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Cardiovascular Autonomic Dysfunction in Ehlers-Danlos Syndrome — Hypermobile Type

FOR NON-EXPERTS

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The autonomic nervous system controls important functions like heart rate and blood pressure. Problems with this system (autonomic dysfunction) contribute to a worse quality of life in the hypermobile type of Ehlers-Danlos syndrome (hEDS). Typical signs and symptoms include fast heart rate, low blood pressure, digestive system problems, disturbed bladder function and sweating regulation. Autonomic dysfunction that impacts the heart and blood vessels (cardiovascular) may cause symptoms when you stand up, like lightheadedness and fainting. The occurrence of these conditions aren't well understood, but specialists suggest they are frequently seen in hEDS. Checking cardiovascular symptoms in hEDS should include thorough examination and inquiry. Tests of autonomic function range from clinic room observation to more specialized techniques and laboratory investigations. Non-drug treatments are very important

in managing cardiovascular autonomic dysfunction in hEDS, but drugs may be useful for patients with significant impairment of daily function and who don't see benefit from other treatments.

Introduction

There is growing recognition of a link between autonomic nervous system dysfunction and Ehlers-Danlos syndrome—hypermobile type (hEDS). Many symptoms of autonomic dysfunction have been observed in hEDS, including heart and blood vessel (cardiovascular) issues, pupil, bladder, sweating dysfunction, and digestive system problems. The purpose of this review is to explore what is known about the association between cardiovascular autonomic dysfunction and hEDS, provide guidance on these in the context of hEDS, and consider areas for further research.

Associations and Evidence for Underlying Mechanisms in hEDS

The causes of cardiovascular problems in hEDS are unclear. Suggested mechanisms include: low blood pressure, increased blood pooling *e.g.* in the legs on standing or around the gut after eating, low circulating blood volume, medications with side effects that trigger or make problems worse, auto-immunity (immune responses to the patient's own body) to things that regulate heart rate and blood pressure as well as other autonomic functions, excessive amounts of chemicals related to allergy (histamine), and rarely, brainstem or spinal cord restriction.

Research has found an excessive ability to stretch in major blood vessels in those with joint hypermobility syndrome. A link between problems with standing in hEDS could be due to abnormal connective tissue in blood vessels with veins distending excessively in response to ordinary pressures when standing, although this has not been confirmed by research. This, in turn, could lead to increased pooling of blood in the lower half of the body, causing lightheadedness and sometimes fainting when standing up. Nerve damage, loose connective tissue, and medication have been suggested as playing a role in blood vessel problems in hEDS, although the exact mechanism is not clear at this time. In various patient groups (not specifically hEDS) researchers have found over-responsiveness to signals related to noradrenaline (also known as norepinephrine). One study found an overactive noradrenaline state in 29% of patients with an excessively fast heart rate upon standing (postural orthostatic tachycardia syndrome, POTS). Signs of immune attack against key parts of nerve signal transmission has been found in POTS and some people with low blood pressure on standing. These changes may be a relevant cause of symptoms in patients with

hEDS, but further research is needed. Some hEDS patients may have problems with their mast cells that can contribute to symptoms like low blood pressure or lightheadedness. Mast cells are immune system cells which help regulate allergic responses. When the mast cells respond to an allergic trigger, they release histamine and many other substances that can influence heart rate and blood pressure. Compressed nerves through overly moveable joints may also trigger cardiovascular problems that resolve after surgery.

Controversies

Certain heart valve problems can produce signs similar to autonomic dysfunction in hEDS. Heart valve conditions are not common in patients with hEDS, and in most cases is not harmful. Inactivity (deconditioning) and poor fitness are common findings in patients unwell with hEDS for a long time. Symptoms of cardiovascular autonomic dysfunction following a long period of reduced physical activity is not uncommon. Symptoms when standing have been related to deconditioning. However, as to which is the cause and which is the consequence remains open to debate. Increased physical fitness may improve cardiovascular autonomic problems. Research has shown that after a three-month training program, moderate gradual endurance and strength training can improve measures of cardiovascular health, and improve quality of life. The extent to which physical deconditioning triggers problems, and the role of physical reconditioning in managing symptoms, warrants further research.

Management and Care Guidelines

High-quality evidence for care and management best practice is lacking in hEDS autonomic dysfunction. Guidance is mainly based on expert agreement but draws on the evidence available from treating other patients with autonomic dysfunction. For a doctor, initially defining a patient's history is important: symptoms, triggers, modifying factors, impact on daily life, possible causes, and family history. Many of the common cardiovascular autonomic symptoms relate to changes in posture. They occur when changing from a lying or sitting to a standing position, or with maintaining upright posture, and are improved but not always completely relieved by sitting or lying down.

The more common symptoms of cardiovascular autonomic dysfunction are: fast heart rate (tachycardia), palpitations, lightheadedness, a temporary greying out of vision, limited concentration and poor memory (often described by patients as "brain fog") with mental performance problems including word finding difficulties,

chest pain, shakiness, long-term tiredness, exercise intolerance and feeling worse after exercise, swelling and/or discoloration in the legs after standing for short periods of time, cold, dusky hands and feet, temperature dysregulation, sleep disturbance, and a sense of being about to blackout or actually fainting. The history may reveal states that trigger or exacerbate these symptoms – heat, prolonged standing, alcohol, dehydration, having a cold, *etc*. A detailed examination is always warranted. Other common causes of low blood pressure or fast heart rate should be considered, like medications, dehydration and deconditioning. Formal evaluation of cardiovascular autonomic dysfunction should be made with a tilt table test usually done by an autonomic neurologist or electrophysiologist, but if this if not available, a simple clinic room ten-minute standing test can help assess whether a brief period of standing can provoke symptoms upon standing.

Treatment

Several treatments used together are often needed. There is not yet evidence for specific treatments for hEDS subgroups. Education, advice, and non-drug treatments should be offered first to all patients, and include education on avoiding or reducing exposure to triggering factors, withdrawing medications that might worsen symptoms, maintaining good water intake and salt balance, raising legs when resting, compression garments, increasing exercise (adapted to hEDS needs). When prescribing exercise, the program might be adapted: aerobic activities with a local resistive component, dynamic exercise (involving joint movement), exercising lying down, exercising in water (depending on temperature). Training at a target heart rate of 75% of the estimated maximum heart rate (explain how to calculate this) for about 30 minutes per session, two to three times per week is advised, adapted according to level of disability. Increase of fluid intake, with added sodium, and the use of medical compression stockings during and after exercise can be helpful. Meals should be avoided one hour prior to an exercise session. To prevent a sudden drop in blood pressure after training, a person should cool down with more gentle movements. In those with more significant impairment of daily function, and poor response non-drug treatments, medication that may help include: fludrocortisone, midodrine, beta blockers, ivabradine, methylphenidate/dextroamphetamine, hormonal contraceptives, desmopressin, pyridostigmine, clonidine, dihydroxyphenylserine, and octreotide. Saline infused into a vein over one to two hours may help in extreme cases, but carries risks.

What We Need to Know

The occurrence and cause of cardiovascular autonomic dysfunction in the hEDS population are poorly understood. Clinical trials are required to move beyond the limitations of current evidence and expert opinion. Studies also need to assess the effect of treatment on quality of life and tiredness.

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