NEW EDEN SCHOOL OF NATURAL HEALTH

A Holistic View of Postural Orthostatic Tachycardia Syndrome (POTS)

A DISSERTATION

SUBMITTED IN FULFILLMENT OF THE REQUIREMENTS

for the degree

DOCTOR OF TRADITIONAL NATUROPATHY

NEW EDEN SCHOOL OF NATURAL HEALTH

By

Christina Morgan

2019

Acknowledgements

I would like to thank all of those who have helped me along the way during my healing journey these last few years. This includes my many friends, family members, health practitioners and instructors who have all been so instrumental in teaching me. You are all very dear to me.

The subject of Postural Orthostatic Tachycardia Syndrome (POTS) is a very personal one. I became debilitated with POTS in December 2012. I first pursued traditional medicine, which included dozens of doctors, specialists, hospital visits, medications, and tests. After realizing that this got me nowhere and I found myself again at square one, I began researching natural healing. I came across a few people who had been healed of POTS, or put it into remission. I only saw these stories on natural health blogs or social media groups, and not in the groups focused on traditional medicine. I began implementing strategies and ideas based on the concept that the body is a whole system, and cannot be successfully treated by attempting to compartmentalize, or separate out, and treat individual body systems. Based on my success with natural healing methods, including also putting my POTS symptoms into remission, along with a newfound drive to begin helping others follow a similar path to health, I began studying to complete my Naturopathic Doctor degree.

This paper is the result of numerous hours and months of research, and attempting to dig further into the research of POTS to find ways to marry both the documented scientific research and naturopathic or holistic principles.

I sincerely hope that the information presented helps others who are in need and inspires new ideas for further research.

Table of Contents

Introduction

Postural orthostatic tachycardia syndrome (POTS) is a form of dysautonomia, which is a dysfunction of the Autonomic Nervous System (ANS). There is currently no known root cause for POTS, and therefore, also no cure. Traditional medicine focuses solely on symptom management in POTS patients.

There has been an overall lack of understanding of what exactly causes POTS in previously healthy patients. The objective of this research is to uncover and propose possible etiology connections, which may allow scientists and practitioners to further research and knowledge for this syndrome.

Context / Framework for Understanding

POTS is a syndrome that is still not yet widely recognized, however, it is not considered a rare disorder by definition, as it is estimated to impact between 1 and 3 million Americans, with 80-85% being female and mostly of childbearing age.[1]

The current diagnostic criteria is presented by Dysautonomia International:[2]

> "The current diagnostic criteria for POTS is a heart rate increase of 30 beats per minute (bpm) or more, or over 120 bpm, within the first 10 minutes of standing, in the absence of orthostatic hypotension. In children and adolescents, a revised standard of a 40 bpm or more increase has recently been adopted. POTS is often diagnosed by a Tilt Table Test, but if such testing is not available, POTS can be diagnosed with bedside measurements of heart rate and blood pressure taken in the supine (laying down) and standing up position at 2, 5 and 10 minute intervals."

POTS, being a syndrome, is a collection of symptoms and is not a "root cause" disease in and of itself. As Dr. Satish Raj states: "Postural tachycardia syndrome (POTS) is not a single

[1] Dysautonomia International, Postural Orthostatic Tachycardia Syndrome, http://www.dysautonomiainternational.org/page.php?ID=30

[2] Dysautonomia International, Diagnostic Criteria, http://www.dysautonomiainternational.org/page.php?ID=30

disease. It is best viewed as a 'disorder' or a syndrome in which excessive orthostatic tachycardia can be a final common pathway of many underlying pathophysiological processes."[3]

With POTS, the ANS does not work properly. To further delve into the dysfunction within POTS, we should first look at what the ANS does.

The ANS works automatically (without conscious effort) to control many body systems and processes. Just some of its functions include regulating blood pressure, heart rate, respiratory rate, digestion, body temperature regulation, blood flow, muscle response, pupillary response, urination, defecation, and sexual arousal. The ANS has two main branches: the sympathetic and parasympathetic systems. These systems are antagonistic of each other, but work together in tandem to regulate body functions.

The sympathetic system has been coined the "fight or flight" system, and is usually triggered by stress of some sort. The sympathetic system is excitatory and prepares the body to confront a stressor or prepares the body to flee the stressor. Such activations may include increasing or releasing norepinephrine (NE), which increases heart rate, constricts pupils and blood vessels, and opens airways, but it also shuts down digestion, reproductive systems, and other systems it deems unnecessary for immediate survival requirements.

The parasympathetic system is the opposite of the sympathetic system and is coined the "rest and digest" system. It stimulates digestion, the reproductive system, muscle repair, and allows for rest and sleep in order to further rebuild and repair the body. These systems should work in tandem, where the sympathetic system activates to address a stressor (such as running from a threat to life or limb), but when the stressor has passed the parasympathetic system kicks

[3] Raj, Satish R. 2012. "Mechanisms of Postural Orthostatic Tachycardia Syndrome." Primer on the Autonomic Nervous System (3rd Ed), 521-523. Academic Press. Accessed June 9, 2018. https://doi.org/10.1016/B978-0-12-386525-0.00107-4

in so that normal bodily processes can continue and the body can rebuild. In POTS, these systems do not work properly and are imbalanced. This dysfunction causes a myriad of symptoms and disablement.

Symptoms of POTS are diverse and varied by patient, and may include some or all of the following: high or low blood pressure, high or low heart rate and racing heart, chest pain, dizziness and/or lightheadedness especially upon standing, prolonged sitting in one position, or on long walks, fainting or near-fainting (syncope or presyncope), exhaustion or fatigue, abdominal pain and bloating, nausea, temperature dysregulation (hot or cold), nervous and jittery feeling, forgetfulness and trouble focusing ("brain fog"), blurred vision, headaches and body pain or aches, neck pain, insomnia and frequent awakenings from sleep, chest pain and racing heart rate during sleep, excessive sweating, shakiness or tremors especially with adrenaline surges, discoloration of feet and hands, exercise intolerance, excessive or lack of sweating, and diarrhea and/or constipation.[4] Due to the severity of symptoms, many POTS patients are partially or fully disabled, and unable to live "normal" lives.

One of the basic mechanisms of POTS is that there is insufficient constriction of blood vessels (also called vasoconstriction) and often, also, an inadequate level of blood volume in the body. In both normal individuals and in POTS patients, blood vessels are dilated upon sitting or laying (supine) position. When normal individuals stand up from a sitting or supine position, the blood vessels constrict in their lower extremities, which keeps adequate levels of blood circulating in the top half of the body, thereby providing adequate oxygen supply to the internal organs and brain. However, with POTS, upon standing, the blood vessels in the extremities fail

[4] Cleveland Clinic, Postural Orthostatic Tachycardia Syndrome (POTS), https://my.clevelandclinic.org/health/diseases/16560-postural-orthostatic-tachycardia-syndrome-pots

to properly constrict causing pooling of blood in the lower extremities as gravitational force is exerted. Blood volume, circulation, and oxygen is thereby drastically lowered to the rest of the body, including the brain. The heart begins to pump faster in an attempt to increase blood circulation, which results in tachycardia. The decreased level of circulation to the organs result in a wide range of symptoms, as these different areas of the body are deprived of blood and oxygen. In some patients, fainting may also occur as the brain is deprived of sufficient oxygen. The majority of POTS patients also show an increased level of serum norepinephrine upon standing, which reflects activation of the sympathetic nervous system when in an upright position.[5]

Subtypes

In POTS, the blood vessels in the lower extremities do not properly constrict upon standing, which causes blood pooling in the feet and legs, resulting in low blood volume and oxygen in the brain and other internal organs. The heart attempts to rectify this situation by beating harder and faster, causing tachycardia. The tachycardia that follows changing positions to an upright one can be due to several mechanisms which may vary based on the "subtype" of POTS. The initial blood pooling in the feet and legs may be due to peripheral denervation (loss of nerve supply) of the lower extremities, which leads to poor blood vessel tone in these areas, and thereby, causes a lack of constriction and pooling upon standing. This type of POTS is called Neuropathic POTS.

Neuropathic POTS patients often report a viral infection prior to POTS onset, and also show a loss of sweating on a QSART test (a test that measures autonomic nerves that control

[5] Raj, Satish R. "The Postural Tachycardia Syndrome (POTS): Pathophysiology, Diagnosis & Management." Indian Pacing Electrophysiology Journal 6(2): 84-99. Accessed June 8 2018. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1501099/

sweating). These patients have evident denervation, particularly of the limbs, which may lead to a loss of vasoconstriction in the lower limbs following upright position change. These patients also noted more frequent gastrointestinal complaints such as bloating, nausea, abdominal pain and constipation. These patients may also have diminished NE release in their legs, but not in their arms.[6]

Hyperadrenergic POTS is another subtype of POTS in which patients have excessive levels of serum norepinephrine upon standing. This type also has overall higher levels of norepinephrine, which increase further and drastically upon changing to an upright position. The excessive levels of norepinephrine (also known as noradrenaline) affect the heart rate, causing tachycardia upon standing or exertion. Hyperadrenergic POTS patients may also show an increased or fluctuating blood pressure upon upright positioning. These patients have symptoms of an overactive sympathetic nervous system, which can either be episodic or constant. These symptoms may include tachycardia, hypertension, and hyperhidrosis. The episodes can be spontaneous or have an unknown trigger, or are provoked by stress, activity, or being upright for a period of time. By using a suggested criteria for hyperadrenergic POTS of a plasma NE level of greater than 600pg/mL, the prevalence of hyperadrenergic POTS patients at the American POTS referral centers would range from 30% to over 60% of POTS patients. Therefore, the mechanism behind Hyperadrenergic POTS of an overactive sympathetic nervous system response may be the main underlying mechanism of POTS.[7]

---

[6] Robertson, Biaggioni, Burnstock, Low, Paton. 2012. *Primer on the Autonomic Nervous System*, Third Edition (p.522). London, UK: Academic Press.

[7] Robertson, Biaggioni, Burnstock, Low, Paton. 2012. *Primer on the Autonomic Nervous System*, Third Edition (p.521). London, UK: Academic Press.

Another POTS subtype is characterized by low overall blood volume (low blood volume POTS).[8] Low overall blood volume in the body is exacerbated upon standing, and the body fails to return proper amounts of blood and oxygen to the brain and the rest of the body.

Some researchers also consider poor physical conditioning (or lack of exercise and movement) as another subtype in many patients. Patients with POTS as a result of deconditioning may respond favorably to an exercise training and reconditioning program.[9]

Treatment

As POTS is a symptom (and not a disease with a known etiology), there is no known cure. Traditional Medical Doctors attempt to treat patients by focusing on symptom management. Here is a summary from the book *Primer on the Autonomic Nervous System (3rd Ed)* regarding how POTS is viewed and treated by traditional medicine:[11]

> "POTS is common and is heterogeneous in presentation and pathophysiologic mechanisms. Common mechanisms are denervation (neuropathic POTS), hyperadrenergic state, and deconditioning. Management always involves expansion of plasma volume with high salt and high fluid intake. Additional steps include compression garments. Medications that are commonly used include beta-blockers, midodrine, and fludrocortisone. Exercise training and reconditioning is emerging as a very important strategy in the deconditioned subject."

Doctors may attempt to decrease symptoms by working to increase blood volume via increasing fluid and sodium intake, wearing compression stockings, raising the head of the bed, and prescribing medications to increase sodium retention and vasoconstriction.[10] Other medications used are cholinergics that may help stimulate the parasympathetic response in the

---

[8] "Postural Orthostatic Tachycardia Syndrome (POTS)." The Cleveland Clinic. Accessed June 8, 2018. https://my.clevelandclinic.org/health/diseases/16560-postural-orthostatic-tachycardia-syndrome-pots

[9] Robertson, Biaggioni, Burnstock, Low, Paton. 2012. *Primer on the Autonomic Nervous System*, Third Edition (p.519). London, UK: Academic Press.

[10] Dysautonomia International, Treatment, http://www.dysautonomiainternational.org/page.php?ID=30

body, thus calming the overactive sympathetic response symptoms. Benzodiazepines or beta-blockers may also be used to decrease heart rate and induce a calming effect on the body. Symptom management usually only partially returns the patient to a "normal life." Many patients do not experience symptom relief with the current management strategies or medications and remain disabled.

Statement of Problem

As previously mentioned, POTS is classified as a syndrome, or a collection of symptoms. This means that it is not, in and of itself, a "root cause" disease. A syndrome has an implied underlying cause. The root cause for POTS is currently unknown. What is known is that most POTS patients have an overactive sympathetic nervous system and/or an underactive parasympathetic nervous system, as tested and seen via excessive amounts of norepinephrine in their blood, with this level increasing excessively upon standing.

Many patients report having a sort of trigger prior to the onset of POTS symptoms. Some of these reported triggers include stressors such as an illness (often viral)[5], vaccination[5], surgery, accident or physical trauma, or even pregnancy. In fact, it is noted in the *Primer on the Autonomic Nervous System (3rd Ed)* that 50% percent of POTS patients have an antecedent viral illness. They also noted that 25% had a positive family history of similar complaints.[11]

Since the traditional methods of treating POTS often do not result in a dramatic decrease in symptoms or increased quality of life, a new approach to POTS is needed in order to better serve this patient population. This approach may involve "taking a step back," and looking at the body as a whole instead of attempting to isolate and treat individual body systems. This

[11] Robertson, Biaggioni, Burnstock, Low, Paton. 2012. *Primer on the Autonomic Nervous System*, Third Edition (p. 517). London, UK: Academic Press.

approach may include assessing nutrient and mineral needs, pathogenic influences, and environmental and lifestyle stressors, including toxins and overall stress impacts on the patient. Focus should be put on discovering areas in which the body is out of balance and finding and addressing the possible trigger or "root cause" for that individual. Once these unbalanced areas of the body are brought back into balance, it is possible that the body will resolve the POTS symptoms without direct intervention.

The Role and Importance of Norepinephrine and Acetylcholine

Norepinephrine and Acetylcholine are the two most abundant neurotransmitters in the Autonomic Nervous System.[12] The Britannica Encyclopedia defines Norepinephrine as:[13]

> "Norepinephrine, also called noradrenaline: Substance that is released predominantly from the ends of sympathetic nerve fibres and that acts to increase the force of skeletal muscle contraction and the rate and force of contraction of the heart. The actions of norepinephrine are vital to the fight-or-flight response, whereby the body prepares to react to or retreat from an acute threat. Norepinephrine is classified structurally as a catecholamine—it contains a catechol group (a benzene ring with two hydroxyl groups) bound to an amine (nitrogen-containing) group. The addition of a methyl group to the amine group of norepinephrine results in the formation of epinephrine, the other major mediator of the flight-or-flight response. Relative to epinephrine, which is produced and stored primarily in the adrenal glands, norepinephrine is stored in small amounts in adrenal tissue. Its major site of storage and release are the neurons of the sympathetic nervous system (a branch of the autonomic nervous system). Thus, norepinephrine functions mainly as a neurotransmitter with some function as a hormone (being released into the bloodstream from the adrenal glands).
>
> Norepinephrine, similar to other catecholamines, is generated from the amino acid tyrosine. Norepinephrine exerts its effects by binding to α- and β-adrenergic receptors (or adrenoceptors, so named for their reaction to the adrenal hormones) in different tissues. In the blood vessels, it triggers vasoconstriction (narrowing of blood vessels), which increases blood pressure. Blood pressure is further raised by norepinephrine as a result of its effects on the heart muscle, which increase the output of blood from the heart. Norepinephrine also acts to increase blood glucose levels and levels of circulating free fatty acids. The substance has also been shown to modulate the function of certain types

[12] McCorry, Laurie Kelly. 2007. "Physiology of the Autonomic Nervous System." American Journal of Pharmaceutical Education, v.71(4). Accessed November 4, 2018. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1959222/

[13] "Norepinephrine." Encyclopedia Britannica. https://www.britannica.com/science/norepinephrine

> of immune cells (e.g., T cells). Norepinephrine activity is efficiently terminated through inactivation by the enzymes catechol-*O*-methyltransferase (COMT) or monoamine oxidase (MAO), by reuptake into nerve endings, or by diffusion from binding sites. Norepinephrine that diffuses away from local nerve endings can act on adrenergic receptors at distant sites."

Acetylcholine is also extremely important to the balance of the ANS, as the primary neurotransmitter of the parasympathetic ("rest, repair, and digest") nervous system. The Britannica Encyclopedia defines this neurotransmitter:[14]

> "Acetylcholine, an ester of choline and acetic acid that serves as a transmitter substance of nerve impulses within the central and peripheral nervous systems. Acetylcholine is the chief neurotransmitter of the parasympathetic nervous system, the part of the autonomic nervous system (a branch of the peripheral nervous system) that contracts smooth muscles, dilates blood vessels, increases bodily secretions, and slows heart rate.
>
> Acetylcholine is stored in vesicles at the ends of cholinergic (acetylcholine-producing) neurons. In the peripheral nervous system, when a nerve impulse arrives at the terminal of a motor neuron, acetylcholine is released into the neuromuscular junction. There it combines with a receptor molecule in the postsynaptic membrane (or end-plate membrane) of a muscle fibre. This bonding changes the permeability of the membrane, causing channels to open that allow positively charged sodium ions to flow into the muscle cell (*see* end-plate potential). If successive nerve impulses accumulate at a sufficiently high frequency, sodium channels along the end-plate membrane become fully activated, resulting in muscle cell contraction.
>
> Within the autonomic nervous system, acetylcholine behaves in a similar manner, being discharged from the terminal of one neuron and binding to receptors on the postsynaptic membrane of other cells. Its activities within the autonomic nervous system affect a number of body systems, including the cardiovascular system, where it acts as a vasodilator, decreases heart rate, and decreases heart muscle contraction. In the gastrointestinal system, it acts to increase peristalsis in the stomach and the amplitude of digestive contractions. In the urinary tract, its activity decreases the capacity of the bladder and increases voluntary voiding pressure. It also affects the respiratory system and stimulates secretion by all glands that receive parasympathetic nerve impulses. In the central nervous system, acetylcholine appears to have multiple roles. It is known to play an important role in memory and learning and is in abnormally short supply in the brains of persons with Alzheimer disease."

[14] "Acetylcholine." Encyclopedia Britannica. https://www.britannica.com/science/acetylcholine

To summarize, norepinephrine is important for many functions in the body through the sympathetic nervous system response including wakefulness and alertness, response to stressors or events, regulating blood pressure and heart rate, and blood vessel constriction. Acetylcholine is important for regulating the parasympathetic nervous system, decreasing heart rate, stimulating muscles, digestion, memory, and sleep.

