ORTHOSTATIC INTOLERANCE AND CHRONIC FATIGUE SYNDROME - POSSIBLE RELATED CONDITIONS

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ORTHOSTATIC INTOLERANCE AND CHRONIC FATIGUE SYNDROME - POSSIBLE RELATED CONDITIONS (Abstract): The connection between orthostatic intolerance and chronic fatigue syndrome was first introduced in 1995. It was demonstrated that many patients with chronic fatigue syndrome also had some form of orthostatic intolerance. Some studies suggested that dysautonomia may be the common problem in patients with these syndromes. Although these conditions affect an important number of people, especially younger adults, orthostatic intolerance and chronic fatigue syndrome are among the least understood of the autonomic disorders and sustained research is focused particularly on elucidating their pathogenesis and identifying the most effective methods of treatment. Keywords: ORTHOSTATIC INTOLERANCE, CHRONIC FATIGUE SYNDROME, AUTONOMIC NERVOUS SYSTEM, DYSAUTONOMIA.

Although it is a condition that affects an important number of people, especially younger adults, orthostatic intolerance (OI) is one of the least understood of the autonomic disorders and it is the subject of a sustained research particularly focused on elucidating the pathogenesis and identifying the most effective methods of treatment. It is known by various names: „irritable heart”, „neurocirculatory asthenia”, „partial dysautonomia”, „hyperadrenergic orthostatic hypotension”, „vaso-regulatory asthenia”or „soldier's heart”. This syndrome has described by Da Costa in 1864, during the American Civil War, affecting young soldiers under physical and mental stress and characterized predominantly by cardiovascular symptoms in the absence of organic suffering (1).

In 1996, following a multidisciplinary conference under the auspices of the American Academy of Neurology and the Autonomic American Society, a brief definition of orthostatic hypotension (OH) was published (2). In Europe, the first guidelines for the management of syncope that included orthostatic intolerance syndromes (OIS) were published in 2001 and reviewed in 2004 by the European Society of Cardiology. To highlight the importance of this problem and because of the increasing number of studies regarding this issue an
update was necessary, the latest version of the guidelines, published in 2009 in the European Heart Journal, was developed in collaboration with the European Heart Rhythm Association, Heart Failure and Heart Rhythm Society Association (1). A few years later, progress in understanding OH and OIS has made it necessary to clarify and expand the original definition, so that in 2011, by a consensus statement endorsed by the American Autonomic Society, the European Federation of Autonomic Societies, the Autonomic Research Group of the World Federation of Neurology and the Autonomic Disorders Section of the American Academy of Neurology the definition, path physiology and clinical forms of the OH were updated and published. Also added were the definitions of two highly prevalent disorders of OI: neurally mediated (reflex) syncope and postural orthostatic tachycardia syndrome (POTS) (2).

The connection between OI and CFS was first made public in 1995 by Peter Rowe, MD and associates at Johns Hopkins University, who identified a type of OI called neurally mediated hypotension in CFS patients. Since that year, scientists have learned much more about the kinship between OI and CFS.

ORTHOSTATIC INTOLERANCE–CLINICAL, EPIDEMIOLOGICAL AND PATH PHYSIOLOGICAL ASPECTS

Orthostatic intolerance is the development of a set of characteristic symptoms while standing or sitting upright such as dizziness/lightheadedness, pre-syncope, syncope; weakness, fatigue, lethargy, palpitations, sweating, visual disturbances, hearing disturbances (including impaired hearing and tinnitus) and pain in the neck (occipital/paracervical and shoulder region), low back pain, or precordial pain (3, 4). These conditions are a result of inappropriate reflexive bodily responses, regulated by the autonomic nervous system, to compensate the effect of gravity upon the distribution of blood. Predominately in younger individuals, often under the age of thirty five, these syndromes affect more women than men, both children and adults (3, 4, 5, 6, 7, 8, 9, 10).

According to the 2009 syncope management guidelines, there are three clinical forms of OI, and, of all, POTS is frequently associated with chronic fatigue syndrome (CFS). This condition affects mostly young women (11) in a 5:1 ratio over males and most patients are between 20 to 40 years of age (12). They present with severe complaints of OI, but not syncope, symptoms of cerebral hypo perfusion and autonomic over activity that are relieved by recumbence (2), marked increase in heart rate, greater than 30 beats/min, usually to 120 beats/min or higher, and transient systolic blood pressure decrease of more than 20 mm Hg, with recovery within the first minute of tilt (13), criteria that may not be applicable for individuals with low resting heart rates. For individuals aged 12–19 years the required increment is at least 40 beats/minute.

The etiology and pathophysiology of POTS are unknown, but are likely to be heterogeneous. According to Braunwald, major mechanisms are denervation (neuropathic postural orthostatic tachycardia syndrome), deconditioning, and a hyper adrenergic state, each of these three major mechanisms being exacerbated by hypovolemia (12, 13). An important aspect is that the syndrome is also associated with recent viral illness, a limited or restricted autonomic neuropathy, and CFS (2).
CHRONIC FATIGUE SYNDROME—CLINICAL, EPIDEMIOLOGICAL AND PATH PHYSIOLOGICAL ASPECTS

Chronic fatigue syndrome is the common name for a group of significantly debilitating medical conditions. It is characterized by new, unexplained fatigue that lasts for at least 6 months, is unrelieved by rest, is not due to exertion, is not caused by other medical conditions (14) and may be worsened by physical or mental activity. It is also known as chronic fatigue immune dysfunction syndrome, myalgic encephalomyelitis, post-viral fatigue syndrome or by several other terms.

