Features of Mast Cell Activation Disease in Patients with Mannose Binding Lectin Deficiency and EDS

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Isabelle Brock, MD[1]; Gigia Roizen, MD[2]; Walter Prendergast, BS, MBA[3]; Ilene Ruhoy, MD, Ph.D[4];
Clair A Francomano, MD[1]; **Anne Maitland, MD, Ph.D[3]**

[1]Indiana University School of Medicine, Indianapolis, IN, USA; [2]Clinica Alemana, Santiago, Chile; [3]Comprehensive Allergy & Asthma Care, Tarrytown, NY, USA; [4]Center for Healing Neurology, Seattle, WA, USA

MAIN FINDINGS

- **71% of MBL deficient patients diagnosed with hEDS**
- **URIs occured 10X more often in hEDS subgroup**
- **Recommend screening of hEDS/HSD patients for Mast Cell Activation Disorders**
- **Serum IgA levels were 10% lower in patients with EDS, compared to MBL deficient patients without a connective tissue disorder**
- **Potential impact of EDS on epithelial barrier function could be further investigated.**

BACKGROUND

We sought to identify the prevalence of mast cell activation disorders, including mast cell activation syndrome, in patients with mannose-binding lectin deficiency and hypermobile Ehlers Danlos Syndrome (hEDS) / hypermobile spectrum disorder (HSD).

Several studies have implicated an association between Ehlers-Danlos syndromes (EDS), a group of heritable connective tissue disorders, and mast cell activation disease (MCAD), but clinical studies, which elaborate the basis of these co-segregating disorders, are lacking. Here we show that two disorders, one, a primary immune disorder, the other, a prevalent connective tissue disorder, are associated with mast cell activation disease and disruption of the epithelial borders, leading to multi-organ system pathology.

METHODS

We retrospectively studied 987 patients seen in our allergy/immunology clinic, with suspected mast cell activation syndrome (MCAS), from 2017 -2020. We identified 56 patients with mannose-binding lectin deficiency, presenting with infectious and non-infectious multi-organ system involvement, including mucocutaneous, articular and systemic features. consistent with the hypermobile Ehlers Danlos Syndrome (hEDS)/hypermobile spectrum disorder (HSD).

RESULTS

Out of the 56 MBL deficient patients, 40 (71%) had been diagnosed with hEDS. Symptom distribution for all cases was as follows: Rhino-conjunctivitis (98%), Neurocognitive impairment (93%), Gastrointestinal symptoms (88%), Skin manifestations (Urticaria, angioedema) (78%), musculoskeletal complaints (93%), Asthma (55%), neuropsychiatric disorders (58%), Cardiovascular manifestations (60%), Orthostatic intolerance, POTS (58%), Anaphylaxis (35%), Dysuria (20%). A significant difference between hEDS/HSD and non-hEDS/HSD subgroups could be seen in cardiovascular and psychiatric manifestations, with the hEDS/HSD subgroup reporting symptoms 20% more often. Upper respiratory tract manifestations including infections occurred on average 10 times more often in the hEDS subgroup.

CONCLUSIONS

Among this cohort of patients with mannose-binding lectin deficiency, mast cell activation disorders and hypermobile Ehlers Danlos Syndrome (hEDS)/hypermobile spectrum disorders (HSD) are common. These observations implicate bi-directional influences of epithelial-derived factors and mast cell activation in barrier function and tissue homeostasis and prompt the recommendation for screening of hEDS/HSD patients, for mast cell activation disorders, including mast cell dysfunction secondary to deficiencies in other immune compartments.

Clinical features of mast cell activation disease in patients with MBL deficiency and Ehlers Danlos Syndrome

Symptom	All patients with MBL deficiency	With EDS diagnosis (number/%) Total 40 patients
Rhinitis	54 (96%)	39 (98%)
Neurological manifestations	50 (89%)	37 (93%)
Joints	44 (79%)	37 (93%)
GI manifestations	49 (88%)	35 (88%)
Skin manifestations	43 (77%)	31 (78%)
Asthma	29 (52%)	22 (55%)
Psychological (anxiety, depression)	30 (54%)	23 (58%)
Cardiovascular	27 (48%)	24 (60%)
POTS/ OI	26 (46%)	23 (58%)
Insect Allergies	22 (39%)	15 (38%)
Anaphylaxis	20 (36%)	14 (35%)