Both of these neurotransmitters also affect the immune system in various ways. Chronically high levels of NE have been shown to cause atrophy of the spleen as well as decreased T cells in a study conducted by Harris, et al.[15] They found that an infusion of epinephrine and norepinephrine over a 4-week period caused atrophy of the spleen in rats and a decrease in T cells. Therefore, being in a sympathetic state with high levels of NE for extended periods could decrease immune activity. Acetylcholine is important to the immune system by helping to lower inflammatory cytokines, which may be produced after an injury or infection. This protects the body against inflammatory damage via activation of the vagus nerve.[16]

Due to the importance of these two neurotransmitters in regulating the autonomic nervous system, pharmacological drugs that decrease the response to norepinephrine or increase the action of acetylcholine are often used to treat symptoms in POTS patients.

Choline, a precursor to acetylcholine which helps to regulate autonomic function, has been documented to be deficient in POTS patients. In a 2015 study, it was found that:[17]

> "The choline transporter-like protein 1/solute carrier 44A1 (CTL1/SLC44A1) and mRNA expression were 2-3 times lower in POTS fibroblasts, and choline uptake was reduced 60% ($P < 0.05$). Disturbances of membrane homeostasis were observed by reduced ratios between PC:phosphatidylethanolamine and sphingomyelin:cholesterol, as well as by

[15] Harris, Waltman, Carter, Maisel. 1995. "Effect of prolonged catecholamine infusion on immunoregulatory function: implications in congestive heart failure." Journal of the American College of Cardiology, Vol 26 (1), 102-109. Accessed December 25, 2018. https://www.ncbi.nlm.nih.gov/pubmed/7797738

[16] Kevin J. Tracy. 2009. "Reflex control of immunity." Nat Rev Immunol. 2009 Jun; 9(6):418-428. Accessed January 25, 2019. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4535331/

[17] Schenkel, Singh, Michel, Zeisel, da Costa,

> modified phospholipid fatty acid composition. Choline deficiency also impaired mitochondria function, which was observed by a reduction in oxygen consumption, mitochondrial potential, and glycolytic activity. When POTS cells were treated with choline, transporter was up-regulated, and uptake of choline increased, offering an option for patient treatment."

Another article discusses how increasing acetylcholine via the inhibition of acetylcholinesterase may help POTS patients:[18]

> "Since ganglionic synaptic transmission is a common pathway for all autonomic traffic, enhancement of autonomic function through inhibition of acetylcholinesterase is a potential specific therapeutic strategy for autonomic disorders. Increasing the strength of ganglionic transmission can ameliorate neurogenic orthostatic hypotension without aggravating supine hypertension. Recent evidence also suggests a potential role for acetylcholinesterase inhibitors in the treatment of postural tachycardia syndrome."

A study from 2011 looked specifically at the successfulness of using an acetylcholinesterase inhibitor, Pyridostigmine, in treating POTS symptoms.[19] It found that the drug " improved symptoms of orthostatic intolerance in 88 of 203 (43%) of total patients or 88 of 172 (51%) who were able to tolerate the drug. The symptoms that improved the most included fatigue (55%), palpitations (60%), presyncope (60%), and syncope (48%). Symptom reduction correlated with a statistically significant improvement in upright HR and diastolic blood pressure after treatment with pyridostigmine as compared to their baseline hemodynamic parameters."

Beta blockers, or beta-adrenergic blocking agents, decrease the effect of norepinephrine on the body. These drugs are often used in the treatment of symptoms in POTS patients, as they have been found to decrease tachycardia and other POTS-related symptoms.[20]

---

[18] Vernino, Sandroni, Singer, Low. 2008. "Autonomic ganglia: target and novel therapeutic tool." Neurology 2008 May 13; 70(20):1926-32. Accessed January 25, 2019. https://www.ncbi.nlm.nih.gov/pubmed/18474849

[19] Kanjwal, Karabin, Sheikh, Elmer, Kanjwal, Saeed, Grubb. 2011. "Pyridostigmine in the treatment of postural orthostatic tachycardia: a single-center experience." Pacing Clin Electrophysiol. 2011 Jun; 34(6):750-5. Accessed January 25, 2019. https://www.ncbi.nlm.nih.gov/pubmed/21410722

[20] Raj, Black, Biaggioni, Paranjape, Ramirez, Dupont, Robertson. 2009. "Propranolol decreases tachycardia and improves symptoms in the postural tachycardia syndrome: less is more." Circulation. 2009 Sep 1; 120(9):725-34. Accessed January 25, 2019. https://www.ncbi.nlm.nih.gov/pubmed/19687359

In summary, POTS patients are found to have dysregulated levels or functioning of the two major neurotransmitters of the autonomic nervous system. Both norepinephrine, which regulates the sympathetic branch of the ANS, as well as acetylcholine, which regulates the parasympathetic branch of the ANS, are impacted, resulting in chaos in the ANS and resultant symptoms.

Degradation of Norepinephrine

Norepinephrine that is not stored intracellularly is deanimated via one of two enzymes: MAO (monoamine oxidase) or COMT (catechol-o-methyltransferase).[21] These enzymes require several cofactors to work properly. The cofactors that are currently identified for each enzyme include oxygen and FAD (flavin adenine dinucleotide, a derivative of Riboflavin or Vitamin B2) for proper functioning of MAO-A[22], and SAM-e (S-adenosyl-L-methionine, a derivative of amino acid methionine), vitamin B12, and Magnesium for proper functioning of COMT.[23] [24]

Since POTS patients typically have higher levels of NE, and decreased expression of these NE-degrading enzymes may lead to increased levels of NE in the body, the functioning of, and nutrient cofactors for, the MAO and COMT enzymes should be considered by the clinician.

Inhibitors of these enzymes should also be considered. Chronic stress has been shown to decrease the activity of the both the MAO-A and COMT enzymes over time.[25] [26] A decrease in

---

[21] Robertson, Biaggioni, Burnstock, Low, Paton. 2012. *Primer on the Autonomic Nervous System*, Third Edition (p.41). London, UK: Academic Press.

[22] Helena Gaweska and Paul F. Fitzpatrick. 2012. "Structures and Mechanisms of the Monoamine Oxidase Family." Biomol Concepts, 2011 Oct 1; vol 2(5): 365-377. Accessed December 25, 2018. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3197729/

[23] Tsao, Diatchenko, Dokholyan. 2011. "Structural Mechanism of S-Adenosyl Methionine Binding to Catechol O-Methyltransferase." PLoS One, vol 6(8): e24287. Accessed December 25, 2018. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3164188/

[24] Oner, Guven, Tavli, Mese, Yilmazer, Demirpence. 2014. "Postural Orthostatic Tachycardia Syndrome (POTS) and Vitamin B12 Deficiency in Adolescents." Pediatrics, Vol 133 (1). Accessed December 25, 2018. http://pediatrics.aappublications.org/content/133/1/e138

[25] Kvetnansky, Torda, Jahnova, Saleh. 1975. "Activity of catecholamine degrading enzymes in rat adrenal medulla and cortex after acute and repeated stress." Endocrinol Exp. 1975 Jun; 9(2): 79-86. Accessed December 25,2018. https://www.ncbi.nlm.nih.gov/pubmed/1079183

ATP production in the brain may also inhibit the COMT enzyme.[27] High levels of estrogen have also been found to decrease COMT expression.[28]

Recent studies have also found that POTS may have (at least in some patients) an autoimmune component, whereby the adrenergic and cholinergic receptors (where norepinephrine and acetylcholine, respectively, are taken up into the cell) are being attacked by the body[29]. This will be discussed later in more detail.

NET Protein

It was previously discussed how POTS patients have a lack of vasoconstriction in the lower extremities, causing blood pooling and resultant decreased overall volume and tachycardia. It was also discussed how norepinephrine (NE) constricts vessels, yet many POTS patients have too much circulating NE. This may, at first, seem like a contradiction, however, this is where NET protein comes into play.

Researchers have uncovered that many POTS patients have issues with their norepinephrine transporter (NET) function. "The norepinephrine transporter (NET) is responsible for the neuronal reuptake of norepinephrine (NE) and is located presynaptically on noradrenergic nerve terminals. Reuptake of NE by the NET contributes to the termination of noradrenergic transmission (Barker and Blakely, 1995)."[30]

---

[26] Armando, Lemoine, Segura, Barontini. 1993. "The stress-induced reduction in monoamine oxidase (MAO) A activity is reversed by benzodiazepines: Role of peripheral benzodiazepine receptors." Cellular and Molecular Neurobiology, vol 13(6): p. 593-600. Accessed December 25,2018. https://link.springer.com/article/10.1007/BF00711559

[27] Osiezagha, Ali, Freeman, Barker, Jabeen, Maitra, Olagbemiro, Richie, Bailey. 2013. "Thiamine Deficiency and Delirium." Innov Clin Neurosci, vol 10(4): 26-32. Accessed December 25,2018. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3659035/

[28] Hart, Charkoudian, Miller. 2010. "Sex, Hormones and Neuroeffector Mechanisms." Acta Physiol (Oxf). 2011 Sep; 203(1): 155-165. Accessed December 31, 2018. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3025263/

[29] Ruzieh, Batizy, Dasa, Oostra, Grubb. 2017. "The role of autoantibodies in the syndromes of orthostatic intolerance: a systemic review." Scandinavian Cardiovascular Journal 51, no. 5. Accessed May 25, 2018. https://doi.org/10.1080/14017431.2017.1355068.

[30] Zhu, Shamburger, Li, Ordway. 2000. "Regulation of the Human Norepinephrine Transporter by Cocaine and Amphetamine." The Journal of Pharm., vol 295(3): 951-959. Accessed January 25, 2019. https://pdfs.semanticscholar.org/540c/adb62a994cf194a9115149aefad7298a13b9.pdf

The role of NET protein is to reuptake and recycle NE back into the synapse. When NET protein is not functioning properly, there is insufficient recycling of NE with higher levels of NE flowing out into the bloodstream. The effect of this is a decrease in the function of NE in being able to sufficiently constrict blood vessels (thereby leading to blood pooling), while also leaving an excessive amount of NE in the circulating bloodstream (also called "norepinephrine spillover"). This excessive NE or noradrenaline coursing through the bloodstream increases sympathetic dominance symptoms which can include tachycardia, anxiety, sweating, and nausea.

Researchers have also demonstrated the importance of sufficient "functional" or usable NE in POTS by recreating a POTS patient phenotype in a laboratory by simply inhibiting NET protein, via pharmacological methods, in a 2012 research study.[31]

NET protein deficiency is evident in POTS[32], but studies to pinpoint genetic mutations have been inconclusive, with genetic mutations in the SLC6A2 gene found only in one familial group in a POTS study.[33] However, in a small POTS study, researchers found that epigenetic expression of this NET gene, regardless of SLC6A2 genetic mutations, is being down-regulated to the point that it is not making sufficient levels of NET protein in the majority of POTS patients examined.[34] The downregulation or dysfunction of NET protein is also called "NET protein silencing."

---

[31] Robertson, Biaggioni, Burnstock, Low, Paton. 2012. *Primer on the Autonomic Nervous System*, Third Edition (p.522). London, UK: Academic Press.

[32] E. Lambert, Eikelis, Esler, Dawood, Schlaich, Bayles, Socratous, Agrotis, Jennings, G. Lambert, Vaddadi. 2008. "Altered Sympathetic Nervous Reactivity and Norepinephrine Transporter Expression in Patients with Postural Tachycardia Syndrome." Circulation: Arrhythmia and Electrophysiology. 2008; 1: 103-109. Accessed May 25, 2018. https://doi.org/10.1161/CIRCEP.107.750471

[33] Khan, Corcoran, Esler, Osta. 2015. "Epigenomic changes associated with impaired norepinephrine transporter function in postural tachycardia syndrome." Neuroscience & Biobehavioral Reviews Volume 74, Part B, 342-355. Accessed May 25, 2018. https://doi.org/10.1016/j.neubiorev.2016.06.015

[34] Khan, Ziemann, Corcoran, K.N, Okabe, Rafehi, Maxwell, Esler, El-Osta. 2017. "NET silencing by let-7i in postural tachycardia syndrome." JCI Insight volume 2, issue 6. Accessed May 25, 2018. https://insight.jci.org/articles/view/90183

The book *Primer on the Autonomic Nervous System (3rd Ed)* further discusses NET expression and its impact on NE:[35]

> "Modest decreases in NET expression might reset the synaptic content of NE to a lower level, thus lowering basal plasma levels, whereas, following activation of the sympathetic nervous system and increased NE release, NET deficiency would contribute to an enhanced cardiovascular response. Small decreases in NET might also influence central NE neurons that regulate sympathetic outflow that, without dramatic changes in the periphery, might shift the balance to one of lower sympathetic tone. Overall, the consequences of NET SNPs associated with diminished NET activity are to alter NE homeostasis and cardiovascular responses, perhaps dependent upon the level of engagement of sympathetic nervous system activity.

The book goes onto explain how NET is the primary way that released NE may be terminated:[36]

> "NE is inactivated mainly by uptake into cells, with subsequent intracellular metabolism or storage. Reuptake into nerve terminals - Uptake 1 - via the cell membrane NET is the predominant means of terminating the actions of released NE."

NET protein silencing was confirmed via epigenetic expression in a 2012 study. They also discuss possible reasons why NET reuptake may be inhibited:[37]

> "In the present study, we estimated the proportionality of norepinephrine spillover to plasma per burst of sympathetic activity as an index of norepinephrine uptake, noting that the amount of norepinephrine overflowing into the circulation per sympathetic burst was significantly higher in the POTS patients, in keeping with impaired norepinephrine reuptake. Although this may have arisen from a defect in norepinephrine reuptake, it could also occur if the quanta of norepinephrine released per action potential was elevated. Further, if norepinephrine reuptake is reduced, this might be the consequence to swamping of the transporter by high synaptic levels of the transmitter in POTS. Supporting this premise, in response to yohimbine, cardiac norepinephrine spillover was elevated to a greater extent in POTS patients compared with controls, and once cardiac norepinephrine spillover exceeded ≈200 pmol/min, the cardiac extraction of tritiated norepinephrine declined appreciably, suggesting there was a diminution in the action of NET during periods of extreme sympathetic activation in POTS patients."

---

[35] Robertson, Biaggioni, Burnstock, Low, Paton. 2012. *Primer on the Autonomic Nervous System*, Third Edition (p. 441). London, UK: Academic Press.

[36] Robertson, Biaggioni, Burnstock, Low, Paton. 2012. *Primer on the Autonomic Nervous System*, Third Edition (p.39). London, UK: Academic Press.

[37] Bayles, Harikrishnan, Lambert, Baker, Agrotis, Guo, Jowett, Esler, Lambert, El-Osta. 2012. "Epigenetic modification of the norepinephrine transporter gene in postural tachycardia syndrome." Arterioscler Thromb Vasc Biol. 2012 Aug; 32(8):1910-6. Accessed January 19, 2019. https://www.ahajournals.org/doi/pdf/10.1161/ATVBAHA.111.244343

> "The findings presented are novel at least in 2 aspects that identify a role of epigenetic regulation of NET in POTS patients. First, they demonstrate that in the POTS individuals, the promoter sequence of the SLC6A2 gene is subject to significant alterations of histone modifications that are associated with gene-suppressive transcriptional events."
>
> "Studies by our group and others have shown that gene regulating events involve transcription factors, remodeling enzymes, and chromatin modifications. Why the SLC6A2 gene in the leukocytes of POTS patients is suppressed is poorly understood. In noradrenergic cell types, the transcription factors Hand2 and Gata3 are regulated by cytokines and associated with SLC6A2 expression. Hand2 interacts directly with the histone acetyltransferase p300 to alter chromatin structure. We found reduced expression of p300 in POTS patients in this study. The dysregulation of transcriptional networks in POTS in relation to inflammation may be an important area for future research, given that POTS often develops after prolonged febrile illness."

As discussed, NET protein may be silenced by excessive levels of NE being released, "swamping" the transporter, or via other epigenetic modifications. NET protein can also be downregulated by oxidative stress[38], cytokines[39], and insulin[40]. Therefore, stress, diet, and inducers of inflammatory cytokines, including toxins or pathogenic infections, should also be carefully examined and considered in POTS patients. NET protein, being a sodium-dependent transporter, is also "absolutely dependent on extracellular Na+ and Cl-,"[41] therefore, the mineral status should also be examined in POTS patients.

Summary of Dysregulated Norepinephrine

[38] Mao, Iwai, Qin, Liang. 2005. "Norepinephrine induces endoplasmic reticulum stress and downregulation of norepinephrine transporter density in PC12 cells via oxidative stress." American Journal of Physiology May 2005; 288(5); H2381-9. Accessed January 25, 2019. https://www.physiology.org/doi/full/10.1152/ajpheart.00904.2004

[39] Pellegrino, Parrish, Zigmond, Habecker. 2011. "Cytokines inhibit norepinephrine transporter expression by decreasing Hand2." Mol Cell Neurosci. 2011 Mar; 46(3): 671-680. Accessed January 25, 2019. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3046314/

[40] Robertson, Matthies, Owens, Sathananthan, Christianson, Kennedy, Lindsley, Daws, Galli. 2010. "Insulin Reveals Akt Signaling as a Novel Regulator of Norepinephrine Transporter Trafficking and Norepinephrine Homeostasis." Journal of Neuroscience. Aug 2010; 30(34): 11305-11316. Accessed January 25, 2019. http://www.jneurosci.org/content/30/34/11305

[41] Bönisch, Hammermann, Brüss. 1997. "Role of Protein Kinase C and Second Messengers in Regulation of the Norepinephrine Transporter." Advances in Pharmacology, 1997; vol 42: 183-186. Accessed January 25, 2019. https://www.sciencedirect.com/science/article/abs/pii/S1054358908607231

Most, if not all, POTS patients have issues with norepinephrine via three insults: 1) too much norepinephrine being created and released due to an overactive sympathetic nervous system, especially during standing or exertion, 2) insufficient NET protein in order to efficiently recycle NE back into the synapse and decrease the amount of NE circulating in the bloodstream (and possibly also decrease excessive NE release in the first place, via feedback mechanisms), and, as briefly mentioned, 3) the adrenergic receptors on the cells are being attacked by the body via autoantibodies, so the patient is unable to use NE efficiently, for functions such as energy, alertness, and constricting blood vessels upon standing.