Although biological, genetic, infectious and psychological mechanisms have been proposed, the etiology of CFS is not clearly understood and it may have multiple causes.

We know that symptoms may vary in number, type, and severity from person to person and, unfortunately, there is no specific diagnostic laboratory test or biomarker for chronic fatigue syndrome (15). Although it’s name does not express the importance of this illness, CFS brings with it a number of debilitating symptoms: bone-deep fatigue, which is accompanied by other symptoms like sleep difficulties (falling asleep, staying asleep and waking up feeling unrefreshed), concentration and short-term memory problems, joint pain (without swelling), muscle pain, tender lymph nodes, sore throat, and headache. A distinctive symptom is post-exertional malaise, a worsening of symptoms following even very modest physical or mental exertion that can persist for days or weeks. About 25% of people with this syndrome are fully disabled by the illness (16).

Because these symptoms are common with many other conditions and in the absence of any specific laboratory test or biomarker, it is frequently misdiagnosed. Even so, at least one million people in the United States are affected and many others worldwide (17). Another research has shown that CFS is about four times as common in women as men, but it does not make any differences when it comes to age, racial, ethnic and socioeconomic group (18, 19).

We know now that CFS is not a form of depression, and many patients have no diagnosable psychiatric disorder. Also, some abnormalities of the brain have been found in CFS patients using magnetic resonance imaging scans, single photon emission computed tomography and positron emission tomography, predominantly affect the temporal lobes of the brain. Cognitive impairment is common in these patients, the most frequently documented abnormalities being the difficulty in information processing, memory, and/or attention.

CFS patients have disordered expression of genes that are important in energy metabolism.

They have a state of chronic low-grade immune upregulation and substantial evidence of poorly functioning natural killer cells. There is a growing body of evidence of more frequent latent active infection with various herpesviruses and enteroviruses in CFS patients, Epstein Barr virus and cytomegalovirus. Other infectious agents can also trigger CFS, including the bacterium that causes Lyme disease, Giardia duodenalis, West Nile virus and human parvovirus B19.

Abnormalities of the autonomic nervous system have been found by numerous independent researchers. These include a failure of the body to maintain blood pressure several minutes after a person stands up,
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abnormal responses of the heart rate to standing, and unusual pooling of blood in the veins of the legs. Some have also found low levels of blood volume (20, 21).

DISCUSSION

It was demonstrated that many CFS patients (up to 97% in some studies) have some form of OI and it seems to be a particular problem in young people (3, 10, 22, 23, 24). Some studies have suggested that dysautonomia may be the common problem in patients with this syndrome. During tilt-table testing, more than 60% of patients with CFS show abnormal blood pressure or heart rate responses (sudden hypotension or severe bradycardia or tachycardia), along with decreased consciousness (12). OH can result in fainting very quickly after standing and can be diagnosed with a simple in-office test (measuring the blood pressure first while lying down and again upon standing) (3). Unlike patients with OH, in which case the drop of the blood pressure occurs within the first three minutes of standing, chronic fatigue syndrome patients with OI often have a delayed form of OI (25), meaning that the changes do not develop for many minutes after standing, the standard test for acute OH being ineffective in diagnosis. A tilt table test in CFS is considered to be positive if a patient experiences orthostatic symptoms and blood pressure and/or heart rate changes, whether or not he or she faints (3, 5).

There are several hypothesized causes of OI syndrome relevant to CFS, all leading to inadequate blood circulation that may reduce the amount of blood getting back to the heart and brain. Researchers have also identified several physiological abnormalities in CFS patients that are related with autonomic nervous system problems such as POTS. In five studies, adults and adolescents with CFS had elevated heart rates at rest compared to healthy and sedentary controls (8, 10, 23, 26, 27), although two studies found no difference (5). Heart rate further increased when patients underwent a tilt test, a common finding in POTS (3, 8, 10, 27, 28, 29). In addition, three studies - one in adults (27) and two in adolescents (9, 30) found that heart rate variability is significantly reduced in CFS compared to controls. This means that instead of having a heart rate that change appropriately when faced with orthostatic stress, many CFS patients have reduced modulation of their heart rate, suggesting impairment of the autonomic nervous system (9). In contrast, one study of adults with CFS found that heart rate variability is similar to that in controls (3, 30). An important issue is that the effective treatment for patients with OI and CFS must be individualized. Since no cause or cure has been identified, treatment programs should be directed at relieving symptoms, which can allow patients to live almost a normal life (21).

The first line of treatment should be non-medical interventions, such as increasing fluids and salt intake, tilting the head of the bed up a few degrees, wearing compression garments and learning to avoid the situations that can make OI worse (standing in long lines, being in warm environments, and eating large, heavy meals)(4). Also, the therapeutic importance of exercise training and improved physical conditioning is becoming an important strategy for the deconditioned patient (12). Because they often experience guilt, anger, anxiety and depression, it is important to include counseling for emotional and mental health. Educating patients, cognitive behavioral therapy, a form of psychological therapy
often used to treat chronically ill patients are moderately effective treatments (31, 32) that, sometimes, can be useful in treating some patients (30). If these are not effective, doctors may initiate pharmaceutical treatments (4).

Whether relief of any dysautonomic symptoms in these patients may relieve the symptoms of fatigue is unclear. In general, treatment for POTS helps greatly to alleviate some symptoms, but rarely fully resolves the CFS (3).

**CONCLUSIONS**

Further research is required to determine how orthostatic intolerance is involved in chronic fatigue syndrome. It is clear from past studies that orthostatic intolerance is associated with chronic fatigue syndrome, but the degree and meaning of that association is still a focus of vigorous research (3).

**REFERENCES**

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