Autoinflammatory Syndromes

John J. Cush, MD

KEYWORDS

• Autoinflammatory • CAPS • Periodic fever • Still disease

KEY POINTS

- Autoinflammatory disorders are enigmatic and diagnostic challenges for clinicians.
- Advances in understanding of genetic perturbations and role of the inflammasome have improved diagnostic and treatment approach to these disorders.
- Many of the autoinflammatory disorders are suggested on the basis of individual age, duration of (febrile) attacks, and cutaneous manifestations.
- Although many of the monogenic autoinflammatory disorders begin in neonates and children, adults may also be affected with new-onset or continued inflammatory disease.

INTRODUCTION

The autoinflammatory syndromes comprise a clinically distinct set of disorders unified by recurrent febrile episodes accompanied by inflammatory cutaneous, mucosal, serosal, and osteoarticular manifestations.[1–3] Although these rare disorders often have a striking onset and inflammatory features, they are without an infectious or autoimmune cause. Instead, many are unified by a genetically driven dysregulated innate immune response with resultant activation of the inflammasome and cytokine excess. Hence, these disorders respond to interleukin (IL)-1 or tumor necrosis factor (TNF)-α and generally not to immunosuppressives. Manifestations include periodic fevers, neutrophilic rashes or urticaria, serositis, hepatosplenomegaly, lymphadenopathy, elevated acute phase reactants, neutrophilia, and a long-term risk of secondary amyloidosis.

The identification of the genetic origins underlying certain disorders has rapidly advanced understanding of the immunopathogenesis of autoinflammatory disorders. Affected individuals often have first- or second-degree relatives with similar features. A monogenic defect has been identified for familial Mediterranean fever (FMF), TNF receptor–associated periodic syndrome (TRAPS), hyperimmunoglobulinemia D with periodic fever syndrome (HIDS), and cryopyrin-associated periodic syndromes (CAPS)—which include a spectrum of disorders: familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), and neonatal-onset multisystem inflammatory disease (NOMID). Additional disorders also fall under the autoinflammatory umbrella, because they manifest similar inflammatory features but may or may not have an identifiable genetic cause. Etiologic defects have been discovered for cyclic neutropenia; pyogenic arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome; pyoderma gangrenosum, acne, and suppurative hidradenitis (PASH) syndrome; deficiency of the IL-1 receptor antagonist (IL-1Ra) (DIRA); and deficiency of the IL-36R antagonist (DITRA). Those without a known cause include systemic-onset juvenile idiopathic arthritis (SoJIA);

Disclosures: Clinical investigator for Genentech, Pfizer, UCB, Celgene, Novartis, Amgen, NIH, and CORRONA; advisor and consultant to Janssen, Abbott, UCB, Pfizer, BMS, Amgen, Genentech, Savient, and Celgene. Dr Cush holds no stock or investments in these companies and does not partake in industry "speaker's bureaus" or give industry-guided "promotional lectures."
Funded by: NIH U19 082715.
Baylor Research Institute, Rheumatology Research, 9900 North Central Expressway, Suite 550, Dallas, TX 75231, USA
E-mail address: cushj@msn.com

Dermatol Clin 31 (2013) 471–480
http://dx.doi.org/10.1016/j.det.2013.05.001
0733-8635/13/$ – see front matter

adult-onset Still disease (AOSD); periodic fever, aphthous stomatitis, pharyngitis, and adenopathy (PFAPA) syndrome (or Marshall syndrome); and Schnitzler syndrome.[1–5]

Although these disorders are often rare, some are more frequently seen than others. A federally funded German registry was established in 2009 and in a 9-month period they identified 117 patients (65 male and 52 female; ages 1–21 years) with a diagnosis of FMF (n = 84), SoJIA (n = 22), clinically confirmed AIDS (n = 5), TRAPS (n = 3), CAPS (n = 1), HIDS (n = 1), and PFAPA (n = 1).[6] This review focuses on the distinguishing clinical features, onset, fever/flare duration, etiology, and effective treatments—each of which is crucial to establishing an accurate diagnosis.