This lack of "functional NE," where NE is too high in the serum, yet too low in the cells to initiate normal functions, can cause the excessive sympathetic symptoms which include postural tachycardia as well as the feeling of being simultaneously "wired yet tired."

Autoimmune Basis for POTS

Both acetylcholine receptor antibodies (AChR-ab) and adrenergic (norepinephrine) autoantibodies have been found in POTS patients. One study[42] found that almost 25% of POTS patients studied showed positive AChR-ab. These patients also had more severe symptoms than those who were AChR-ab negative, including higher rates of syncope and fatigue. The AChR-ab positive patients also had higher rates of infection preceding POTS.

[42] Li, Zhang, Liao, Zhang, Hao, Du. 2015. "The value of acetylcholine receptor antibody in children with postural tachycardia syndrome." Pediatr Cardiol. 2015 Jan; 36(1):165-70. Accessed January 25, 2019. https://www.ncbi.nlm.nih.gov/pubmed/25087056

Another study from 2018 found that 29% of POTS patients studied were positive for circulating anti-ganglionic acetylcholine receptor (gAChR) antibodies.[43] The researchers also noted:[44]

> "Antecedent infections were frequently reported in patients in POTS patients. Moreover, autoimmune markers and comorbid autoimmune diseases were also frequent in seropositive POTS patients. Anti−gAChR antibodies were detectable in significant number of patients with POTS, and POTS entailed the element of autoimmune basis."
>
> "We found that anti−gAChR antibodies were detected more frequently in patients with POTS compared to NMS and controls, suggesting that anti−gAChR antibodies may be associated with POTS and its underlying autonomic dysfunction."
>
> "Anti−gAChR antibodies may impair autonomic ganglionic synaptic transmission, and antibodies that interfere with ganglionic transmission may contribute to dysautonomia in patients with POTS. Although POTS is pathophysiologically categorized into four subtypes (neuropathic, hyperadrenergic, volume dysregulation, and physical deconditioning), it is not clear which subtype corresponds to gAChR autoimmunity−related POTS, or whether anti−gAChR antibodies have stimulatory functions that produce overactivity of sympathetic ganglia (i.e., type V hypersensitivity)."

A study from 2014 examined fourteen POTS patients for autoimmune antibodies.[45] The results showed that all POTS patients studied demonstrated a possible alpha-1 adrenergic receptor (a1AR) autoimmune response and also had beta-1 adrenergic receptor (b1AR) autoantibodies present. Beta-2 adrenergic receptor antibodies were found in one-half of the subjects. Also of note is that Five of the 14 (36%) POTS subjects reported a viral-like illness in

---

[43] Watari, Nakane, Mukaino, Nakajima, Mori, Maeda, Masuda, Takamatsu, Kouzaki, Higuchi, Matsuo, Ando. 2018. "Autoimmune postural orthostatic tachycardia syndrome." Ann Clin Transl Neurol. 2018 Feb 28; 5(4):486-492. Accessed January 25, 2019. https://www.ncbi.nlm.nih.gov/pubmed/29687025

[44] Watari, et al. 2018. "Autoimmune postural orthostatic tachycardia syndrome." Ann Clin Transl Neurol. Vol 5(4): 486-492. Accessed December 25,2018. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5899914/

[45] Li, Yu, Liles, Khan, Vanderlinde-Wood, Galloway, Zillner, Benbrook, Reim, Collier, Hill, Raj, Okamoto, Cunningham, Aston, Kem. 2014. "Autoimmune basis for postural tachycardia syndrome." J Am Heart Assoc. 2014 Feb; 3(1):e000755. Accessed January 25, 2019. https://www.ncbi.nlm.nih.gov/pubmed/24572257

the 6 months prior to the onset of POTS symptoms. Another study from 2017[46] found that of the 17 POTS patients studied, "Eight, 11, and 12 of the 17 POTS patients possessed autoantibodies that activated a1AR, b1AR and b2AR, respectively." This means that 47% of the patients showed a1AR autoantibodies, 65% showed b1AR autoantibodies, and 71% showed b2AR autoantibodies.

Some Chronic Fatigue Syndrome (CFS) patients have also been shown to have antibodies to both beta adrenergic and muscarinic cholinergic receptors.[47] The study that found this also mentions: "What are potential mechanisms leading to induction of β AdR and M AChR antibodies in CFS patients? There is evidence that a subset of patients experienced major distressing life events before CFS onset and that CFS is frequently triggered by an infection. Thus it is tempting to speculate that chronic adrenergic stimulation may lead to conformational changes of receptors resulting in more immunogenic epitopes and that infection-triggered immune activation induces the autoantibody response."

So, why might the body attack its own adrenergic receptors? One study from 2010 proposed that it could be related to the HLA (or Human Leukocyte Antigen) genes. Per the NIH's Genetics database,[48] "The HLA gene family provides instructions for making a group of related proteins known as the human leukocyte antigen (HLA) complex. The HLA complex helps the immune system distinguish the body's own proteins from proteins made by foreign

---

[46] Fedorowski, Li, Yu, Koelsch, Harris, Liles, Murphy, Quadri, Scofield, Sutton, Melander, Kem. 2017. "Antiadrenergic autoimmunity in postural tachycardia syndrome." European Society of Cardiology, vol 19: 1211-1219. Accessed January 25, 2019. https://www.ncbi.nlm.nih.gov/pubmed/27702852

[47] Loebel, Grabowski, Heidecke, Bauer, Hanitsch, Wittke, Meisel, Reinke, Volk, Fluge, Mella, Scheibenbogen. 2016. "Antibodies to β adrenergic and muscarinic cholinergic receptors in patients with Chronic Fatigue Syndrome." Brain, Behavior, and Immunity, Feb 2016; 52: 32-39. Accessed January 25, 2019. https://www.sciencedirect.com/science/article/pii/S0889159115300209

[48] "Histocompatibility complex." NIH Genetics Home Reference, 2009, https://ghr.nlm.nih.gov/primer/genefamily/hla

invaders such as viruses and bacteria." The referenced study regarding HLA and autoimmunity stated:[49]

> "The auto-antibodies against α(1)-adrenergic receptors (α(1)-AAs) with agonist activity likes norepinephrine have been discovered in patients with essential hypertension but the mechanism of α(1)-AA production remains unclear. We supposed the α(1)-AAs be correlated to the HLA-DQB1 and DRB1 alleles."

Another Japanese study looked at the prevalence of HLA alleles in patients with autoimmune hepatitis and anti-ganglionic nicotinic acetylcholine receptor (gAChR) antibodies. They concluded that "particular HLA class II molecules might control the development of anti-gAChR antibodies in the autoimmune response to gAChR."[50]

As previously discussed, there have been some significant findings connecting acetylcholine and NE receptor antibodies to some POTS patients. Therefore, it may be worthwhile to consider HLA gene alleles as a factor in the autoimmune basis of some phenotypes of POTS. Some HLA genes are strongly correlated with autoimmune diseases. It seems that those with certain types of HLA genes may have a more difficult time distinguishing self from pathogen.

More research is required to study HLA genes and POTS. Dr. Ritchie Shoemaker has found a connection between those with certain HLA gene alleles and susceptibility toward mold illness. He theorizes that these patients may have immune systems that are not able to properly "tag" and remove certain pathogens or toxins, including mycotoxins from mold exposure. It is possible that, if there is indeed a correlation with certain HLA genes and POTS patients, that an

---

[49] Sun, Zhu, Wang, Ma, Liao. 2010. "Association analysis about HLA-DRB1, -DQB1 polymorphism and auto-antibodies against α(1)-adrenergic receptors in Chinese patients with essential hypertension. Clinical and Experimental Hypertension Vol 32 (8). Accessed July 1, 2018. https://doi.org/10.3109/10641963.2010.496520

[50] Maeda, et al. 2016. "Association between Anti-Ganglionic Nicotinic Acetylcholine Receptor (gAChR) Antibodies and HLA-DRB1 Alleles in the Japanese Population." PLoS One, vol 11(1): e0146048. https://www.ncbi.nlm.nih.gov/pubmed/26807576

exposure to mold (which has been noted by many POTS patients on social media as a possible trigger for their POTS symptoms) may allow an infiltration of mycotoxins from mold, with the inability to properly detoxify these mycotoxins due to HLA gene variants, and thereby causing immune dysregulation.[51]

When looking at data for POTS, one may also look at research conducted on CFS, as there is a significant overlap with POTS and CFS. CFS patients have been shown to also have POTS in greater than 60% of cases. Those with POTS have also been shown to have CFS in up to 77% of cases.[52]

There are currently no known studies on POTS and mycotoxins. However, some studies have found a link between mycotoxin levels and patients with CFS. This study from 2013 documented a significant correlation between positive mycotoxin levels and those with CFS (93% of subjects were positive for at least one of the mycotoxin types tested), with noted exposure to water damaged buildings in over 90% of cases:[53]

> "Over the past 20 years, exposure to mycotoxin producing mold has been recognized as a significant health risk. Scientific literature has demonstrated mycotoxins as possible causes of human disease in water-damaged buildings (WDB). This study was conducted to determine if selected mycotoxins could be identified in human urine from patients suffering from chronic fatigue syndrome (CFS). Patients (n = 112) with a prior diagnosis of CFS were evaluated for mold exposure and the presence of mycotoxins in their urine. Urine was tested for aflatoxins (AT), ochratoxin A (OTA) and macrocyclic trichothecenes (MT) using Enzyme Linked Immunosorbent Assays (ELISA). Urine specimens from 104 of 112 patients (93%) were positive for at least one mycotoxin (one in the equivocal range). Almost 30% of the cases had more than one mycotoxin present. OTA was the most prevalent mycotoxin detected (83%) with MT as the next most common (44%). Exposure histories indicated current and/or past exposure to WDB in over 90% of cases. Environmental testing was performed in the WDB from a subset of these patients. This

---

[51] "The Biotoxin Pathway." *Surviving Mold*, Accessed December 25,2018. https://www.survivingmold.com/diagnosis/the-biotoxin-pathway

[52] Robertson, Biaggioni, Burnstock, Low, Paton. 2012. *Primer on the Autonomic Nervous System*, Third Edition (p. 533). London, UK: Academic Press.

[53] Brewer, Thrasher, Straus, Madison, Hooper. 2013. "Detection of Mycotoxins in Patients with Chronic Fatigue Syndrome." Toxins (Basel), 2013 Apr; 5(4):605-617. Accessed December 25, 2018. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3705282/

> testing revealed the presence of potentially mycotoxin producing mold species and mycotoxins in the environment of the WDB. Prior testing in a healthy control population with no history of exposure to a WDB or moldy environment (n = 55) by the same laboratory, utilizing the same methods, revealed no positive cases at the limits of detection."

Possible Triggers

Based on the correlation found between mold mycotoxins and CFS patients, and due to the high overlap between POTS and CFS, providers should consider exposure to mold as a possible significant factor in POTS.

Antecedent viral illness has also been noted in numerous studies and articles on POTS. Many of those notes have already been documented earlier in this paper. Therefore, viral illness seems to be a likely trigger.

Lyme Disease has also been linked to POTS in two case studies described in an article entitled: "A Tale of Two Syndromes: Lyme Disease Preceding Postural Orthostatic Tachycardia Syndrome." In this article, a case is described of a female with POTS who had a history of Lyme Disease contracted 6 months prior to onset of POTS symptoms. A second case of a female with a history of Lyme Disease is described, whose POTS symptoms began approximately 3 months after contracting Lyme. The authors postulate on the connection between Lyme Disease and POTS:[54]

> "Borrelia burgdorferi, the spirochete responsible for the tick-borne illness LD [Lyme Disease], results in a multisystem disorder that frequently begins with erythema migrans and may later involve the nervous, musculoskeletal, and cardiovascular systems. While LD usually responds to antibiotic treatment, there is a subgroup of patients who later develop PLDS [Post-Lyme Disease Syndrome]. The syndrome describes patients who experience prolonged subjective symptoms of myalgias, headache, fatigue, irritability, and cognitive dysfunction following treated LD. This condition of subjective complaints is defined by a Borrelia-associated infection adequately treated with antibiotics while

[54] Noyes, Adam M. and Kluger, Jeffrey. 2015. "A Tale of Two Syndromes: Lyme Disease Preceding Postural Orthostatic Tachycardia Syndrome." Ann Noninvasive Electrocardiol 2015; 20(1):82-86. Accessed December 29, 2018. https://doi.org/10.1111/anec.12158

objective findings of other diseases are absent. These patients initially improve with the use of antibiotics and have resolution of physical symptoms and signs of LD. However, after a quiescent period, they again develop symptoms of fatigue, pain, and cognitive dysfunction. Interestingly, these symptoms usually develop within 6 months following successful treatment with antibiotics. The exact etiology of this syndrome remains unclear. The best estimates of the prevalence of PLDS come from studies of patients with erythema migrans who received appropriate antibiotic treatment, of which 10-20% of such patients have persistent or intermittent subjective symptoms of mild to moderate intensity 12 months after completion of therapy.

There are approximately 500,000 patients in the United States known to suffer from POTS, with the majority of cases showing a female predominance of 5:1, and ages between 20 and 50 years. The symptoms of POTS frequently include palpitations, fatigue, weakness, and impaired quality of life in more than 50% of patients. Many of these symptoms can be vague and may overlap with the symptoms seen in other diseases, but importantly with PLDS. The etiopathogenesis between the two syndromes may have a common immunological connection, though remains theoretical at this time. Theories suggest bacterial persistence or autoimmune phenomena such as molecular mimicry causing antibody reactivity to borrelial antigens from the original spirochetal infection that may exist in PLDS. Antineural antibody reactivity was found to be significantly higher in the patients suffering from PLDS (49%) as compared to post-Lyme healthy individuals (18.5%) or healthy individuals without a history of LD (15%) with a $P < 0.01$. The relationship between PLDS and POTS may be explained by this interaction.

Primary neuropathic and secondary type POTS is commonly reported to be precipitated by a febrile illness, often viral, and peripheral autonomic deinnervation, and has been observed with medical illnesses and autoimmune diseases. Studies suggest that the pathophysiology in some POTS patients is related to the production of enzyme-linked immunosorbent assay positive autoantibodies that block the acetylcholine receptor, and against muscarinic and β1/2-adrenergic receptors. The activation of autoantibodies to these receptors produce vasodilation of the vasculature that may contribute to the autonomic changes seen in POTS. Additionally, patients with LD have shown evidence of lymphoplasmoceullular infiltrates in the autonomic ganglia, resulting in sympathetic denervation in the lower extremities and kidneys causing significant sympathetic stimulation related to prolonged orthostatic stress. Consequently, the increased redistribution of blood in the peripheral circulation and relative hypovolemia, cause venous return to the heart to abruptly fall leading to a reflex tachycardia and sympathetic cardiac activity without vasoconstriction."

Another study examined five patients with a history of Lyme disease who later developed POTS. The onset of POTS after contracting Lyme disease ranged from three to twelve years.

They noted that all patients showed a benefit from receiving a pharmacological medication targeted toward increasing acetylcholine availability:[55]

> "Pyridostigmine augments the availability of acetylcholine at the synaptic cleft by inhibiting acetylcholinesterase, an enzyme that causes hydrolysis of acetylcholine. Pyridostigmine has been shown to improve symptoms in patients suffering from POTS or OI. Clinical symptoms of post LD syndrome are debilitating and have been reported to impair quality of life. In our patients, symptoms of fatigue, orthostatic palpitations, cognitive dysfunction and syncope had resulted in substantial impairment of the quality of life in each patient. After diagnosis and initiation of the treatment, all but one patient reported a marked improvement in their symptoms and quality of life. While there is no proven therapy for symptom control in patients suffering from post-treatment LD syndrome, it is possible that some of these patients might have OI as a contributor to their symptoms. Recognition of orthostatic intolerance in this subset of patients may lead to the initiation of appropriate treatment earlier, with subsequent improvement in their symptoms and quality of life. Physicians need to have a high index of suspicion for OI in patients suffering from post-treatment LD syndrome."

A reverse correlation of POTS patients with Lyme Disease may also be found. In the study published in 2018 "Precision Medicine: The Role of the MSIDS Model in Defining, Diagnosing, and Treating Chronic Lyme Disease/Post Treatment Lyme Disease Syndrome and Other Chronic Illness: Part 2," researchers found that, of 200 Lyme Disease patients studied, a significant amount of patients (41.5%) showed evidence of POTS or dysautonomia.[56]

Whether mold, viruses, or pathogens such as *B. burgdorferi*, which causes Lyme Disease, are triggers in POTS has yet to be determined. However, there are correlations with all of these factors. It is also likely that POTS may not have only one identifiable trigger, but may be the result of an accumulation of several factors or triggers.

Norepinephrine, Acetylcholine, and the Immune System

[55] Kanjwal, Karabin, Kanjwal, Grubb. 2011. "Postural orthostatic tachycardia syndrome following Lyme disease." Cardiology Journal, 2011: 18(1), pp. 63-66. Accessed December 29, 2018. https://www.ncbi.nlm.nih.gov/pubmed/21305487

[56] Richard I. Horowitz and Phyllis R. Freeman. 2018. "Precision Medicine: The Role of the MSIDS Model in Defining, Diagnosing, and Treating Chronic Lyme Disease/Post Treatment Lyme Disease Syndrome and Other Chronic Illness: Part 2." Healthcare 2018; 6(4):129. Accessed January 25, 2019. https://www.mdpi.com/2227-9032/6/4/129/htm

Neurotransmitters are now being recognized as having a role in the body that is more complex than "only" regulating nervous system activity. Neurotransmitters have also been found to play an important role in the regulation of the immune system. As previously briefly mentioned, norepinephrine plays not only a role in regulating the autonomic nervous system, but it is also important within the immune system.

Norepinephrine has been shown in animal models to be immunosuppressive. It may compromise the host's ability to fight infection, and may also increase bacterial growth.[57]

One study looked at the effects of various neurotransmitters on T-cell function, and concluded:[58]

> "These results suggested that neurotransmitters can substantially affect various cytokine-dependent T-cell activities. As a whole, our studies suggest an important and yet unrecognized role for neurotransmitters in directly dictating or modulating numerous T-cell functions under physiological and pathological conditions."

