11-2023

Evaluating Patients With Recurrent Fever and Elevated IgD

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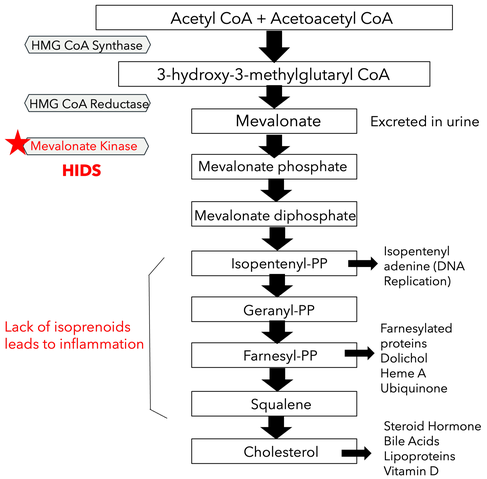
Introduction

- Hyperimmunglobulinemia D with Periodic Fever Syndrome (HIDS) also known as Mevalonate Kinase Deficiency is an autoinflammatory disease characterized by recurrent fever that may lack periodicity, chills, headache, diffuse tender lymphadenopathy, rash, and abdominal pain
- Febrile episode usually occur within the first year of life and last between 3 to 7 days
- It is usually precipitated by childhood vaccinations
- In evaluating patients with recurrent fever, a thorough history and examination is necessary to delineate between various periodic fever syndromes

Figure 1: Suspected Pathogenesis of HIDS



Clinical Course

- At 2-months-of age, she developed fevers as high as 104°F and required a hospital admission, but blood, urine, and CSF cultures were all negative
- She required re-admission due to persistent high-grade fever three days later and had repeat blood cultures and a whole-body scan, but no infectious etiology was determined
- She continued to have monthly fevers without symptoms consistent with an upper respiratory infection
- At 18-months-of age, she was diagnosed with Periodic Fever, Aphthous Stomatitis, Pharyngitis, and Adenitis (PFAPA)
- At 2-years of age, she had an adenotonsillectomy without resolution or improvement of the frequency of her fevers
- Fevers continued to range from one to two times a month and she would use prednisone with each febrile episode
- Other associated symptoms included headaches, body aches, pain, and fatigue
- At 10-years-of-age, due to her recurrent fevers an immunoglobulin (Ig) D was completed and elevated to 936 mg/dL and an elevated C-Reactive Protein (CRP) of 50.5 mg/dL
- It was recommended the patient continue to use prednisone as needed and to expect febrile episodes to improve and potentially resolve with puberty
- At 16-years-of-age, she presented to Children's Mercy Immunology clinic for evaluation
- Additional lab evaluation showed elevation in CD8+ cells, elevated IgG, IgD, and suboptimal pneumococcal titers
- Patient was started on cimetidine 600mg by mouth twice a day, with some improvement in her fevers
- Repeat labs 6 months later continued to show elevated IgD and improvement in pneumococcal titers after receiving Pneumovax-23
- Genetic testing for periodic fever panel confirmed diagnosis of HyperIgD syndrome (HIDS) with compound heterozygous pathogenic variants on *MVK,* c.1129 G>A and c.1139 A>G

Laboratory Evaluation

Labs Obtained at 16-years-of-age	
CBC w/ diff	Mild anemia, otherwise normal
Lymphocyte Subsets	Normal CD3+ and CD4+. CD8+ elevated to 1,274 mm3, normal CD19+ and NK cells
C-Reactive Protein	0.5mg/dL
Immunoglobulin G	1,350 mg/dL
Immunoglobulin A	164 mg/dL
Immunoglobulin M	232 mg/dL
Immunoglobulin E	85mg/dL
Immunoglobulin D	56 mg/dL
Diphtheria IgG	Normal (reactive)
Tetanus IgG	Normal (reactive)
Pneumococcal Titers	Suboptimal, 59% protection

Repeat Labs 6 Months Later	
CBC w/ diff	Mild anemia, otherwise normal
Immunoglobulin D	52 mg/dL
Pneumococcal Titers After Pneumovax	Appropriate response, now 100% protection

Diagnostic Criteria for HIDS

1. Polyclonal elevation of serum IgD (>100 IU/mL or >14.1 mg/dL) on two occasions at least 1 month apart
2. Autosomal recessive inheritance with noted mutations in *MVK,* located on chromosome 12
3. Increased urinary mevalonic acid during an attack

Differential Diagnoses for Recurrent Fever

	Familial Mediterranean Fever (FMF)	Tumor Necrosis Factor Receptor-Associated Periodic Syndrome (TRAPS)	Periodic Fever, Aphthous Stomatitis, Pharyngitis, and Adenitis (PFAPA)	Hyperimmunoglobulin D Syndrome (HIDS)
Age of Onset	Usually <20	Usually in adulthood	Usually ages 2-5	Infancy (<1 year)
Frequency and Duration of typical attack	Variable frequency, each lasts a few days (12-72 hours)	Usually last upward of weeks (longest individual fever episodes)	Usually occurs every 3-8 weeks and lasts for 3-6 days	Fevers last 3-7 days
Presentation	• Associated with abdominal pain (peritonitis) • Chest pain (pleuritis) • Arthritis • Erysipelas-like rash • Most serious side effect is amyloidosis (occurs in 10% of patients)	• Myalgia • Periorbital swelling • Conjunctivitis • Headache • Abdominal pain • Pleuritis with pleural effusion • Deep, migratory erythematous inflammation that migrates caudally	• Regular recurring fevers with early age • Sx with absence of URI • Exclusion of cyclic neutropenia • Completely asymptomatic between episodes • Must have at least 1 (exudative tonsillitis w/ negative culture, cervical lymphadenitis, aphthous stomatitis) • Normal growth and development	• Painful LAD (usually cervical) • Aphthous ulcers • Mild abdominal pain • Arthritis/Arthralgia • Skin findings such as erythematous macules or urticaria-like lesions

Discussion

- HIDS may be diagnosed with an elevated of IgD, but it can also be elevated in other autoinflammatory syndromes
- Utilizing other methods for evaluation such as genetic testing or elevated urinary mevalonic acid can provide additional information and allow for earlier diagnosis
- HIDS is considered a disorder of the inflammasome complex due to lack of regulation in the pyrin inflammasome
- Treatment for HIDS can include targeted anti-interleukin 1 (IL-1) therapy with either anakinra (an IL-1 receptor antagonist) or canakinumab (recombinant, human anti-human IL-1B monoclonal antibody) and result in significantly improved quality of life
- Our patient discontinued cimetidine and started anakinra, with significant improvement in her fevers without recurrence outside of a viral infection

Acknowledgement

We would like to thank Brenda Snyder, APRN who has also helped care for this complex patient.

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