DUB) activity of A20 and lead to increased NF-κB signalling and phosphorylation of c-Jun N-terminal kinase and p38 mitogen-activated protein kinases (MAPKs). [37]

It is transmitted as an autosomal dominant disorder. Families present clinically with a (Bechet's like disease) and systemic inflammation in early childhood, recurrent fever, oral, genital ulceration, CNS vasculitis, arthritis or SLE like presentation, recurrent skin rash, uveitis. Recurrent upper respiratory tract infection, otitis media, and tonsillitis have been also reported in some patients.

Gastrointestinal manifestations in Haploinsufficiency of A20 are common with wide range of manifestations from abdominal pain to severe gut inflammation with intestinal perforation. Recurrent diarrhoea, malabsorption, and recurrent bloody diarrhoea giving the impression of inflammatory bowel disease. Before the description of this disorder, most of patients were diagnosed as Bechet's disease. Although typical similarities with polygenic Bechet's disease, several distinguishing features in patients with HA20 were reported including younger age at presentation, family history, scarring oral ulcers, recurrent fever, severe intestinal inflammation, elevated acute-phase reactants, the fluctuating presence of various autoantibodies, isolated anterior uveitis or retinal vasculitis with necrotising inflammation and a disease course refractory to standard lines of treatment in BD. Other common differential diagnoses include SLE, mixed CT disease and PFAPA. [37,38]

Laboratory evaluation of these patients revealed elevation of the acute phase reactants during the episodes of inflammation. Presence of autoantibodies like ANA, anti dsDNA in many patients complicates the clinical scenario and may lay behind being misdiagnosed as SLE. Diagnosis requires high index of suspicion; presence of family history of suggestive symptoms is a strong factor to suggest the diagnosis. [38]

Lines of treatment in haploinsufficiency of A20 include colchicine as a single agent or in combination with corticosteroids or methotrexate, anti IL1 and anti IL6, anti TNF, and thalidomide. Most of patients survive the disease course with repeated episodes of flare of systemic inflammation, however, CNS vasculitis and uveitis may be severe complications to HA20. [38,39]

6. NLR-family CARD domain-containing protein 4 (NLRC4)

A recently identified autoinflammatory disease was first described in 2014 as a gain-of-function

mutation in the gene encoding NLR-family CARD domain-containing protein 4 (NLRC4) in four patients with recurrent, life-threating episodes of autoinflammation and infantile enterocolitis (AIFEC). [40,41] NLRC4 inflammasome was initially identified in the cells of myeloid lineage, then it was identified in the lung and is well expressed in the GIT.

In AIFEC, early onset neonatal secretory diarrhoea has been described, associated with severe episodes of inflammation and MAS like presentation including fever, coagulopathy, hyper inflammation. A differentiating point between AIFEC and primary HLH is the markedly elevated level of IL 18 in AIFEC.

After the initial identification of NLRC4 to present with AIFEC and MAS like presentation, several other phenotypes have been described including recurrent fever, urticarial like rash, arthralgia and arthritis. Several agents have been used in treatment of NLRC4 including corticosteroids, anti IL1, anti TNF, while IL-18BP is the new drug target in several clinical trials. [41]

Table 1. Gastrointestinal manifestations of some autoinflammatory disorders in infants and children

Disorders		**Gastrointestinal involvement**
Periodic fever syndromes	FMF	Abdominal pain, diarrhea, vomiting, mucosal gastrointestinal ulceration, GIT disturbances with colchicine
	MKD	Abdominal pain, vomiting, diarrhea with the attacks
Haploinsuffiency of A20		Oral ulcer, recurrent diarhea, bloody diarrhea, mucosal inflammation, intestinal perforation
Very early onset inflammatory bowel dieases		Diarrhea, abdominal pain, mucosal inflammation , colitis, perianal ulceration
NLRC4		Episodic severe enterocolitis
NON monogenic disorders	Pediatric Behcet's diseases	Oral ulcers, perianal ulcers, diarrhea, gastrointestinal mucosal inflammation

Conclusion

Gastrointestinal involvement in systemic autoinflammatory syndromes is common with wide range of clinical presentations ranging from abdominal pains, oral ulcers to sever enterocolitis and inflammatory bowel disease. Thorough clinical evaluation with consideration of the possible differential diagnoses remains the cornerstone in the initial assessment of a patient, to provide the framework for subsequent investigations and management. Genetic testing is increasingly used in diagnosis and guiding therapeutic process. Emerging targeted treatments can be curative, control flares, and minimize sequelae.

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