In the paper "Nerve Driven Immunity: Noradrenaline and Adrenaline," the authors discuss termination and degradation of norepinephrine, as well as the importance of noradrenaline in the immune system:

> "2.3.3 Mechanisms for Removal
>
> Signal termination of noradrenaline and adrenaline as neurotransmitters and hormones is the result of reuptake through specific membrane transporters and/or of degradation, mainly through monoamine oxidase (MAO)- and catechol-O- methyltransferase (COMT)-mediated pathways (Fig. 2.2).
>
> In the synapse of noradrenergic neurons, termination of the action of noradrenaline is brought about by NET (NorEpinephrine Transporter) (see e.g. Mandela and Ordway 2006)."

---

[57] Stolk, van der Poll, Angus, van der Hoeven, Pickkers, Kox. 2016. "Potentially Inadvertent Immunomodulation: Norepinephrine Use in Sepsis. American Journal of Respiratory and Critical Care Medicine, vol 194(5). Accessed December 25,2018. https://www.atsjournals.org/doi/full/10.1164/rccm.201604-0862CP

[58] Levite, M. 2000. "Nerve-driven immunity. The direct effects of neurotransmitters on T-cell function." Ann N Y Acad Sci. 2000;917:307-21. Accessed December 25, 2018. https://www.ncbi.nlm.nih.gov/pubmed/11268358

"Possible strategies to study the role and the functional relevance of endogenous noradrenaline and adrenaline production in immune cells include:

- Effect of AR [adrenergic receptor] antagonists
- Interference with synthesis/degradation
- Interference with intracellular storage/release/uptake"[59]

"It is thus suggested that noradrenaline and adrenaline directly activate NFkB at least in rodent phagocytes, causing enhanced release of proinflammatory cytokines such as tumor necrosis factor-a, IL-1b and IL-6, resulting in amplification of the acute inflammatory response via a2-ARs (Flierl et al. 2009)."

"In summary, at least circumstantial evidence exists for each of the criteria needed to establish the role of noradrenaline and adrenaline as transmitters in immune cells."

"Noradrenaline and adrenaline exert extensive effects on innate immunity, as discussed in previous sections. Monocytes/macrophages as well as granulocytes are affected by catecholamines and can themselves produce and utilize these transmitters (reviewed by Flierl et al. 2008), which may have significant relevance for bacterial infections and sepsis. The therapeutic effects of a2-AR antagonism or pharmacological inhibition of catecholamine synthesis in rodent models of acute lung injury has been discussed previously (Flierl et al. 2007, 2009). Recently, it has been shown that the b-AR antagonist propranolol may control the susceptibility of severely burned patients to opportunistic pathogens by reducing the occurrence of immunosuppressive M2 monocytes (Kobayashi et al. 2011).

Evidence exists that highly stressful events may promote viral infections (e.g. herpes simplex virus type-1 and varicella zoster virus) through activation of the sympathetic nervous system. For instance, catecholamines directly stimulate the human cytomegalovirus immediate-early (IE) enhancer/promoter in monocytic cells via beta-2 adrenergic receptors, possibly leading to the development of an active human cytomegalovirus infection in latently infected patients (Pr€osch et al. 2000). Noradrenaline has also been shown to accelerate human immunodeficiency virus (HIV) replication in quiescently infected PBMC via b-AR and PKA activation (Cole et al. 1998). In the central nervous system, HIV coat protein gp120 may interfere with the b-AR-mediated regulation of astrocytes and microglia and may alter astroglial 'reactivity' thus promoting neuroinflammation and impairing defense against viral and opportunistic infections (Levi et al. 1993)."

[59] Cosentino, Marco and Marino, Franca. "Nerve Driven Immunity: Noradrenaline and Adrenaline." *Nerve-Driven Immunity*, edited by M. Levite. Wien: Springer-Verlag, 2012, pp. 47-96.

> "Sympathoadrenergic mechanisms represent the main channel of communication between the nervous system and the immune system, and the origins of neuroimmunology itself can be traced back to the understanding of the role of noradrenaline and adrenaline in the modulation of the immune response."[60]

Note that noradrenaline receptor blockers may decrease susceptibility to pathogenic infections in susceptible patients. The authors also have discussed how stressful events may increase the proliferation of viral infections and reactivation of latent viral infections.

Microbial Endocrinology

The neurotransmitters norepinephrine and acetylcholine are very important to more than just the functioning of humans or mammalian species. These neurotransmitters, that are so important to us, are also used by the bacteria and other microbes that live inside of us. Researchers are discovering that these neurotransmitters, along with many other chemicals in the human body, are necessary for certain microbes to be able to reproduce, adapt, and communicate with each other. Exactly how these microbes use our neurotransmitters and other chemicals is an area of research that is still relatively new. We do not yet fully understand how microbes may use the chemicals we generate and circulate, or how the analogous chemicals they generate affect us, but we do have some documented research beginning to emerge. Much more focus, resources, and research is needed in this area of study, which has been termed "Microbial Endocrinology." Mark Lyte, Editor of the textbook *Microbial Endocrinology: The Microbiota-Gut-Brain Axis in Health and Disease* further expands upon this subject:

> "Microbial endocrinology is defined as the study of the ability of microorganisms to both produce and recognize neurochemicals that originate either within the microorganisms themselves or within the host they inhabit. As such, microbial endocrinology represents

[60] Cosentino, Marco and Marino, Franca. "Nerve Driven Immunity: Noradrenaline and Adrenaline." *Nerve-Driven Immunity*, edited by M. Levite. Wien: Springer-Verlag, 2012, pp. 47-96.

> the intersection of the fields of microbiology and neurobiology. The acquisition of neurochemical-based cell-to-cell signaling mechanisms in eukaryotic organisms is believed to have been acquired due to late horizontal gene transfer from prokaryotic microorganisms. When considered in the context of the microbiota's ability to influence host behavior, microbial endocrinology with its theoretical basis rooted in shared neuroendocrine signaling mechanisms provides for testable experiments with which to understand the role of the microbiota in host behavior and as importantly the ability of the host to influence the microbiota through neuroendocrine-based mechanisms." [61]

In another article, Dr. Lyte explains how bacteria may interact with a host's neuroendocrine system, and can even produce chemicals that are similar to our own:[62]

> "The ability of bacterial pathogens to influence behavior has been recognized for decades, most notably bacteria that directly invade the nervous system. However, increasing evidence is mounting that microorganisms may directly interact with elements of the host's neurophysiological system in a noninvasive manner that ultimately results in modification of host behavior. This ability of microorganisms contained within the microbiome to influence behavior through a noninfectious and possibly non-immune-mediated route may be due to their ability to produce and recognize neurochemicals that are exactly analogous in structure to those produced by the host nervous system. This form of interkingdom signaling, which is based on bidirectional neurochemical interactions between the host's neurophysiological system and the microbiome, was introduced two decades ago and has been termed microbial endocrinology."

> "The ability of bacteria to produce neuroendocrine hormones suggests that the interaction of the microbiome with the host may go far beyond the role of such host neuroendocrine-bacterial interactions in infectious disease. It is perhaps underappreciated by most microbiologists that the gut is a highly innervated organ that possesses its own nervous system known as the enteric nervous system (ENS) that is in constant communication with the central nervous system (CNS) through nerves such as the vagus, which directly connect portions of the gut to the brain..."

> "We are just at the beginning of comprehending the meaning of gut-to-brain microbiome interactions and what it ultimately means for host homeostasis including behavior. Recently, the role of bacteria in determining appetite and food preference was proposed. It is intriguing to speculate that microbes play a far larger role in normal homeostasis than previously imagined."

---

[61] Lyte, Mark. 2014. "Microbial endocrinology and the microbiota-gut-brain-axis." Adv Exp Med Biol, 2014; 817:3-24. Accessed January 1, 2019. doi: 10.1007/978-1-4939-0897-4_1.

[62] Lyte, Mark. 2013. "Microbial Endocrinology in the Microbiome-Gut-Brain Axis: How Bacterial Production and Utilization of Neurochemicals Influence Behavior." PLoS Pathog. 2013 NO; 9(11): e1003726. Accessed January 1, 2019. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3828163/

Norepinephrine is one of the neurotransmitters that has been found to be very important to certain bacteria. Norepinephrine has actually been found to potentiate the growth of many different kinds of bacteria. Paul Everest explains in his article "Stress and bacteria: microbial endocrinology" how stress and norepinephrine affect the host, as well as potentiates the growth of certain bacteria:[63]

> "Thus, ill human patients in hospital—whether due to acute illness, infection, any form of accidental/induced trauma or animals reared and transported under some food production conditions—have a neurophysiological response to stress by the local (enteric) and systemic release of catecholamine hormones and, in particular, norepinephrine (noradrenaline) by the enteric nervous system.
>
> It has been recognised for some time that norepinephrine potentiates bacterial growth both in vivo and in vitro and induces expression of virulence determinants in enteric pathogens, particularly *Escherichia coli*. In this issue of *Gut*, Cogan *et al* provide evidence that norepinephrine also regulates virulence in the important intestinal food−borne pathogen *Campylobacter jejuni*. Norepinephrine, in the presence of iron−limiting conditions, increases *C jejuni* growth, motility and bacterial invasion into cultured intestinal (Caco−2) cells and decreases the time taken for the organism to affect Caco−2 cell tight junction barrier function. The implications for animal husbandry in particular and the physiological state of the organism for transmission and disease causation in a human host are intriguing."

He goes on to discuss how norepinephrine may be used by bacteria to assist in their signaling and communication:

> "It has recently been shown that epinephrine/norepinephrine is involved in the quorum sensing of bacteria. Quorum sensing is a cell to cell signalling mechanism in which bacteria respond to hormone−like molecules called autoinducers (AIs) produced by other growing bacteria of the same species in the same environment."

Further into the paper, he discusses the response of the bacteria *E. coli* to norepinephrine:

> "Use of an ex vivo tissue culture model has shown that norepinephrine or dopamine stimulation of enteric nerves in the tissue increases the adhesion of *E coli* 0157 to caecal epithelium which could be prevented by prior treatment with adrenergic receptor antagonists."

---

[63] Everest, Paul. 2007. "Stress and bacteria: microbial endocrinology." Gut, Vol 56(8). Accessed June 29, 2018. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1955526/

In his summary, he makes an important observation regarding the potential impact that stress has on our health:

> "All of us are 'stressed' at some time, and it is intriguing to speculate whether that translates into a particular susceptibility to gastrointestinal or, indeed, any type of infection due to increased production of enteric norepinephrine."

These findings give us a glimpse into the potential consequences of stress. The increased norepinephrine released during a stressful period can increase the growth of pathogenic bacteria, which can cause or proliferate an infection within the host. This may have even deeper impacts if one has prolonged periods of stress (or "chronic stress"), as is becoming the norm for many in the 21st century.

Other researchers are documenting similar findings to what Paul Everest stated regarding norepinephrine and certain bacteria. In a study published in 2007, it was found that epinephrine and norepinephrine increase *E.Coli* infection and virulence, by increasing motility, biofilm formation, upregulating gene expression, and increasing attachment to epithelial cells.[64] The effect of NE on several microbes was also noted in a study performed in 2002:[65]

> "Norepinephrine and dopamine had the greatest enhancing effects on growth of cultures of Pseudomonas aeruginosa and *Klebsiella pneumoniae*, while epinephrine and isoproterenol also enhanced growth to a lesser extent. The growth of *Escherichia coli* in the presence of norepinephrine was greater than growth in the presence of the three other neurochemicals used in the study. Growth of *Staphylococcus aureus* was also enhanced in the presence of norepinephrine, but not to the same degree as was the growth of gram negative bacteria. Addition of culture supernatants from *E. coli* cultures that had been grown in the presence of norepinephrine was able to enhance the growth of *K. pneumoniae*."

---

[64] Bansal, Englert, Lee, Hegde, Wood, Jayaraman. 2007. "Differential Effects of Epinephrine, Norepinephrine, and Indole on *Escherichia coli* O157:H7 Chemotaxis, Colonization, and Gene Expression." Infection and Immunity Vol 75(9). Accessed June 29, 2018. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1951185/

[65] Belay, T. and Sonnenfeld, G. 2002. "Differential effects of catecholamines on in vitro growth of pathogenic bacteria." Life Sci, 2002 Jun 14; 71(4):447-56. Accessed December 25, 2018. https://www.ncbi.nlm.nih.gov/pubmed/12044844

This article titled "Communication between Bacteria and Their Hosts" summarizes how certain bacteria may use their host's norepinephrine:[66]

> "The epinephrine and norepinephrine neurotransmitters play important roles in gut physiology and motility. Of note, epinephrine and norepinephrine play a central role in stress responses in mammals, and stress has profound effects on GI function. Bacterial enteric pathogens exploit these neurotransmitters as signals to coordinate the regulation of their virulence genes."

The article goes further into the subject, explaining the affinity of bacteria for norepinephrine, in particular, as well as mechanisms in which NE may stimulate bacterial growth as well as increase the ability of bacteria to attach themselves to the host tissues:[67]

> "This study found a distinct preference of all the bacteria for the gut catecholamines noradrenaline and dopamine over adrenaline. In the case of *Y. enterocolitica*, there was no growth responsiveness to adrenaline, and the adrenergic catecholamine actually competitively blocked *Y. enterocolitica* responses to noradrenaline and dopamine. These results suggest that bacteria have evolved catecholamine response systems specific for the hormone they will encounter within their particular host niche."
>
> "Catecholamines are physiologically ubiquitous in terms of their signalling functions and they are utilised in organs and tissues throughout the mammalian body. Thus, it might be expected that bacteria occupying a variety of in vivo niches will at some point come into contact with catecholamines and so have cause to evolve sensory systems for monitoring the stress hormone levels of their host. The fact that microbes inhabiting other regions of the body such as the lungs or skin are catecholamine responsive seems to support this hypothesis. In serum-based media, several log-fold increases in cell numbers of *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Bordetella pertussis*, and *B. bronchiseptica* have been reported. Although no effects on growth were observed, O'Neal et al. used microarrays to show that noradrenaline upregulated expression of genes required for host tissue attachment in *Mycoplasma hyopneumoniae*"
>
> "Noradrenaline, adrenaline, dopamine, and the synthetic catecholamine inotropes dobutamine and isoprenaline, were all able to increase staphylococcal growth in blood or serum based media by up to 100,000-fold over controls."
>
> "Blood or serum containing media are bacteriostatic through the sequestration of free Fe by high affinity ferric iron binding proteins such as transferrin and lactoferrin. Because

[66] Moreira, Russell, Mishra, Narayanan, Ritchie, Waldor, Curtis, Winter, Weinshenker, Sperandio. 2016. "Bacterial Adrenergic Sensors Regulate Virulence of Enteric Pathogens in the Gut." mBio vol 7(3) e00826-16. Accessed December 25, 2018. https://mbio.asm.org/content/7/3/e00826-16.full

[67] Freestone, Primrose. 2013. "Communication between Bacteria and Their Hosts." Scientifica, vol 2013, article ID 361073, 15 pages. Accessed December 25,2018. https://www.hindawi.com/journals/scientifica/2013/361073/

iron is so essential for the in vivo proliferation of bacterial pathogens, its limitation by transferrin and lactoferrin is a key innate immune defence against infection. In terms of how catecholamine stress hormones induce growth, it has been shown that catecholamines can act as a kind of siderophore which enables bacteria to access the normally unavailable Fe within transferrin and lactoferrin. Mechanistically, adrenaline, noradrenaline, and dopamine have been shown to form a complex with the ferric Fe present within transferrin and lactoferrin. The use of electron paramagnetic resonance spectroscopy and biochemical analyses showed that catecholamines reduce the ferric iron to ferrous, a valency for which the iron binding proteins have a much lower affinity. The Fe(III) to Fe(II) reduction weakens the bond between the iron and transferrin and lactoferrin, causing Fe release which can then be taken up by bacteria. This bacterial hijacking of host hormones to steal normally secure host Fe is highly relevant to the infectious disease process, as in less than 24 hours the growth enhancement in serum or blood resulting from the addition of catecholamines can be >100,000-fold over control cultures."

"Another mechanism by which catecholamines can induce growth of Gram-negatives involves the production of a bacterial stimulator of growth. This growth stimulator was termed the noradrenaline-induced autoinducer (NE-AI) because it induces its own synthesis and also to distinguish it from the homoserine lactone AIs involved in quorum sensing. The NE-AI is principally produced by Gram-negative enteric bacteria; it is heat stable and has broad cross-species functionality, inducing increases in growth in blood or serum to a level similar to that obtained with the catecholamines. The mechanism by which the NE-AI stimulates growth is unclear but is independent of transferrin or lactoferrin. The NE-AI may have a role in bacterial pathogenicity as it was found to revive viable but nonculturable E. coli and Salmonella. In terms of induction of the NE-AI production, Lyte et al. showed that only a single 4–6 hour exposure to the catecholamines is needed after which the activity induces its own synthesis. This suggests that enteric bacteria are able to retain a 'memory' of even a transient encounter with their host's stress hormones and that catecholamine release during a short-term acute stress could have lasting and widely acting effects on different species of the gut microflora even after stress hormone levels in their host have returned to normal."

"During stress, as well as catecholamines (which are released by the sympathetic nervous system) the hypothalamic-pituitary adrenal axis also induces glucocorticoid stress hormone release by the adrenal gland. It is therefore interesting that exposure to adrenocorticotropic hormone increased attachment of E. coliO157:H7 to colonic mucosa. A study by Verbrugghe et al. showed pig social stress and starvation result in elevated serum cortisol levels and that cortisol increased intracellular proliferation of Salmonella in primary porcine alveolar macrophages."

Another scientific article discusses a specific link and affinity of *Borrelia burgdorferi* for epinephrine (adrenaline) and norepinephrine (noradrenaline):[68]

> *"B. burgdorferi* specifically binds the neuroendocrine stress hormones adrenaline and noradrenaline; it has been proposed that OspA expression is upregulated in response to the production of these hormones in the skin, which is in turn induced by the combined mechanical and pharmacological assault of larval feeding. OspA-deficient spirochaetes cannot bind to tick receptor for OspA (TROSPA) on tick midgut epithelial cells and are eventually expelled from the larval digestive tract with the blood meal waste."

Scientists have also discovered that several pathogens can disrupt neurotransmitters in their hosts. One article discusses how the Lyme Disease pathogen Borrelia burgdorferi can alter these neurotransmitters and cause symptoms that lead to illness:[69]

> "What this means is that *Borrelia burgdorferi* toxins are strongly attracted to fatty cells (such as those of the nervous system), and exert effects that disrupt normal functioning of these cells. These bio-toxins are thought to alter various specific sites in the brain on molecular, structural and chemical levels, interfering with all the major neurotransmitters (dopamine, serotonin, norepinephrine, acetylcholine, GABA). In this way they can cause all manner of neurological and psychiatric symptoms that mimic (or cause) many illnesses, from degenerative diseases such as Parkinson's Disease and Alzheimer's (2), to depression (3) and autistic disorders. Indeed, Dr. Paul Fink, a former president of the American Psychiatric Association, has acknowledged that Lyme disease can contribute to every single psychiatric disorder in the Diagnostic Symptoms Manual IV (DSM-IV), the manual used to diagnose psychiatric disorders."