ETIOLOGY

Immune responses are either innate or adaptive. The adaptive immune response recognizes self from nonself and generates antigen-specific cellular and cytokine responses, and, with activation-driven autoantibody production, the adaptive responses can establish immunologic memory or immune tolerance. By contrast, the innate immune response acts with immediacy to danger or pathogen signals, termed *pathogen-associated molecule patterns* (*PAMPs*) and endogenous *damage-associated molecular patterns* (*DAMPs*). PAMPs and DAMPs activate intracellular inflammasomes to set forth an inflammatory cascade of effector molecules.[3,4] For example, the NLRP3 inflammasome is a cytosolic scaffold of proteins triggered by PAMPs (microbial pathogens, monosodium urate, and toxins) and DAMPs (ATP, membrane disruption, oxygen radicals, and hypoxia). A disrupted, dysregulated innate immune system yields a proinflammatory state, with the final common pathway being activation of the NLRP3 gene and the inflammasome, with resultant unopposed cytokine excess. Activation of the inflammasome yields increased production of proinflammatory cytokines, such as IL-1, IL-18, TNF-α, IL-6, IL-17, type 1 interferons (IFN-α and IFN-β), and the complement system. The inflammasome is a complex of proteins that activates caspase-1, leading to cleavage of inactive pro-IL-1β to active IL-1β. The critical role of the inflammasome in these disorders has led some to refer to the autoinflammatory disorders as *inflammasomopathies*.[7]

TRAPS

TRAPS is also known as familial Hibernian fever, owing to a higher frequency of this syndrome in those of Irish, Scottish, or Austrian or Northern European dissent. Nevertheless, it has been described in other ethnic groups, including Mediterraneans. TRAPS differs from FMF and HIDS by having febrile attacks that last 1 to 3 weeks and occasionally up to 6 weeks. Characteristic features include fever, arthralgia, myalgia, migratory rash, abdominal pain, pleuritis, conjunctivitis, periorbital edema, oral ulcers, and scrotal swelling. Skin manifestations include migratory macular erythematous rash or patches, ecchymoses, edematous dermal plaques, serpiginous or annular lesions, and periorbital edema.[5,8,9] Limited skin biopsies showed perivascular and interstitial lymphocytic and mononuclear infiltrates without evidence of granulomatous or vasculitic change.

The genetics underlying this disorder was clarified by studies of a large Irish multiplex family who demonstrated an autosomal dominant syndrome characterized by recurrent fever, rash, and abdominal pain. Fevers last more than 5 days and less than 6 weeks. The vast majority (75%–88%) has childhood onset, usually as toddlers at approximately age 3 years and most occurring before age 10 years. Adult onset may occur. Manifestations of TRAPS depend on the mutations for the gene encoding p55 TNF receptor type I (CD120a). There are 46 known missense mutations involving TNF receptor type I, all of which are localized to distal chromosome 12p. The R92Q and P46L mutations are seen in 4% and 1% of the population, respectively, and tend to have low penetrance and less severe disease. The R92Q and T61I polymorphisms may be found with an adult onset and are often associated with rheumatoid arthritis, lupus, or multiple sclerosis. There is effective treatment with etanercept, which has been shown to reduce the frequency and severity of flares.[9] There are reports of efficacy with anakinra and worsening with infliximab.

HYPER IgD SYNDROME

HIDS is a rare disorder that begins early in life, usually before 2 years of age. Most reports have been seen in those of northern European, Dutch, or French ancestry.[1,2,10,11] HIDS has inflammatory symptoms lasting 3 to 7 days with recurrent fever, chills, cervical lymphadenopathy, abdominal pain, hepatosplenomegaly, diarrhea, arthralgia or arthritis, aphthous ulcers, skin rash (usually palmar/plantar), and headaches. Vaccinations may precipitate in inflammatory attacks in some patients. High levels of erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and serum amyloid A are seen, and IgD levels greater than 100 IU/dL are sensitive but not specific for HIDS. In 1999, mevalonate kinase (MVK) gene mutations