H for Human Leukocyte Antigen (HLA)

(HLA B27 and HLA B51)

Introduction

The human MHC, known as Human Leukocyte Antigen (HLA) region, is located on chromosome 6. This genetic region contains Class I and Class II genes coding for “classical” antigen-presenting HLA glycoproteins involved in immune recognition and regulation.

HLA Class I molecules are expressed on all nucleated cells and are composed of HLA-A, HLA-B, HLA-C. HLA Class II molecules (HLA-DR, HLA-DP, HLA-DQ) are expressed on certain immune cells.

When should HLA B 27 be advised? What is the preferred method ?

Usually, we do the test in a young boy aged more than 6 years with

- Inflammatory lumbosacral pain and/or
- Sacroiliac (SI) joint tenderness or
- Acute symptomatic anterior uveitis (AAU) or
- Family history of HLA B27 associated disease (AS, ERA, Inflammatory bowel disease (IBD), ReA, AAU).

This is in accordance with the ILAR Classification of ERA.

The preferred method is always a PCR Method.

Practice tips - ‘B’ for Boy , ‘B’elow the umbilicus Joints(SI /Hips/Knees/ Ankle/Feet)=B27 (PCR)

(No need for an ANA or a rheumatoid factor in this clinical phenotype)

What are entheses ? How do children with enthesitis related arthritis (ERA) present ?

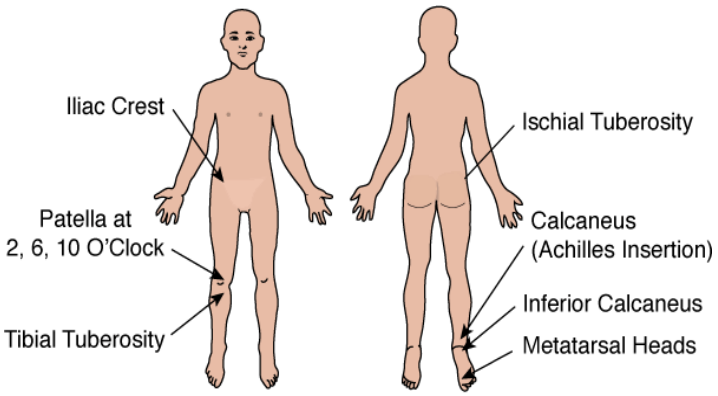

Fig 1. Common entheses in lower extremity

Children with ERA have inflammation predominantly affecting the joint and enthesis of the lower extremities which may eventually affect the SI joint. **Entheses are sites where ligaments, tendons, fascia, or capsules attach to the bone.** (Fig 1) The most common sites are insertion of the infrapatellar tendon on the tibial tuberosity, quadriceps insertion to the patella, and Achilles and plantar fascia insertion to the calcaneum. Children with ERA are also classified as Juvenile Ankylosing spondylitis (JAS)/ Spondylarthritis (JSpA) which categorize patients into axial and predominantly peripheral forms.

Role in Pathogenesis of HLA B27 in Enthesitis Related Arthritis (ERA) / Reactive arthritis (ReA) / Juvenile Ankylosing spondylitis (JAS)

HLA-B27 has three distinct mechanism which separate it from other MHC class I

1. Peptide binding specificity (Arthritogenic Peptide Hypothesis).
2. Tendency to form heavy chain homodimers.
3. Propensity to misfold→leads to excessive (Interleukin) IL-23 production →stimulates Th 17 cells to produce IL-17.

What are the clinical Implications of HLA B27 positivity?

HLA B27 is positive in 90 % of the children with JAS, 60-80% of ERA patients, 30-80 % of patients with reactive arthritis (ReA) and 20-35% of patients with psoriatic arthritis.

It does not constitute a diagnostic test but rather an indicator of risk and prognosis. It is associated with earlier disease onset, more inflammatory back pain, higher disease activity, decreased likely hood of remission or more likelihood of using biologicals.

The risk of developing some form of SpA in an HLA B27 positive individual in a general population is estimated to be around 5%.

HLA B51

What is the association of HLA B51 and Behcets disease ?

Pediatric Behcet disease (BD) belongs to variable vessel vasculitis characterized by **recurrent painful aphthous ulcer** (at least 3/ year), genital ulcers, skin lesions (Erythema nodosum, Pseudo folliculitis or papulopustular lesions, acneiform nodules), anterior/ posterior uveitis, arterial/ venous thrombosis, and neurological signs.

HLA B51 has got the strongest genetic association with BD. It is likely that B51 confers significant risk (Odds ratio of 3.49- 5.78), particularly in patients with a family history of rheumatic disease.

The frequency of HLA-B∗51 has been reported in 50–80% of patients with Behçet's syndrome in the endemic geographies. Though not diagnostic of Behcets , a positive HLAB51 does seem to affect clinical phenotypes (higher mucosal ulcers and ocular lesions and a lower risk of GI involvement .

Practice tip:- Not to be used routinely unless the clinical index of suspicion for Behcets disease is very high as its an expensive test .

Suggested reading

- Petty RE, Cassidy JT. Textbook of pediatric rheumatology. Philadelphia: Saunders Elsevier; 2016.
- Bodis G, Toth V, Schwarting A. Role of human leukocyte antigens (HLA) in autoimmune diseases. Rheumatology and therapy. 2018 Jun;5:5-20.
- Petty RE, Southwood TR, Manners P, et al. International League of Associations for Rheumatology (ILAR) classification of juvenile idiopathic arthritis: Second revision, Edmonton, 2001. J Rheumatol 2004;31:390-2.
- Kone-Paut I., Shahram F., Darce-Bello M., Cantarini L., Cimaz R., Gattorno M., Anton J., Hofer M., Chkirate B., Bouayed K., et al. Consensus classification criteria for paediatric Behcet's disease from a prospective observational cohort: PEDBD. *Ann. Rheum. Dis.* 2016;75:958–964. doi: 10.1136/annrheumdis-2015-208491.

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