In the article titled "Microbial Endocrinology," the affinity of and interaction with certain microbes for specific host neurotransmitters is discussed:[70]

> "Microbial Endocrinology has as its foundation the tenet that through their long co-existence with animals and plants, micro-organisms have evolved detection systems for detecting host-associated chemicals such as hormones."

---

[68] Radolf, Caimano, Stevenson, Hu. 2012. "Of ticks, mice and men: understanding the dual-host lifestyle of Lyme disease spirochetes." Nat Rev Microbiol. Vol 10(2): 87-99. Accessed December 25, 2018. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3313462/

[69] "Lyme Disease." The Environmental Illness Resource. Accessed December 25,2018. http://www.ei-resource.org/illness-information/related-conditions/lyme-disease/

[70] Sharaff, Fathima and Freestone, Primrose. 2011. "Microbial Endocrinology." Central European Journal of Biology, vol 6(5): 685-694. Accessed December 28, 2018. DOI: 10.2478/s11535-011-0067-z

> "Most Microbial Endocrinology investigations have concentrated on the interaction of bacteria with the hormones released during stress, such as the catecholamine fight and flight hormones adrenaline, noradrenaline and dopamine."
>
> "While hormones released during stress (principally adrenaline and noradrenaline) have been shown to significantly reduce cell based immune function, Microbial Endocrinology takes the broader view and considers the impact of the stress event from the perspective of the microbe causing the infection."

A table included in this paper lists dozens of pathogenic microbes and the catecholamines documented to have an effect on the specific microbes (with noradrenaline being the most widely listed catecholamine in the list). The paper goes on to discuss how catecholamines may influence pathogen growth or virulence:

> "An obvious question is what is the mechanism by which catecholamines induce bacterial growth?"
>
> "Iron is essential for growth of all bacterial pathogens, and its limitation in blood and mucosal secretions via transferrin and lactoferrin represents one of the most important innate immune defences against infection. Mechanistically, we have shown that catecholamines form complexes with transferrin and lactoferrin, weakening the normally high affinity ferric iron complex to the point of iron loss. This enables bacteria that lack specific systems for acquiring transferrin and lactoferrin sequestered iron to obtain the Fe needed for growth in serum or blood. Recent work from our laboratory used electron paramagnetic resonance spectroscopy used electron paramagnetic resonance spectroscopy and chemical analyses to show that catecholamine complex formation with transferrin and lactoferrin results in reduction of the iron, from ferric to ferrous, a valency for which transferrin and lactoferrin have a much lower affinity, resulting in rapid Fe loss. This iron theft process by catecholamines is significant, as the growth stimulation of bacteria resulting from addition of catecholamines to serum or blood can be over 5 log orders."
>
> "Catecholamines therefore enable bacterial pathogens that lack siderophores or specific acquisition systems for transferrin and lactoferrin- Fe to acquire the iron needed for growth *in vivo*.
>
> Another mechanism by which catecholamines can induce growth of Gram-negative bacteria, particularly enteric species, involves induction of a bacterial growth stimulator. This growth stimulator was termed the NE-AI (noradrenaline-induced autoinducer) to distinguish it from homoserine lactone type autoinducers. The NE-AI induces its own synthesis, is heat stable, and has cross-species functionality, inducing increases in bacterial growth to a magnitude similar to that seen with the catecholamines. The mechanism by which the NE-AI stimulates growth is unsure but has been shown to be

> independent of transferrin or lactoferrin. In terms of its production, investigations into the induction of the *E. coli* NE-AI suggest only a transient 4-6 hour exposure to catecholamines is needed after which the activity induces its own synthesis. This suggests that bacteria can retain a 'memory' of their encounter with their host's stress hormones, and that catecholamine release during a short term acute stress could have lasting and wide acting effects on the bacterial microflora long after catecholamine levels in their host have returned to normal."
>
> "A number of in vitro reports have shown that stress hormones enhance bacterial attachment to gut tissues."
>
> "Chicks directly given noradrenaline by crop instillation had elevated levels of S. enterica serovar Enteritidis in the caeca and liver compared to un-treated control animals. In addition to the catecholamines, glucocorticoid-type hormones are also released during stress which may be significant as the adrenocorticotropic hormone has been shown to significantly increase attachment of E. coli O157:H7 to colonic mucosa. "
>
> A number of in vivo studies exist which show that stress can directly affect the microflora of an animal. Physical stress of mice caused by surgery (partial hepatectomy) or a short-term period of starvation induced significant increases in the number of E. coli adhering to the caecal mucosa of stressed mice compared to control animals. Overgrowth of commensal E. coli, which can cause serious systemic infection, has been shown to occur in the intestines of mice exposed to psychological stressors such as restraint. Recently, Bailey et al. showed that psychologically stressing mice altered the microbial diversity of the gut to such an extent that it directly increased the capacity for an invading enteric pathogen (Citrobacter rodentium) to establish an infection."
>
> "Lyte and Bailey found that numbers of bacteria in the gastrointestinal tract (caeca) of the chemically stressed mice increased by up to 4 log-orders during the 24 hours following administration of the neurotoxin, with commensal E. coli showing the greatest increase. Binding of bacteria to the mouse caecal wall and translocation to the mesenteric lymph nodes (potentially the beginning of a gut-associated infection) were similarly increased."

The paper also discusses the effect of steroid hormones and estrogen on Candida albicans:

> "Yeast can respond to, and bind, steroid hormones, while oestrogen can significantly enhance Candida infectivity, inducing the morphological switch from yeast to the invasive hyphal form. The presence of high affinity binding proteins for oestradiol in the pathogenic yeast C. albicans may provide some explanations for the observed increase in the susceptibility of pregnant women to fungal infections."

The authors also review how pathogens may have adapted, as well as the proven effect of antagonists of catecholamine receptors on bacteria:

> "This ubiquitous distribution of catecholamines throughout nature suggests that microorganisms in general have had ample time preceding the evolution of plants and animals to come into contact with catecholamine-like hormones, and to develop mechanisms by which to recognize them as indicators they are within proximity of a suitable host."
>
> "Interestingly, antagonists of mammalian adrenergic and dopaminergic receptors can also block catecholamine effects in bacteria. Addition of specific a- (but not b-) adrenergic receptor antagonists blocked bacterial growth responses to noradrenaline and adrenaline but did not affect growth stimulation by dopamine. Conversely, dopaminergic receptor antagonists could block growth responses to dopamine but not to either adrenaline or noradrenaline. This suggests that bacterial response systems exist for catecholamine recognition that possess a degree of specificity similar to that demonstrated for catecholamine receptors in animals. In terms of a bacterial catecholamine receptor, there is so far no genomic evidence for the existence of adrenergic or dopaminergic receptors in bacterial species. However, Clarke et al. used in vitro constructs to show that noradrenaline and adrenaline were recognised by the E. coli O157:H7 two-component regulator sensor kinase QseC, leading to the proposal that this could be a bacterial receptor for these catecholamines."[71]
>
> "On the other side, reversal of the inhibitory effects of noradrenaline and adrenaline on human monocytes may result in immunostimulation. In agreement with this hypothesis, recently the b2-AR antagonist propranolol has been shown to reduce circulating immunosuppressive M2b monocytes in severely burned children, suggesting that the increased susceptibility of severely burned patients to opportunistic pathogens might be controlled by propranolol (Kobayashi et al. 2011)."

These studies all show how chronic or frequent stress, and other causes of high NE and catecholamine release, has major implications in regard to host immune health as well as directly impacting the proliferation and strength of certain pathogenic microbes within the human body.

Acetylcholine has also been shown to be very important to immunity against other pathogens, parasites, and overall immune response[72]:

> "Recent data indicate that acetylcholine (ACh), a neurotransmitter which regulates a variety of physiological functions, also influences the immune system, and that lymphocytes have the capacity to synthesise and release ACh, controlling local innate

[71] Sharaff, Fathima and Freestone, Primrose. 2011. "Microbial Endocrinology." Central European Journal of Biology, vol 6(5): 685-694. Accessed December 28, 2018. DOI: 10.2478/s11535-011-0067-z

[72] Darby, Schnoeller, Vira, Culley, Bobat, Logan, Kirstein, Wess, Cunningham, Brombacher, Selkirk, Horsnell. 2015. "The M3 Muscarinic Receptor Is Required for Optimal Adaptive Immunity to Helminth and Bacterial Infection." PLoS Pathogens 11(3): e1004727. Accessed May 25, 2018. https://doi.org/10.1371/journal.ppat.1004636

> immune responses and suppressing inflammation. Thus far however there has been little evidence to suggest that ACh influences adaptive immunity, characterised by activation and effector functions of lymphocytes. We show here that during the immune response to two different pathogens, ACh signals through muscarinic receptors, and the M3 receptor subtype specifically, resulting in enhanced activation and cytokine production by 'helper' T lymphocytes which protect the host against infection."

ACh also protects the body against pathogenic infection, including *Candida albicans*. This study shows that acetylcholine modulates inflammatory responses, and inhibits Candida's biofilm:[73]

> "Acetylcholine was shown to have the ability to inhibit *C. albicans* biofilm formation *in vitro* and *in vivo*. In addition, acetylcholine protected *G. mellonella* larvae from *C. albicans* infection mortality. The *in vivo* protection occurred through acetylcholine enhancing the function of hemocytes while at the same time inhibiting *C. albicans* biofilm formation. Furthermore, acetylcholine also inhibited inflammation-induced damage to internal organs. This is the first demonstration of a role for acetylcholine in protection against fungal infections, in addition to being the first report that this molecule can inhibit *C. albicans* biofilm formation. Therefore, acetylcholine has the capacity to modulate complex host-fungal interactions and plays a role in dictating the pathogenesis of fungal infections."

Candida, which produces acetaldehyde, has further been implicated as a possible factor in causing autonomic imbalance via the potential blocking of acetylcholine:[74]

> "Autonomic Imbalance Other frequently occurring symptoms are those characteristic of imbalance of the autonomic nervous system. Acetylcholine is the neurotransmitter at both sympathetic and parasympathetic synapses of the autonomic nervous system, and also mediates the action of post-ganglion parasympathetic neurons. Acetaldehyde is a potent synaptic blocking agent and could be responsible for the autonomic imbalance in these patients, perhaps in part by binding to the sulfhydryl group of CoA, thus affecting the availability of the acetyl group required for the synthesis of acetylcholine."

---

[73] Rajendran, Borghi, Falleni, Perdoni, Tosi, Lappin, O'Donnell, Greetham, Ramage, Nile. 2015. "Acetylcholine Protects against *Candida albicans* Infection by Inhibiting Biofilm Formation and Promoting Hemocyte Function in a *Galleria mellonella* Infection Model." Eukaryotic Cell Vol 14 no. 8. Accessed May 25, 2018. http://ec.asm.org/content/14/8/834.full

[74] C. Orian Truss, M.D. 1984. "Metabolic Abnormalities in Patients with Chronic Candidiasis " Journal of Orthomolecular Psychiatry, vol 13(2). Accessed January 25, 2019. http://orthomolecular.org/library/jom/1984/pdf/1984-v13n02-p066.pdf

Parasites have also been found to degrade acetylcholine. The relationship between parasites and ACh is further explained in an article from 2015[75]:

> "We started to look at these neurotransmitters in relation to the adaptive immune response because of work that we had been doing on helminth parasites," explained Professor Murray Selkirk, Head of the Department of Life Sciences at Imperial College London."
>
> "These parasitic worms have sophisticated ways of suppressing the immune system of their host. They release an enzyme that degrades acetylcholine. We suspected that this must be benefitting them in some way, suggesting that the neurotransmitter is doing something which is detrimental to the parasite."

Candida has not only been linked to ACh, but also to NE. Studies have shown that *Candida albicans*, and other fungi and bacteria, can directly inhibit beta-adrenergic receptor binding:[76]

> "Several fungi produce inhibitors of beta-adrenergic and dopaminergic binding. The inhibition is similar to that previously observed with bacteria, although the fungal inhibitor may be more potent than that produced by bacteria."
>
> "Beta-adrenergic and dopaminergic receptor binding were both inhibited by products of *Fusarium sp*. And *E. coli* when tested in C6 and Y1 cells. Activation of adenylate cyclase secondary to beta-adrenergic hormone binding occurs in C6 cells, but not in Y1 cells. If binding had been inhibited in only one cell type, it could be possible that bacteria or fungal products, or both, affect the internal cell mechanisms first, and that such an alteration would then modify the external binding site as a secondary effect. Since this is not the case, it is likely that the inhibitor blocks binding directly."

The study summarized that "Strains of *Aspergillus flavus*, *Fusarium* sp., *Rhizopus* sp. and *Candida albicans* all produced inhibitors of beta-adrenergic receptor binding."

Viruses have also been implicated in benefitting from host NE. A study from 2015 showed that plasma norepinephrine (NE) and epinephrine (EP) levels of patients with ANS

---

[75] Gallagher, Laura. 2015. "Scientists uncover new role for neurotransmitter that helps fight infection." Imperial College London. Accessed May 25, 2018. http://www.imperial.ac.uk/news/164064/scientists-uncover-role-neurotransmitter-that-helps/

[76] Coleman, Donta. 1993. "Inhibition of beta-adrenergic binding by fungal metabolites." Journal of Medical Microbiology 38: 44-48. Accessed May 25, 2018. https://dx.doi.org/10.1099/00222615-38-1-44

dysregulation infected with a virus (EV71) were higher than controls. The study concluded:[77] "The plasma levels of NE and EP elevated in EV71-infected patients with ANS dysregulation and PE. Both NE and EP enhanced the percentages of infected cells and virus titers in EV71 infection *in vitro*. NE and EP may play a role in the pathogenesis of EV71 BE complicated with ANS dysregulation and PE."

In summary, the well-documented dysregulation of various neurotransmitters (norepinephrine and acetylcholine) in POTS may have a deeper role than currently recognized. These neurotransmitters may also be playing a role in immune system dysregulation as well as in the growth and virulence of various pathogens. These neurotransmitters may also be disrupted by certain pathogens.

Mechanisms of Autoimmunity

With the importance of the specific chemicals norepinephrine and acetylcholine to not only the host, but also to many pathogens (including bacteria, fungi, and viruses), as well as the documented link indicating a viral or other infection preceding POTS, and the patient creating auto-antibodies against the receptor sites for these chemicals, it begs the question: why is the body creating auto-antibodies against these receptors? And, is there a pathogenic influence?

Pathogens have been able to survive throughout history by using their ability to adapt and use various protective mechanisms. Is it therefore possible that certain pathogens may begin somehow attacking acetylcholine or adrenergic receptors? If so, then, perhaps the body recognizes this attack, and in an effort to target and remove the pathogen, also targets the body's own receptors in the process, thereby causing increased levels of acetylcholine or adrenergic

[77] Liao, S. Wang, J. Wang, Yu, Liu. 2015. "Norepinephrine and Epinephrine Enhanced the Infectivity of Enterovirus 71." PLoS ONE 10(8): e0135154. Accessed May 25, 2018. https://doi.org/10.1371/journal.pone.0135154

receptor autoantibodies. There are currently no studies analyzing this theory, but this idea may warrant further research. It is currently widely accepted that the body may, instead, be "confused" or "misguided" when it creates auto-antibodies, but perhaps the idea that the body has a specific purpose for this activity should not be overlooked or ignored.

It is feasible that pathogens are "docking" on these receptor sites, possibly to either hijack the host's chemicals in order to strengthen their own viability, or to decrease the host's ability to use these chemicals in the support of immune system. If so, the body might be attempting to remove the pathogens docked at those receptor sites via auto-antibodies produced against those receptors. *Todar's Online Textbook of Bacteriology* explains how bacteria can interact directly with host cell receptors:[78]

> "In its simplest form, bacterial adherence or attachment to a eucaryotic cell or tissue surface requires the participation of two factors: a receptor and an ligand. The receptors so far defined are usually specific carbohydrates or peptide residues on the eucaryotic cell surface. The bacterial ligand, called an adhesion, is typically a macromolecular component of the bacterial cell surface which interacts with the cell receptor."

It also states:

> "Tissue tropism: particular bacteria are known to have an apparent preference for certain tissues over others…"
>
> "Mechanisms of Adherence to Cell or Tissue Surfaces
>
> The mechanisms for adherence may involve two steps:
>
> 1. Nonspecific adherence: reversible attachment of the bacterium to the eucaryotic surface (sometimes called "docking")
> 2. Specific adherence: reversible permanent attachment of the microorganism to the surface (sometimes called "anchoring").
>
> Specific adherence involves permanent formation of many specific lock-and-key bonds between complementary molecules on each cell surface. Complementary receptor and adhesin molecules must be accessible and arranged in such a way that many bonds form

[78] Kenneth Todar, PhD. "*Mechanisms of Bacterial Pathogenicity*." Todar's Online Textbook of Bacteriology. 2012. http://textbookofbacteriology.net/pathogenesis_2.html

over the area of contact between the two cells. Once the bonds are formed, attachment under physiological conditions becomes virtually irreversible.

The article also links bacteria receptor docking with receptor antibodies:

"Adhesion (of the bacterium to the eucaryotic cell surface) is inhibited by:

a. Isolated adhesin or receptor molecules
b. Adhesin or receptor analogs
c. Enzymes and chemicals that specifically destroy adhesins or receptors
d. Antibodies specific to surface components (i.e., adhesins or receptors)"

This information implies that one possible reason that a host body would create autoantibodies toward its own cell receptors is due to docking of a bacteria onto this specific type of receptor on a cell surface, in an attempt to remove the bacteria from the receptor.

There may be other mechanisms that link pathogens and receptor autoantibodies. Host-Pathogen Interactions (HPIs) is a newer area of research. In an article from 2018, different mechanisms by which pathogens can subvert the host immune system are discussed, including how pathogens may directly interfere with protein binding on cell surfaces:[79] "To evade host defense, pathogens hijack host proteins at different levels: sequence, structure, motif, and binding surface, i.e., interface. Interface similarity allows pathogen proteins to compete with host counterparts to bind to a target protein, rewire physiological signaling, and result in persistent infections, as well as cancer."

