AGA Clinical Practice Update: GI Manifestations and Autonomic or Immune Dysfunction in Hypermobile Ehler-Danlos Syndrome: Expert Review

By Jason Nasser, MD

Introduction: EDS, hEDS, and HSD

Hypermobile Ehler-Danlos syndrome (hEDS) accounts for up to 90% of EDS subtypes, which are characterized by musculoskeletal symptoms, joint hypermobility, and tissue fragility.

Hypermobility spectrum disorders (HSDs) can be diagnosed in patients with joint hypermobility and symptoms such as pain who do not satisfy diagnostic criteria for hEDS.

hEDS/HSD Associations

hEDS/HSDs are associated with postural orthostatic tachycardia syndrome (POTS), dysautonomia, and mast cell activation syndrome (MCAS).

Many experience GI symptoms, often diagnosed with a disease of gut-brain interaction (DGBI).

Mechanistic links include connective tissue pathology, vascular laxity, neuropathy, and autoimmunity. Infections are common triggers.

Screen all patients with DGBI for joint hypermobility via inquiry and ideally the Beighton score.

hEDS/HDS Diagnosis: 2017 International Criteria

Three criteria:

1. Beighton score for joint hypermobility
2. 2+ features of:
   a. Connective tissue pathology (skin, prolapse, hernias,…)
   b. Musculoskeletal pathology (pain, joint instability or dislocation,…)
   c. Family history (1st degree)
3. Absence of unusual skin fragility (suggests classical or vascular EDS)

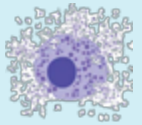
Test for POTS and/or MCAS if patients exhibit suggestive symptoms. Universal testing is not recommended.

POTS Diagnosis

- A symptomatic increase in heart rate of 30+ bpm within 10 min of upright posture (or tilt table test).
- Orthostatic intolerance should be present for at least 6 months without an alternative explanation.

MCAS Diagnostic Criteria

1. Clinical symptoms: episodic symptoms involving at least 2 organ systems (eg pain, pruritis, flushing, sweating, angioedema, wheezing, tachycardia, nausea, emesis, diarrhea, urogyn, neurological,…)
2. Biochemical evidence: increase in serum tryptase from baseline by 20% + 2 ng/mL within 1-4 hours of symptom onset
3. Response to therapy: with antihistamines/mast cell stabilizers



MCAS is divided into primary (clonal), secondary (IgE-mediated or other immune activation trigger), and idiopathic.

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Diagnosing MCAS cnt'd

Counting mast cells on biopsies has limited utility in MCAS, in which mast cells are often normal in count but abnormal in function/ degranulation. There is no consensus on cut-offs.

Consider referral to an allergy specialist or mast cell disease research center, where additional testing can be considered.
Tests can include urinary N-methylhistamine, leukotriene E4, and 11$\mathcal{B}$-prostaglandin F2.

Diagnostic evaluation of DGBI in patients with hEDS/HSD/POTS/ MCAS should follow a similar approach as in the general population.

Management

Start with standard treatments for GI symptoms/ diagnoses, **then add** specific therapies for POTS-/MCAS-related symptoms.

POTS-specific therapies: fluid intake of 2L/d, salt intake of 10g/d, exercise training, and compression garments. Refer non-responders to cardiology or neurology.

MCAS-specific therapies:

Medications: antihistamines (H1RA, H2RA), mast cell stabilizers (cromolyn, ketotifen), and leukotriene receptor antagonists (montelukast).

Trigger avoidance: specific foods, alcohol, odors, temperature shifts, mechanical stimuli, emotional distress, allergens (pollen/mold), and medications (opioids, NSAIDs, iodinated contrast).

Dietary therapy trials: low FODMAP, gluten-free, dairy-free, and low-histamine diets. **Discuss or refer for** nutritional guidance to avoid overly restrictive eating.

Association with celiac disease

Test for celiac disease early even in the absence of diarrhea.

Association with gastroparesis

Consider testing for gastric emptying and/or accommodation with upper GI symptoms.

Association with pelvic floor dysfunction (eg rectal hyposensitivity)

Consider testing with anorectal manometry, balloon expulsion test, or defecography in lower GI symptoms.