THE TRIPLE THREAT

POTS, MCAD & Connective Tissue Disorders by Lisa Klimas, MS

Dysautonomia refers to a group of symptoms that suggests poor control of the autonomic nervous system (ANS). Diminished action of involuntary control mechanisms results in a number of symptoms, including exercise intolerance, shortness of breath, excessive fatigue, and heart rate and blood pressure disturbances. A number of conditions are marked by autonomic dysfunction, including postural orthostatic tachycardia syndrome (POTS) and orthostatic intolerance (OI), among others. Dysautonomia is thought to affect over 70 million people worldwide.

Dysautonomia can occur secondarily to a number of other conditions. Associations have been made between autonomic dysfunction and heritable connective tissue disorders, including Ehlers Danlos Syndrome (EDS). These disorders are associated with a wide array of clinical manifestations and range from superficial to life-threatening. Most heritable connective tissue disorders are associated with known mutations, though some have no known associated mutation, as in hypermobility type EDS (HEDS).[1]

HEDS patients often suffer recurrent joint dislocations and chronic pain, but the symptoms most frequently linked to impairment and poor quality of life involve other systems. Symptoms can include syncope, palpitations, diarrhea, constipation, severe fatigue, and orthostatic intolerance. These can be triggered or worsened by standing upright, physical exercise, consumption of large meals, and exposure to heat, including hot water. Fatigue is the second most common patient complaint in HEDS, following pain.

One study found that in one cohort with HEDS, 74% of the patients had orthostatic intolerance, with POTS the most common form (41%). HEDS was associated with increased sympathetic activity while resting, including higher heart rate. Sympathetic compensation was diminished in response to cardiovascular challenge, such as tilt table tests and Valsalva maneuvers.[2]

Degree of skin extensibility was a significant predictor for severity of dysautonomia. Higher levels of pain were associated with increased heart rate during rest and testing. Findings point to insufficient vasoconstriction by sympathetic nerves.[3] Peripheral neuropathy has been offered by multiple researchers as the link between dysautonomia and heritable connective tissue disorders, but evidence is not yet available to support this suspicion.

The association of mast cell activation disease (MCAD) with EDS and dysautonomia has emerged over time. Mast cell activation disease (MCAD) is marked by allergic-type reactions in response to a variety of triggers, including foods, physical and emotional stress, temperature extremes, fragrances, vibration, and sunlight, among many others. These reactions primarily occur independently of IgE signaling. Common symptoms include flushing, hives, itching, GI symptoms, and sleep disturbances. MCAD patients can experience severe anaphylaxis to

seemingly inert stimuli that causes them to require aggressive management, including epinephrine.[4]

MCAD may be proliferative (systemic mastocytosis, SM) or not (mast cell activation syndrome, MCAS). MCAS offers a similar clinical experience without elevation of the most well-known SM marker, tryptase. Diagnosis often relies upon use of 24-hour urine tests for n-methylhistamine and D2 or 9a, 11b-F2 prostaglandin.

MCAD is marked by release of mast cell mediators, including vasoactive moieties, including histamine.[5] A 2006 paper reported the co-occurrence of mast cell activation in some POTS patients, as determined by urinary methylhistamine level ≥ 230 μg/g creatinine associated with a flushing episode. The population of interest in this study also demonstrated an increased heart rate of ≥ 30 mm Hg within five minutes of standing, as opposed to the more commonly observed orthostatic hypotension or gradual decrease in heart rate more often seen in patients with neurogenic POTS.[6]

The most common presentation of these co-occurring conditions is MCAS/HEDS/POTS. A recent communication found that in a cohort of 15 POTS/hypermobility patients, 66% of patients with verified POTS and EDS were positive for symptoms of a mast cell disorder.[6] This triple threat of dysautonomia, heritable connective tissue disorder, and mast cell activation disease can result in disability and poor quality of life for patients.

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3 De Paepe, A., Malfair, F., 2012. The Ehlers-Danlos syndrome, a disorder with many faces. Clin Genet. 82, 1-11.

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5 Shibao C. et al. Hyperadrenergic postural tachycardia syndrome in mast cell activation disorders. Hypertension 2005; 45:385-390.

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Lisa Klimas is a Senior Scientist at the Novartis Institute for Biomedical Research with expertise in both microbiology and molecular biology. With a focus on diagnostics development, she currently develops companion diagnostics for clinical trial drugs for both oncology and rare diseases. With microbiology expertise in infectious diseases, she has co-authored two papers on the use of FISH assays for diagnosing bloodstream infections. She received her BS in Biological Sciences and MS in Biology from the University of Massachusetts and has been working in research and development environments for many years. She is a strong believer that current, accurate health related information should be easily accessible to anyone who wants it, especially in rare disease communities. When she's not writing about mast cell disease and related conditions, she is talking fast, listening to punk music, doing yoga, hanging out with her dogs, avoiding undercooked egg whites and direct sunlight, and living a pretty great life with multiple chronic diseases.
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