Another theory is that the pathogens themselves create proteins that the body then targets via autoantibodies. These proteins may be so similar to other proteins on the host receptor site that the receptors themselves also get targeted by the antibodies. This idea is termed "molecular mimicry."

---

[79] Guven-Maiorov, Tsai, Ma, Nussinov. 2018. "Interface-Based Structural Prediction of Novel Host-Pathogen Interaction." *Computational Methods in Protein Evolution* pp 317-335. Accessed January 4, 2019. https://www.ncbi.nlm.nih.gov/pubmed/30298406

Molecular mimicry has been documented as a possibility with another autoimmune disease, myasthenia gravis (MG), which, similar to POTS, is also linked to antibodies targeting acetylcholine receptors (AChR). In MG, this molecular mimicry has been observed with antibodies targeting both the AChR as well as peptides produced by the herpes simplex virus (HSV):[80]

> "We suggested the possibility that amino acid sequences shared between an infectious agent and a host protein (molecular mimicry) might enable the microbe to initiate an immunologic response that subsequently cross-reacts with the 'self' determinant, leading to an autoimmune disorder."
>
> "Relatively little is known about the etiology of MG, although its pathogenesis is well understood and its autoantigens have been characterized. We have identified a sequence homology between HuAChR alpha-chain 160-167 [Human AChR amino acid residues 160-167] and HSV-1 GpD residues 286-293 [herpes simplex virus type 1 glycoprotein D amino acid residues 286-293] and shown immunochemically that the four shared amino acids are sufficient to induce significant cross-reactivity against both peptides and native proteins."
>
> "Perhaps an immune response generated against a microbe like HSV could cross-react with host AChR. This could result in a virus induced autoimmune response leading to autoimmune disease. The disease- causing microbe may be cleared by the initial immune response and thus be difficult to detect or could persist in a latent state. Subsequent reactivation would enable the microbe to serve as a potent modulator of the autoimmune disease by antigenic stimulation."
>
> "The ability of molecular mimicry to cause disease has been shown experimentally. Others have documented immunologic cross-reactivity with bacteria and AChR, further suggesting that several microbial agents may play a role in MG."

This claim has been substantiated in further studies, as in this article titled "Antigen Mimicry in Autoimmune Disease. Can immune responses to microbial antigens that mimic acetylcholine receptor act as initial triggers of Myasthenia gravis?," which further states that

[80] Schwimmbeck, Dyrberg, Drachman, Oldstone. 1989. "Molecular Mimicry and Myasthenia Gravis. An autoantigenic site of the acetylcholine receptor alpha-subunit that has biologic activity and reacts immunochemically with herpes simplex virus." J Clin Invest. 1989 Oct; 84(4): 1174-1180. Accessed January 1, 2019. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC329775/

several pathogens may cross-react with the human acetylcholine receptor and trigger autoimmune disease:[81]

> "Myasthenia gravis (MG) is an autoimmune disease caused by autoantibodies against self acetylcholine receptor (AChR). Although a great deal of information is known about the molecular and cellular parameters of the disease, its initial trigger is not known. In order to study the possibility of the involvement of microbial antigens that mimic AChR in triggering MG, we have searched the microbial proteins in the data bank for regions that are similar in structure to the regions of human (h) AChR alpha chain recognized by autoAbs in MG patients. Hundreds of candidate structures on a large number of bacterial and viral proteins were identified. To test the feasibility of the idea, we synthesized four microbial regions similar to each of the major autodeterminants of hAChR (alpha12-27, alpha111-126, alpha122-138, alpha182-200) and investigated their ability to bind autoAbs in MG and normal sera controls. It was found that MG sera recognized a significant number of these microbial regions. The results indicate that in some MG cases immune responses to microbial antigens may cross-react with self antigen (in this case hAChR) and could constitute initial triggers of the disease."

Another study from 2014 determined a link between West Nile Virus and Myasthenia Gravis, specifically noting molecular mimicry as a possibility based on the details of the research study: [82]

> *"Introduction*: Viruses are commonly cited as triggers for autoimmune disease. It is unclear if West Nile virus (WNV) initiates autoimmunity. *Methods*: We describe 6 cases of myasthenia gravis (MG) that developed several months after WNV infection. All patients had serologically confirmed WNV neuroinvasive disease. None had evidence of MG before WNV. *Results*: All patients had stable neurological deficits when they developed new symptoms of MG 3 to 7 months after WNV infection. However, residual deficits from WNV confounded or delayed MG diagnosis. All patients had elevated acetylcholine receptor (AChR) antibodies, and 1 had thymoma. Treatment varied, but 4 patients required acetylcholinesterase inhibitors, multiple immunosuppressive drugs, and intravenous immune globulin or plasmapheresis for recurrent MG crises. *Conclusions*: The pathogenic mechanism of MG following WNV remains uncertain. We hypothesize that WNV−triggered autoimmunity breaks immunological self−tolerance to initiate MG, possibly through molecular mimicry between virus antigens and AChR subunits or other autoimmune mechanisms."

---

[81] Deitiker, Ashizawa, Atasssi. 2000. "Antigen mimicry in autoimmune disease. Can immune responses to microbial antigens that mimic acetylcholine receptor act as initial triggers of myasthenia gravis?" Human Immunology, 2000 Mar; 61(3): 255-65. Accessed January 4, 2019. https://doi.org/10.1016/S0198-8859(99)00117-2

[82] Leis, Szatmary, Ross, Stokic. "West nile virus infection and myasthenia gravis." Muscle & Nerve. 2014 Jan; 49(1): 26-9. Accessed January 4, 2019. https://doi.org/10.1002/mus.23869

Other studies have further determined the ability of viruses (such as HSV-1) to cross-react with the human acetylcholine receptor, such as this one titled, "Evidence for antigenic cross-reactivity between herpesvirus and the acetylcholine receptor." Summarizing the results of the study: "The results indicate that there are one or more antigenic epitopes shared by herpesvirus and the AChR. Studies are in progress to define the pathogenetic significance of this molecular mimicry."[83]

The following article discusses the evidence pointing to MG being a disease driven by a pathogenic component:[84]

> "Students of autoimmune diseases are witnessing a revolutionary movement that can be summarized by the difference between etiology and pathogenesis. Before the revolution, hazy images of 'forbidden clones' and a faulty understanding of immunologic tolerance led to the assumption that that autoimmunization was the etiology - the cause - of certain diseases. Now, however, the process of immunologic self-destruction seems better understood as a pathogenesis - i.e., as a mechanism that produces a lesion. The distinction that we draw is more than semantic. For example, there is abundant evidence from animal models that clinically silent, chronic viral infections can lead to deposits of antigen-antibody complexes that mimic all the features of an autoimmune disease. The essential feature in these models is that the immune response is unable to neutralize the infectious agent, which thus persistently stimulates the formation of antibody against itself."

> "If the thymic abnormalities of myasthenia gravis do represent the effects of persistent stimulation by a virus, we would expect an increased number of B cells in the thymus and new antigenic determinants on the surface of thymocytes. Abdou and his colleagues, as they report elsewhere in this issue, have found both. The increased number of intrathymic B cells may reflect the presence of lymphoid follicles in the gland. The appearance of new antigenic determinants on cell membranes is typical of nonlytic infection with viruses, such as the Epstein-Barr and C-type RNA viruses. Such surface antigens can be recognized in vitro by sensitized lymphocytes that transform into lymphoblasts. Abdou et al. observed this reaction when cells from the hyperplastic thymuses of patients with myasthenia gravis were incubated with autologous blood

---

[83] Gebhardt, BM. 2000. "Evidence for antigenic cross-reactivity between herpesvirus and the acetylcholine receptor." Journal of Neuroimmunology, 2000 Jun 26; 105(2): 145-53. Accessed January 4, 2019. https://doi.org/10.1016/S0165-5728(00)00204-6

[84] Datta, Syamal K. and Schwartz, Robert S. 1974. "Infectious (?) Myasthenia." The New England Journal of Medicine. 1974; 291: 1304-1305. Accessed January 2, 2019. DOI: 10.1056/NEJM197412122912711.

> lymphocytes. All the findings mentioned - thymic hyperplasia, intrathymic follicles, increased number of B cells and recognition by autologous lymphocytes of new surface antigens on thymocytes - are consistent with a local, persistent viral infection of the thymus."

In an article titled, "Sharing of Antigenic Determinants between the Nicotinic Acetylcholine Receptor and Proteins in *Escherichia coli*, *Proteus vulgaris*, and *Klebsiella pneumoniae* - Possible Role in the Pathogenesis of Myasthenia Gravis," the authors document cross-reactivity between the acetylcholine receptor and several pathogens:[85]

> "The causes of autoimmune diseases in human beings are in most instances unknown. There are, however, countless hypotheses about what may be responsible for an immunologic attack on autoantigens during autoimmune processes. Some of these hypotheses involve infectious agents. One popular notion is that many autoimmune diseases may be caused directly or indirectly by viral infections. Viruses may launch autoimmune processes by altering the host's immune system, by causing the release or expression of sequestered antigens, or through antigenic determinants shared by the virus and the host cells. There is now considerable published evidence that antigenic determinants are shared by viruses and mammalian cells. Herpes simplex virus and measles virus, for example, contain proteins that share antigenic determinants with human intermediate filaments. It has also been shown that the titer of autoantibodies is often increased both during and after viral infections. But viruses are not the only infectious agents that may be capable of eliciting an autoimmune attack. The sharing of antigenic determinants by proteins in neurons affected by Chagas' disease and by proteins of Trypanosoma cruzi is an example of how a parasitic infection may be responsible for an autoimmune process. The demonstration that in animals immunized with group A streptococcus, antibodies develop that react with myocardium provides an example from the bacterial sphere, when it is viewed in the context of an association between rheumatic heart disease and streptococcal infections."

> "Since it has not been shown that myasthenia gravis is associated with any particular infectious disease, it is difficult, for the time being, to put the blame for immunization on an obligatory pathogen. However, in our search for an environmental antigen that may share epitopes with the acetylcholine receptor, we examined proteins from 10 species of bacteria for their reactivity with antibodies against the acetylcholine receptor. We raised monoclonal antibodies against the acetylcholine receptor and used them on Western blots

[85] Stefansson, Dieperink, Richman, Gomez, Marton. 1985. "Sharing of Antigenic Determinants between the Nicotinic Acetylcholine Receptor and Proteins in *Escherichia coli*, *Proteus vulgaris*, and *Klebsiella pneumoniae* - Possible Role in the Pathogenesis of Myasthenia Gravis." The New England Journal of Medicine. 1985; 312: 221-225. Accessed January 2, 2019. DOI: 10.1056/NEJM198501243120407.

> to examine proteins from homogenates of *Escherichia coli*, *Proteus vulgaris*, *Staphylococcus aureus*, group A beta-hemolytic streptococcus, *Klebsiella pneumoniae*, *Shigella flexneri, Bacillus subtilis*, *Peptostreptococcus putridus*, P*seudomonas aeruginosa*, and *Clostrium perfringens*.
>
> We report that the alpha-subunit of the acetylcholine receptor and two membrane proteins from *E. coli*, as well as two proteins from *K. pneumoniae*, share at least one antigenic determinant, and that the alpha-subunit of the acetylcholine receptor and a protein in *Prot. vulgaris* share at least two antigenic determinants."
>
> "E. coli, K. pneumoniae, and Prot. vulgaris are all normal bacterial flora in the human gut. It also appears that they have all been in contact with the immune system of the host. The data presented here point to the possibility that the primary event in myasthenia gravis is an exposure to antigenic determinants shared by normal bacterial flora and the acetylcholine receptor. These determinants in the bacteria would have to be capable of inducing the formation of antibodies (immunogenic), whereas in the acetylcholine receptor they would merely cross-react with antibodies already formed (antigenic)."

There has been considerably more research completed on MG in comparison to POTS. As of the date of this paper, there were approximately 24 articles on MG for every one article on POTS in PubMed. Therefore, in the effort to expand research on POTS, more consideration should be given to documented research which has already been completed on other conditions that share overlapping features, such as with acetylcholine antibodies found in both MG and in many POTS patients. The research on MG presented documents a clear link between pathogens and acetylcholine antibodies.

In the article "Molecular Mimicry as a Mechanism of Autoimmune Disease," the authors further discuss viral and bacterial pathogens as a trigger of autoimmune disease, as well as findings that several pathogens may cause autoimmunity:[86]

> "Although host genetic background contributes to the induction of an immune response to self, epidemiological and molecular evidence implicates infectious agents (viral and

[86] Cusick, Libbey, Fujinami. 2012. "Molecular Mimicry as a Mechanism of Autoimmune Disease." Clin Rev Allergy Immunol. 2012 Feb; 42(1): 102-111. Accessed January 4, 2019. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3266166/

bacterial) as the principal environmental insults responsible for the induction of autoimmune diseases."

"Prolonged proinflammatory responses to infections have been associated with the initiation and exacerbation of autoimmune diseases."

"Although a number of viruses and bacteria have been linked to the initiation of certain autoimmune diseases, identifying a particular virus or bacteria that is solely responsible for the induction of an autoimmune response is rare. This occurrence is due to the potential for multiple infections being involved in priming the immune system and other infections triggering disease, which could explain why no one viral infection has been conclusively linked to the development of immune mediated autoimmune diseases. However, there are a variety of examples of bacterial infections initiating and exacerbating autoimmune diseases. *Streptococcus pyogenes* is a gram-positive bacterium which causes group A streptococcal infection that is responsible for a number of diseases. The complications associated with *S. pyogenes* are rheumatic fever and glomerulonephritis. The infection causes the production of cross-reactive antibodies in response to the bacteria. Antibodies recognize the M protein (virulence factor) and the N-acetyl-β-D-glucosamine (GLcNAc) of *S. pyogenes*and cross-react with myosin leading to heart damage. Further evidence of molecular mimicry due to the production of cross-reactive antibody includes infection with gram-negative bacteria, such as *Klebsiella pneumonia* and *Campylobacter jejuni*. Infection with *K. pneumonia* or *C. jejuni*leads to the production of cross-reactive antibodies able to recognize the self-antigens histocompatibility leukocyte antigen (HLA)-B27 and gangliosides, which induces ankylosing spondylitis and Guillan-Barre′ syndrome, respectively. Examples of human autoimmune diseases with possible links with molecular mimicry are presented in Table 1."

A study done in 1995 proved that a parasite, *Trypanosoma cruzi*, was able to cause autoimmunity against host beta1-adrenergic receptor (norepinephrine receptor) via molecular mimicry in Chagas' disease:[87]

"A pentapeptide derived from the P0 ribosomal protein of *T. cruzi* showed high similarity with a pentapeptide in the receptor loop. The results presented here show not only that this peptide is a cross-reacting B cell epitope, but also that it is important for the functional activity of the autoantibodies on the receptor."

[87] Ferrari, Levin, Wallukat, Elies, Lebesgue, Chiale, Elizari, Rosenbaum, Hoebeke. 1995. "Molecular mimicry between the immunodominant ribosomal protein P0 of Trypanosoma cruzi and a functional epitope on the human beta 1-adrenergic receptor." J Exp Med. 1995 Jul 1; 182(1): 59-65. Accessed January 4, 2019. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2192084/

> "These results unambiguously prove that *T. cruzi* is able to induce a functional autoimmune response against the cardiovascular human beta 1-adrenergic receptor through a molecular mimicry mechanism."

In the article "Rethinking Molecular Mimicry in Rheumatic Heart Disease and Autoimmune Myocarditis: Laminin, Collagen IV, CAR, and B1AR as Initial Targets of Disease," it is proposed, again, that perhaps not one single pathogen causes autoimmune disease, but possibly a combination of pathogens may cause a specific autoimmune disease:[88]

> "It is worth noting that the model suggested is predicated on a significant departure from Koch's postulates. Koch's postulates have, of course, been the standard for demonstrating disease causation for more than a century but assume that each disease has a single pathogenic cause. The proposition that RHD, AM, and perhaps other autoimmune diseases are due to specific combinations of pathogens runs contrary to the isolation of the single "causative" agent of disease. A multifactorial set of "disease postulates" will be required instead, in which it is demonstrated that more than one pathogen is associated with an autoimmune disease, that no single one of these pathogens can induce the autoimmune disease, but that a combination of the pathogens does induce autoimmune disease."

Based on the research presented, it seems that it is at least possible that the body detects pathogenic influence and then works to either remove or attack the pathogen that is blocking or inhibiting the receptor site, or via molecular mimicry, resulting in the host producing autoantibodies against the receptor site itself. It may, therefore, be beneficial in this scenario to further assist the body in removing the pathogen, via additional immune support or antimicrobials. Doing so may then calm the autoimmune response, and thus, allow the host's neurotransmitters to again be used and processed in an efficient and "normal" manner.

Comorbidities: MCAS and EDS

[88] Root-Bernstein, Robert. 2014. "Rethinking Molecular Mimicry in Rheumatic Heart Disease and Autoimmune Myocarditis: Laminin, Collagen IV, CAR, and B1AR as Initial Targets of Disease." Front Pediatr. 2014; 2: 85. Accessed January 4, 2019. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4137453/

Two common comorbidity of POTS worth mentioning are mast Mast Cell Activation Syndrome (MCAS) and Ehlers-Danlos syndrome (EDS). Due to the overlap in both symptoms and number of patients with both POTS and either MCAS and/or EDS, these other syndromes are both worth going into further detail. One study found that of fifteen surveyed participants, nine (60%) had both POTS and EDS. Six of the nine with both POTS and EDS had symptoms of a mast cell disorder (another 67%).[89] Another study noted that 30% of POTS patients also have MCAS (Mast Cell Activation Syndrome).[90] Symptoms of both MCAS and POTS also greatly overlap, with 17 of 48 MCAS symptoms overlapping with 33 POTS symptoms.[91] Some of the most common symptoms in MCAS include: fatigue, pain, presyncope or syncope, headache, urticaria, paresthesias, nausea or vomiting, chills, migratory edema, and abdominal pain.[92]

Mast cell activation is connected to an overactive sympathetic nervous system response. The parasympathetic nervous system, which is often blunted in POTS, is needed to regulate mast cell function:[93]

> "Often considered as the archetype of neuroimmune communication, much of our understanding of the bidirectional relationship between the nervous and immune systems has come from the study of mast cell-nerve interaction. Mast cells play a role in

---

[89] Ingrid Cheung and Peter Vadas. 2015. "A New Disease Cluster: Mast Cell Activation Syndrome, Postural Orthostatic Tachycardia Syndrome, and Ehlers-Danlos Syndrome." Journal of Allergy and Clinical Immunology, Vol 135(2): AB65. Accessed January 13, 2019. https://doi.org/10.1016/j.jaci.2014.12.1146

[90] Shibao, Arzubiaga, Robertsll, Raj, Black, Harris, Biaggioni. 2005. "Hyperadrenergic Postural Tachycardia Syndrome in Mast Cell Activation Disorders." Hypertension. 2005; 45:385-390. Accessed January 13, 2019. https://www.ahajournals.org/doi/10.1161/01.HYP.0000158259.68614.40

[91] Weinstock, Brook, Myers, Goodman. 2018.
Successful treatment of postural orthostatic tachycardia and mast cell activation syndromes using naltrexone, immunoglobulin and antibiotic treatment." BMJ Case Reports, Volume 2018 Jan. Accessed January 13, 2019. https://www.ahajournals.org/doi/10.1161/01.HYP.0000158259.68614.40

[92] Afrin, Self, Menk, Lzarchick. 2016. "Characterization of Mast Cell Activation Syndrome." Blood, vol 2016(128):3683. Accessed January 13, 2019. http://www.bloodjournal.org/content/128/22/3683?sso-checked=true

[93] Forsythe P. (2015) The Parasympathetic Nervous System as a Regulator of Mast Cell Function. In: Hughes M., McNagny K. (eds) Mast Cells. Methods in Molecular Biology (Methods and Protocols), vol 1220. Humana Press, New York, NY

> resistance to infection and are extensively involved in inflammation and subsequent tissue repair. Thus, the relationship between mast cells and neurons enables the involvement of peripheral and central nervous systems in the regulation of host defense mechanisms and inflammation. Recently, with the identification of the cholinergic anti-inflammatory pathway, there has been increased interest in the role of the parasympathetic nervous system in regulating immune responses. Classical neurotransmitters and neuropeptides released from cholinergic and inhibitory NANC neurons can modulate mast cell activity, and there is good evidence for the existence of parasympathetic nerve-mast cell functional units in the skin, lung, and intestine that have the potential to regulate a range of physiological processes."

Mast cell activation has clear links to stress and injury: "Mental or emotional stress has been shown to cause mast cell degranulation in several different tissues. Several lines of experimental evidence indicate that stress, working through the sympathetic nervous system, or the hypothalamus-pituitary-adrenal axis, stimulates peripheral nerves to release neuropeptides that bind to receptors on the mast cells, causing them to degranulate."[94] Another study confirms this connection: "Mast cells are implicated in brain injuries, neuropsychiatric disorders, stress, neuroinflammation, and neurodegeneration. Brain mast cells are the first responders before microglia in the brain injuries since mast cells can release prestored mediators. Mast cells also can detect amyloid plaque formation during Alzheimer's disease (AD) pathogenesis. Stress conditions activate mast cells to release prestored and newly synthesized inflammatory mediators and induce increased blood-brain barrier permeability, recruitment of immune and inflammatory cells into the brain and neuroinflammation."[95]

[94] Baldwin, AL. 2006. "Mast cell activation by stress." Methods Mol Biol. 206;315:349-60. Accessed January 13, 2019. https://www.ncbi.nlm.nih.gov/pubmed/16110169

[95] Kempuraj, Selvakumar, Thangavel, Ahmed, Zaheer, Raikwar, Iyer, Bhagavan, Beladakere-Ramaswamy, Zaheer. 2017. "Mast Cell Activation in Brain Injury, Stress, and Post-traumatic Stress Disorder and Alzheimer's Disease Pathogenesis." Front Neurosci. 2017; 11: 703. Accessed January 13, 2019. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5733004/

Mast cell activation has also been linked to infections including *Borrelia burgdorferi* (the spirochete which causes Lyme disease):[96]

> "While mast cells are primarily known as effector cells in allergic reactions, recent studies suggest that they can be directly activated by bacterial products and are required for the expression of immunity against certain bacteria via secretion of TNF-alpha, which attracts activated neutrophils to sites of infection. Activated mast cells also appear capable of phagocytizing and killing bacterial pathogens, and they can present antigenic peptides to class II major histocompatibility complex (MHC)-restricted CD4+ or class I MHC-restricted CD8+ T cells. Thus, mast cells activated by pathogens may modulate subsequent immune or inflammatory events."
>
> "In this study, we show that B. burgdorferi spirochetes have the ability to induce degranulation and TNF-alpha release from mouse MC/9 mast cells and rat PMCs in vitro."

Mycotoxins (from fungi or mold), which have been previously mentioned as possibly relevant to POTS, can also affect mast cell release:[97]

> "Exposure to molds is most commonly associated with allergies and asthma. However, it is now thought to be associated with many complex health problems, since some molds, especially Tricho- derma, Fusarium and Stachybotrys spp, produce mycotoxins that are absorbed from the skin, airways, and intestinal lining. People exposed to molds and mycotoxins present with symptoms affecting multiple organs, including the lungs, musculoskeletal system, as well as the central and peripheral nervous systems. Furthermore, evidence has recently implicated exposure to mycotoxins in the pathogenesis of autism spectrum disorder. The effects of mycotoxins can be mediated via different pathways that include the secretion of pro-inflammatory cytokines, especially from mast cells."

The article further discusses the link and how mycotoxins may trigger neurological disorders:

> "Increasing evidence suggests the presence of localized inflammation in the brain in patients with ASD. Environmental triggers, such as mycotoxins, have been associated with ASD. Such triggers could increase the permeability of the gut-blood and

---

[96] Jeffrey Talkington and Steven P. Nickell. 1999. "*Borrelia burgdorferi* Spirochetes Induce Mast Cell Activation and Cytokine Release." Infect Immun. 1999 Mar;67(3): 1107-1115.. Accessed January 13, 2019. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC96436/

[97] Ratnaseelan, Tsilioni, Theoharides. 2018. "Effects of Mycotoxins on Neuropsychiatric Symptoms and Immune Processes." Clinical Therapeutics, vol 40(6): 903-917. Accessed January 13, 2019. https://www.clinicaltherapeutics.com/article/S0149-2918(18)30229-7/pdf

> blood-brain barriers through mast cell mediators, especially cytokines, allowing circulation and environmental toxins to pass into the brain, trigger microglia proliferation, and disrupt neuronal connectivity."

Ehlers-Danlos syndromes (EDS) is another comorbidity of POTS. EDS is defined as "a group of connective tissue disorders that can be inherited and are varied both in how they affect the body and in their genetic causes. They are generally characterized by joint hypermobility (joints that stretch further than normal), skin hyperextensibility (skin that can be stretched further than normal), and tissue fragility."[98] The symptoms of EDS (depending upon type) may include joint hypermobility, loose or unstable joints (which may dislocate or subluxate), joint pain, hyperextensible joints, skin hyper-extensibility, fragile skin, slow and poor wound healing, chronic and early onset musculoskeletal pain, fragility in or rupturing of the arteries or other tissues, scoliosis, poor muscle tone, mitral valve prolapse.[99]

There have been a few studies documenting the connection and overlap between POTS and EDS. One study done in 2014 revealed that of 39 POTS patients studied, 7 patients, or 18%, also had EDS. This was significantly higher than the prevalence of EDS within the general population (0.02%). They concluded that "The presence of EDS may be significantly higher in patients with POTS than that of the general population and in autonomic patients without POTS. We suspect an additional underlying mechanism of POTS caused by EDS."[99]

Another study published in 2017 examined the rate of POTS or orthostatic intolerance in EDS patients (joint hypermobility type, or JHS/EDS-HT). They found that in 35 JHS/EDS-HT adults

---

[98] "What are the Ehlers-Danlos Syndromes?" The Ehlers-Danlos Society, Accessed January 19, 2019. https://www.ehlers-danlos.com/what-is-eds/

[99] Wallman, Weinberg, Hohler. 2014. "Ehlers-Danlos Syndrome and Postural Tachycardia Syndrome: a relationship study." J Neurol Sci, 2014 May 15; 340(1-2):99-102. Accessed January 19, 2019. https://www.ncbi.nlm.nih.gov/pubmed/24685354

tested, 48.6% were positive for POTS via a tilt table test, and 31.4% showed orthostatic intolerance.[100]

Joint hypermobility type of EDS is the one type of EDS whose genes are unknown. Therefore, diagnosis of this type is purely clinical and includes assessment of the mobility of joints in the patient (Beighton Scoring System).[101]

At least some types of EDS may possibly also be connected to a pathogenic infection. Hypermobility-type EDS has been linked to a Bartonella infection in one case study. The patient was confirmed to have a diagnosis of EDS, hypermobility type III, via several experts, and presented with severe hypermobility. Upon successful treatment for Bartonella koehlerae and Bartonella henselae infections, the patient's hypermobility completely resolved:[102]

> "Recent evaluations by rheumatologists and EDS experts at Harvard and Johns Hopkins Hospitals reported that the patient met criteria for EDS, hypermobility type III. Genetic testing was not performed (as there is no genetic lesion known presently to be associated with EDS type III)."
>
> "On presentation to the primary author (BRM) in June 2010, the patient was wearing bilateral wrist and elbow braces. She had cervical lymph node enlargement, extremity edema, ligamentous laxity, tenosynovitis, shoulder and elbow subluxations, and elbow joint crepitus. Immediately prior to this examination, she was being considered for surgical interventions. In view of the joint crepitance and "popping" reproduced with each articulation, her findings of joint subluxation were consistent with mechanisms of meniscal dislocation, articular plica or pannus. In the context of EDS, skin elasticity was normal."

---

[100] Celletti, Camerota, Castori, Censi, Gioffre, Calcagnini, Strano. 2017. "Orthostatic Intolerance and Postural Orthostatic Tachycardia Syndrome in Joint Hypermobility Syndrome/Ehlers-Danlos Syndrome, Hypermobility Type: Neurovegetative Dysregulation or Autonomic Failure?" Biomed Res Int. 2017; 2017:9161865. Accessed January 19, 2019. https://www.ncbi.nlm.nih.gov/pubmed/28286774

[101] "EDS Diagnostics 2017." The Ehlers-Danlos Society. Accessed January 19, 2019. https://www.ehlers-danlos.com/eds-diagnostics/

[102] Mozayeni, Maggi, Bradley, Breitschwerdt. 2018. "Rheumatological presentation of Bartonella koehlerae and Bartonella henselae bacteremias." Medicine (Baltimore). 2018 Apr; 97(17): e0465. Accessed January 13, 2019. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5944489/

> "Four weeks after starting antibiotics, joint pain was decreased. By August 2010, joint hypermobility had resolved (Beighton score 0/9) and the sesamoid bone had united."
>
> "An expanding spectrum of disease manifestations are being associated with the genus *Bartonella*. In this patient, clinical, microbiological and therapeutic results suggest that *Bartonella* spp. may play a role in the pathogenesis of joint hypermobility. In addition to reporting fatigue, muscle pain and joint pain, the veterinarian in this case report experienced a progressive increase in joint laxity resulting in a diagnosis at 2 major medical centers of hypermobile Ehlers–Danlos syndrome (EDS type III). Recent research supports a potential role for mast cell activation and dysregulation in a subset of nongenetically mediated EDS patients with joint hypermobility syndrome. In addition to the lung and gastrointestinal tract, mast cells are prevalent in cutaneous tissues throughout the body. In the context of a plausible pathogenesis, a long-standing *Bartonella* spp. infection, accompanied by chronic mast cell activation could potentially contribute to ongoing damage to connective tissues; thereby resulting in clinical findings indicative of EDS."

Borrelia burgdorferi, which causes Lyme Disease, is also clearly linked with collagen disruption. It has a high affinity for collagen and "can colonize and persist in multiple tissue sites despite vigorous host immune responses," where it "exploit[s] molecular and structural features to establish microcolonial refugia."[103] The study "*Borrelia burgdorferi* Binds to, Invades, and Colonizes Native Type I Collagen Lattices," examined the ability of *B. burgdorferi* to bind directly to collagen structures:[104]

> "*Borrelia burgdorferi* binds strongly to the extracellular matrix and cells of the connective tissue, a binding apparently mediated by specific proteins and proteoglycans."

The paper "Damage of Collagen and Elastic Fibres by *Borrelia Burgdorferi* – Known and New Clinical and Histopathological Aspects" further describes the damage that *B. burgdorferi* can do to collagen:[105]

---

[103] Cabello, Godfrey, Newman. 2007. "Hidden in plain sight: Borrelia burgdorferi and the extracellular matrix." Trends Microbiol. 2007 Aug; 15(8):350-4. Accessed January 25, 2019. https://www.ncbi.nlm.nih.gov/pubmed/17600717

[104] Zambrano, Beklemisheva, Bryksin, Newman, Cabello. 2004. "Borrelia burgdorferi Binds to, Invades, and Colonizes Native Type I Collagen Lattices." Infect Immun. 004 Jun; 72(6):3138-3146. Accessed January 25, 2019. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC415685/

[105] Müller, Kurt E. 2012. "Damage of Collagen and Elastic Fibres by Borrelia Burgdorferi - Known and New Clinical and Histopathological Aspects. Open Neurol J. 2012; 6:179-186. Accessed January 25, 2019. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3751012/

> "Borrelia are capable of breaking down soluble and insoluble ground substance within the extracellular matrix. They activate metalloproteases, cause collagen to dissolve and can colonise as microcolonies in collagen fibres. They inhibit the regeneration of collagen promoted by fibronectin, and hence delay the healing process or prevent it completely."

Based on the affinity of certain microbes for collagen, and the damage they may do which can mimic EDS, it may be beneficial for the patient to be examined by a practitioner who is knowledgeable in specific pathogenic infections, including Borrelia and Bartonella.

Although EDS is currently considered to be an inherited disorder (although, again, the actual genetic links to the hypermobility type have not yet been discovered), the pathophysiology should be examined further, including possible nutrient deficiency links. Zinc status should be checked in those with EDS. A paper from 2017 entitled "Zinc as a Gatekeeper of Immune Function," summarized how a zinc transporter may be malfunctioning in EDS:[106]

> "Ehlers-Danlos syndrome (EDS) is a human disorder characterized by joint hypermobility, hyperelasticity of the skin, progressive kyphoscoliosis, and severe hypotonia of skeletal muscles. The zinc transporter ZIP13 plays crucial roles in bone, tooth, and connective tissue development. Disturbed zinc homeostasis due to ZIP13 malfunction appeared to contribute to EDS pathogenesis, whereby the mutant ZIP13 protein was quickly degraded."
>
> "Elevated levels of inflammatory markers, ROS and MMPs are well known to cause tissue injury in numerous tissues. Since EDS is accompanied by disturbed collagen synthesis, and MMPs are one key factor in collagenolysis, MMP malfunction can be considered as a possible explanation for EDS. In this context, zinc signals are crucial because inflammation, as well as MMP hyperfunction, accompanies serum hypozincemia.
>
> Hence, altered intracellular zinc level in EDS might be due to ZIP13 malfunction. For this reason, a possible therapeutic approach could be based on the regulation of the mutant ZIP13 protein stability."

[106] Wessels, Maywald, Rink. 2017. "Zinc as a Gatekeeper of Immune Function." Nutrients, 2017 Dec; 9(12):1286. Accessed January 19, 2019. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5748737/

A paper titled "A novel therapeutic strategy for Ehlers-Danlos syndrome based on nutritional supplements" discusses how specific nutrients may be beneficial in EDS:[107]

> "Ehlers–Danlos syndrome is a rare disorder, comprising a group of related inherited disorders of connective tissue, resulting from underlying abnormalities in the synthesis and metabolism of collagen. This proposal is specifically concerned with Ehlers–Danlos syndrome classic type (formerly Types I–III), which is characterized by joint hypermobility and susceptibility to injury/arthritis, skin and vascular problems (including easy bruising, bleeding, varicose veins and poor tissue healing), cardiac mitral valve prolapse, musculo-skeletal problems (myopathy, myalgia, spinal scoliosis, osteoporosis), and susceptibility to periodontitis. No treatment is currently available for this disorder. The novel aspect of this proposal is based on: (i) increasing scientific evidence that nutrition may be a major factor in the pathogenesis of many disorders once thought to result from defective genes alone; (ii) the recognition that many of the symptoms associated with Ehlers–Danlos syndrome are also characteristic of nutritional deficiencies; (iii) the synergistic action within the body of appropriate combinations of nutritional supplements in promoting normal tissue function. We therefore hypothesize that the symptoms associated with Ehlers–Danlos syndrome may be successfully alleviated using a specific (and potentially synergistic) combination of nutritional supplements, comprising calcium, carnitine, coenzyme Q10, glucosamine, magnesium, methyl sulphonyl methane, pycnogenol, silica, vitamin C, and vitamin K, at dosages which have previously been demonstrated to be effective against the above symptoms in other disorders."

Based on the major overlap of POTS with both EDS and MCAS, the information found on these comorbidities should also be considered as having potentially a major impact on POTS symptoms in the patient.

Nutrient Deficiencies

Although more research is needed, there have been some studies examining the correlation of specific nutrient deficiencies in POTS patients. Those nutrient deficiencies that

[107] Mantle, Wilkins, Preedy. 2005. "A novel therapeutic strategy for Ehlers-Danlos syndrome based on nutritional supplements." Medical Hypotheses 2005; Vol 64(2):279-283. Accessed January 19, 2019. https://www.ncbi.nlm.nih.gov/pubmed/15607555

have been shown to have a positive correlation with POTS include Vitamin B12, Iron, Vitamin D, C, and E, and Vitamin B1.

One study found a correlation with Vitamin B12 levels and POTS. It noted the importance of B12 in the production of epinephrine from norepinephrine, as a cofactor in the degradation of catecholamines, and also in nerve health via myelin synthesis. The researchers discovered that vitamin B12 levels were significantly lower in the POTS group compared to the control (47% deficient in the POTS group, compared to 18% deficiency in the control group).[108]

Another study by Pektas, et al. discovered a correlation between Vitamin B12 deficiency and children presenting with vasovagal syncope (which can be a comorbidity of POTS). They noted that the prevalence of B12 deficiency was significantly higher in the children with a positive head-up tilt test, compared to controls (80% deficient vs. 52%). 32.5% of the children with a positive tilt test also met the POTS criteria. The prevalence of Vitamin B12 deficiency was even more pronounced in the POTS group vs. controls (with over 92% of children in this group showing a deficiency).[109]

Another study noted that adolescent POTS patients had lower iron storage levels and higher cases of mild anemia when compared to control groups. 50% of the POTS patients had low iron storage compared to 14% of controls. 25% of teenage females and 16% of teenage males with POTS showed an iron deficiency, compared with only 9% and 1% of the control

---

[108] Oner, Guven, Tavli, Mese, Yilmazer, Demirpence. 2014. "Postural Orthostatic Tachycardia Syndrome (POTS) and Vitamin B12 Deficiency in Adolescents." Pediatrics, Vol 133 (1). Accessed December 25, 2018. https://www.ncbi.nlm.nih.gov/pubmed/24366986

[109] Pektas, Koken, Koca. 2018. "Serum vitamin B-12 in children presenting with vasovagal syncope." Asia Pac J Clin Nutr, 27(1): 176-181. Accessed December 25, 2018. https://www.ncbi.nlm.nih.gov/pubmed/29222896

groups, respectively. Finally, 18% of the teenage females and 43% of the teenage males with POTS showed anemia, compared with only 1.5% and 0.1% of controls.[110]

A study conducted by Antiel, et al. showed a correlation between low ferritin levels as well as low Vitamin D levels and patients with POTS. They noted a significant association with low Vitamin D levels and those with orthostatic intolerance.[111]

In a study conducted in 2015, researchers further documented a correlation between low Vitamin D in POTS patients. Out of 180 patients with POTS, 79 had normal levels (greater than 30ng/mL), 10 patients had insufficient levels (between 20.0 and 29.9ng/mL), and 91 patients had deficient levels of Vitamin D (less than 20ng/mL). Therefore, over 56% of POTS patients studied had insufficient or deficient levels of Vitamin D.[112]

One case study also showed a patient with POTS achieve remission by supplementing with Vitamin D over a period of several months.[113]

Note that iron and Vitamin D levels have been found to become dysregulated with pathogenic infections.[114] [115] [116]

---

[110] IT Jarjour and LK Jarjour. 2013. "Low iron storage and mild anemia in postural tachycardia syndrome in adolescents." Clin Auton Res, 23(4): 175-9. Accessed December 25, 2018. https://www.ncbi.nlm.nih.gov/pubmed/23720007

[111] Antiel, Caudill, Burkhardt, Brands, Fischer. 2011. "Iron insufficiency and hypovitaminosis D in adolescents with chronic fatigue and orthostatic intolerance." South Med Journal, 104(8): 609-11. Accessed December 25, 2018. https://www.ncbi.nlm.nih.gov/pubmed/21886073

[112] Chandralekha Ashangari and Amer Suleman. 2015. "Vitamin D Deficiency Study in Postural Orthostatic Tachycardia Syndrome." Circulation: Cardiovascular Quality and Outcomes, 2015; 8:A121. Accessed December 25, 2018. https://www.ahajournals.org/doi/abs/10.1161/circoutcomes.8.suppl_2.121

[113] Shilpa, Sacerdote, Bahtiyar. 2012. "1-α hydroxylation defect in postural orthostatic tachycardia syndrome: remission with calcitriol supplementation." BMJ Case Rep; 2012: bcr0220125730. Accessed December 25, 2018. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3433525/

[114] Gomes, Moreira, Mesquita, Gomes. 2018. "Modulation of Iron Metabolism in Response to Infection: Twists for All Tastes." Pharmaceuticals, 11(3): 84. Accessed June 22, 2019. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6161156/

Vitamin C and Vitamin E have also shown to be helpful in those with POTS. One study found that Vitamin C administration decreased heart rate, increased blood volume, and increased circulation in those with POTS.[117] Another study found that chronic Vitamin E administration decreased the rise in heart rate during a head-up tilt test (which tests postural orthostatic stress) in healthy subjects. They concluded that Vitamin E may exert cardioprotective effects.[118]

Thiamine Deficiency

Dr. Derrick Lonsdale is a practitioner who worked at the Cleveland Clinic for over 20 years. The majority of his research involves Thiamine (Vitamin B1). Per Dr. Lonsdale, there is a major overlap of symptoms in Thiamine (B1) Deficiency (which can manifest as a disease known as beriberi in its later stages) and POTS. In his paper titled "Dysautonomia, A Heuristic Approach to a Revised Model for Etiology of Disease," he states:[119]

> "Beriberi is the prototype of autonomic dysfunction. It is the best known nutritional deficiency disease caused by an imbalance between ingested calories and the vitamins required for their oxidation, particularly thiamin. Long thought to be abolished in modern medical thinking, there are occasional isolated reports of the full-blown disease in developed Western cultures. Apart from genetically and epigenetically determined disease, evidence is presented that marginal high calorie malnutrition, particularly with reference to simple carbohydrates, is responsible for widespread dysautonomia. The brain and heart are the organs that have a fast rate of oxidative metabolism and are

---

[115] Kell, Douglas B. 2018. "No effects without causes: the Iron Dysregulation and Dormant Microbes hypothesis for chronic, inflammatory diseases." Biological Reviews, vol 93 (3): 1518-1557. Accessed June 22, 2019. https://onlinelibrary.wiley.com/doi/full/10.1111/brv.12407

[116] Mangin, Sinha, Fincher. 2014. "Inflammation and Vitamin D: the infection connection." Inflamm Res, 63(10): 803-819. Accessed June 22, 2019. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4160567/

[117] Stewart, Ocon, Medow. 2011. "Ascorbate improves circulation in postural tachycardia syndrome." Am J Physiol Heart Circ Physiol. 2011 Sep; 301(3): H1033-1042. Accessed December 25, 2018. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3191072/

[118] Olatunji, Soladoye. 2008. "Effects of chronic administration of vitamin E on haemodynamic responses to postural stress or cold pressor test in apparently healthy young men." Niger Postgrad Med J, 2008 Dec; 15(4): 225-8. Accessed December 25, 2018. https://www.ncbi.nlm.nih.gov/pubmed/19169338

[119] Lonsdale, D. 2009. "Dysautonomia, a heuristic approach to a revised model for etiology of disease." Evid Based Complement Altern Med. 2009 Mar; 6(1). Accessed December 9, 2018. doi: 10.1093/ecam/nem064

> affected early by any mechanism that reduces oxidative efficiency. It is hypothesized that this results in a chaotic state of the hypothalamic/autonomic/endocrine axis."

Dr. Lonsdale discusses the mechanism by which thiamine may cause autonomic dysfunction, which could be via oxygen deprivation to the brain:

> "Simon suggested a metabolic similarity in WKS [Wernicke's encephalopathy] and autism. It was pointed out that thiamin deficiency, by disabling the aerobic pathway for glucose metabolism, is equivalent to oxygen deprivation. An acute episode of asphyxia brought about by different means, affects the same brainstem nuclei."

He also discusses the connection between thiamine deficiency and the immune system, stating:

> "As the immune response breaks down there is more susceptibility to overwhelming infection. Opportunist organisms may invade where aerobic metabolism is degraded."

In the conclusion of this paper, he states how thiamine is implicated in ANS dysregulation:

> "Evidence has been produced to indicate that various forms of mild to moderate vitamin deficiencies result in functional changes in the autonomic nervous system. This is clearly shown by a study of the clinical effects seen in beriberi. It is hypothesized that the predictable loss of efficiency in oxidative metabolism is the key to understanding the association of dysautonomia with many different diseases.
>
> It is suggested that a gradual increase in oxidative dysfunction also gives rise to changes in organs, causing subsequent organic disease in some cases. The ample evidence of dysautonomia with various nutrient deficiencies, referenced in this article, suggests strongly that the state of redox potential in the high oxygen demand automatic centers of the brainstem and limbic system is impaired."

He goes onto explain how this type of deficiency could come about in modern civilization and first-world countries with supposed adequate nutrition:

> "It has long been known that increasing the ingestion of simple carbohydrate in the diet automatically increases thiamin requirements. Lonsdale and associates provided evidence that the enormous consumption of sugar in America represents high calorie malnutrition."
>
> "It is suggested that high caloric malnutrition, particularly in the form of simple carbohydrates, is a common cause of defective autonomic control mechanisms in the lower brain that can be likened to the early stages of classic beriberi."

Therefore, simple supplementation with thiamine may not be adequate to provide the thiamine required for the ANS. Diet, including ingestion of simple carbohydrates, is an important factor that needs to be closely examined.

Some of the symptoms of Beriberi include: cardiovascular and respiratory disturbances, including tachycardia, low blood pressure, high pulse pressure, and reduced vital capacity, gastrointestinal dysmotility, including gastroparesis, esophagitis, heartburn, constipation, loss of appetite, thirst, nausea, and vomiting, There are also numerous nervous system disruptions. As stated in the book: *Thiamine Deficiency Disease, Dysautonomia, and High Calorie Malnutrition* by Dr. Derrick Lonsdale[120], "As indicated previously in reference to vasomotor function, the ANS was functionally altered early in the course of the disease. Early beriberi must therefore be considered in the differential diagnosis of dysautonomia." Other symptoms of beriberi include peripheral neuropathy, vertigo and ataxia.

He goes on to conclude:

> "Clinically, when high-dose thiamine therapy is administered, in many cases dysautonomia symptoms resolve."
>
> "Thiamine is a rate-limiting cofactor in a set of mitochondrial enzymes that are central to oxidative metabolism. This is in addition to its roles in nerve myelination, neurotransmission, immune function, central sodium (Na+), and potassium (K+) homeostasis, and a veritable array of other important physiological roles."

Also, of importance is the information noted regarding sodium and potassium homeostasis. This balance is often thrown off in those with POTS. Thiamine also has a direct link with acetylcholine, as further stated by Dr. Lonsdale:

---

[120] Derrick Lonsdale and Chandler Marrs. *Thiamine Deficiency Disease, Dysautonomia, and High Calorie Malnutrition*. London, United Kingdom: Academic Press, 2017.

> "Animal studies indicate that thiamine binds to the presynaptic nicotinic receptors exhibiting anticholinesterase activity and increasing ACh release in the central nervous system.
>
> ...A thiamine derivative, thiochrome, allosterically binds to M1- to M4-type muscarinic receptors, increasing ACh affinity to the M4 receptors by three- to fivefold. Since the M4 autoreceptor is inhibitory, slowing ACh release, the impact of thiamine deficiency would result in altered ACh feedback mechanisms at the receptor level. This would potentially activate a more dominant sympathetic response, particularly in the tissues where the M4 receptors in the heart, central nervous system, and musculature predominate."

He further discusses the mechanisms in which thiamine deficiency may cause dysautonomia, and he also discusses POTS, in particular:

> "The brain and heart are the organs that have a fast rate of oxidative metabolism and are affected early by any mechanism that induces oxidative deficiency. Beriberi is a prototype for dysautonomia in its early stages and it may be a combination of autonomic and myocardial failure that produces the typical beriberi heart."
>
> "ANS dysregulation of the heart muscle can be seen clearly in the recently recognized dysautonomia called postural orthostatic tachycardia syndrome (POTS). The primary manifestation of teh syndrome is orthostatic intolerance with an excessive tachycardic response (>30 bpm increase from baseline) upon standing. Secondarily, however, the syndrome is marked by a wide variety of additional autonomic disturbances. As one might expect, the full scope of symptoms comorbid with POTS is quite diverse (Dysautonomia Information Network). Briefly, however, comorbid symptoms of POTS include the following:
>
> - Lightheadedness, fainting, and general weakness
> - Gastrointestinal dysmotility including gastroparesis and/or excessive vomiting
> - Heart palpitations, shortness of breath, and tremulousness
> - Loss of sweating or excessive sweating, and heat and/or cold intolerance
> - Light and/or noise sensitivity
> - Mood lability
>
> As with our discussion of blepharospasm, the diversity of symptoms recognized with POTS is indicative of widespread autonomic disturbance and should point the clinician accordingly. In Dr. Lonsdale's experience, the etiology of POTS, like that of other autonomic disturbances, resides within the chemistry, specifically, mitochondrial chemistry and oxidative capacity. When oxidative capacity is impaired, autonomic dysfunction emerges."

Dr. Lonsdale concludes:

> "Once dysautonomia is considered as a diagnosis, the similarities with beriberi should point the clinician toward thiamine. Indeed, reports of thiamine deficiency, along with the constellation of symptoms indicative of autonomic dysfunction, have emerged across multiple, seemingly disparate, populations."

There have been some studies that that found a thiamine deficiency in some patients diagnosed with dysautonomia or POTS. One study describes a family with dysautonomia and abnormal erythrocyte transketolase levels, indicating thiamine deficiency. The family had symptomatic improvement with dietary changes and supplementation.[121]

In a study done in 2017, researchers found that 6% of POTS patients had vitamin B1 deficiency, and one out of four deficient patients showed significant improvement in their POTS symptoms following B1 supplementation.[122] Although this may not appear to be a significant finding based on numbers, perhaps a better study would have been to trial all POTS patients on high-dose B1 supplementation, since laboratory testing for this vitamin is rather difficult, and high doses of B1 are considered non-toxic, as explained in the article "Thiamine (Vitamin B1) written by Dr. Aviva Fattal-Valevski[123]:

> "The diagnosis of thiamine deficiency is mainly clinical since routine laboratory tests are not available and awaiting the results of a diagnostic assay can lead to a delay in diagnosis. Thiamine is not measured in the blood since blood contains only about 0.8% of the total body thiamine, and the concentration is too low to allow precise extrapolation of the total thiamine status. Urinary excretion of thiamine is not a very reliable method for assessing tissue stores, and similar to the blood levels, it is a reflection of the immediately preceding intake. In contrast, transketolase activity, which is measured by the thiamine

---

[121] Lonsdale, Shamberger, Obrenovich. 2011. "Dysautonomia in autism spectrum disorder: case reports of a family with review of the literature." Autism Research and Treatment Vol 2011, Article ID 129795. Accessed December 9, 2018. http://dx.doi.org/10.1155/2011/129795

[122] Blitshteyn, Svetlana. 2017. "Vitamin B1 deficiency in patients with postural tachycardia syndrome (POTS)." Neurological Research, vol 39 (8). Accessed December 9, 2018. https://doi.org/10.1080/01616412.2017.1331895

[123] Fattal-Valevski, Aviva. 2011. "Thiamine (Vitamin B1)." Journal of Evidence-Based Complementary & Alternative Medicine, 16(1) 12-20. Accessed December 16, 2018. https://journals.sagepub.com/doi/pdf/10.1177/1533210110392941

> pyrophosphate effect assay, is the most reliable indicator of thiamine functional status. Erythrocyte transketolase activity is a sensitive indicator of tissue stores. Red blood cells, which lack mitochondria, have no alternative means of generating NADPH save the pentose phosphate pathway. Also, NADPH is required to reduce glutathione in order to maintain the normal structure of red blood cells and to maintain hemoglobin in the ferrous state. Transketolase is a thiamine pyrophosphate-requiring enzyme, which catalyzes reactions in the pentose phosphate pathway. As such, the level of transketolase activity in red blood cells is a reliable diagnostic indicator of thiamine status. The erythrocyte transketolase test requires a sample of hemolyzed blood to be incubated with excess ribose 5-phosphate in the presence of excess added thiamine pyrophosphate (matched with a control that has no added thiamine pyrophosphate). After the incubation period, the amounts of remaining substrate and the product formed are measured. Any enhancement in enzyme activity resulting from the added thiamine pyrophosphate indicates that the sample was originally deficient in thiamine to some extent. The extent of deficiency in thiamine is expressed in percentage stimulation over the control value (Table 2). An increase of more than 15% in enzyme activity is a definitive marker of deficiency.
>
> Elevated blood pyruvate and lactate measurements are useful, but the many false positive test results make it difficult to establish a diagnosis. For example, sepsis, cardiogenic shock, and meningitis can imitate thiamine deficiency disease and are associated with lactic acidosis. However, the persistence of lactic acidosis and a rise following a glucose load strongly support the diagnosis and should alert the physician to the possibility of thiamine deficiency. Clinical response to thiamine administration is the most practical indication for diagnosis. If the patient responds to treatment, it is safe to assume that a measure of thiamine deficiency had been responsible for the condition. Thiamine is not toxic in high levels, which means that this approach carries little risk."

As of the current date (2018), no laboratories in the United States were found to provide testing for Erythrocyte transketolase activity. Therefore, any testing for B1 may be considered inaccurate.

Thiamine deficiency has also been linked to decreased acetylcholine metabolism, as mentioned earlier. In the paper "The Role of the Cholinergic System in Thiamin Deficiency," the authors state:[124]

[124] Gibson, Barclay, Blass. 1982. "The Role of the Cholinergic System in Thiamine Deficiency." Annals of the New York Academy of Sciences, vol 378(1): 382-403. Accessed January 13, 2019.

> "The formation of acetylcholine by brain slices from thiamin-deficient pigeons declined approximately 40%. The addition of thiamin to the potassium-stimulated brain slices totally reversed these decreases."
>
> "Several factors may cause the decline in acetylcholine turnover in severe thiamin deficiency: decreased availability of acetyl CoA or choline, changes in synthetic or degradative enzymes, or an abnormal release mechanism. Choline availability is not limiting since high affinity uptake is not decreased, and high concentrations of choline do not increase acetylcholine synthesis by thiamin-deficient ganglia. The activities of the synthetic enzyme, choline acetyltransferase, or the degradative enzyme, acetylcholinesterase, do not change (Table 13). The enzymes that require thiamin and are involved in production of acetyl coA show a uniform depression in severe pyrithiamin-thiamin deficiency."
>
> "Thiamin deficiency may also alter the release of acetylcholine. Sacchi et al. concluded from their studies on ganglia that 'the site of thiamin action is located in the mechanism through which transmitter is synthesized and released at the synapse.'"

The paper also discusses the responses of thiamin deficiency to electrophysiological stimulation:

> "Electrophysiological studies on the superior cervical ganglia from thiamin-deficient rats provide considerable insight into the pathophysiology of thiamin deficiency. At slow rates of presynaptic stimulation, control and thiamin-deficient ganglia respond similarly, but at rapid stimulation rates, the synaptic response is lost. These decrements in synaptic transmission occur even though axonal conduction is unaffected and the amplitude and conduction velocity of the compound action potential of the sympathetic trunk is indistinguishable from that of controls. These results imply that acetylcholine synthesis and release in thiamin-deficient animals cannot increase to meet the increased physiological demand."

Based on this information, it appears that increased stress and stimulation would also increase the physiological demand on thiamine and therefore may more quickly deplete it, which would then also affect acetylcholine synthesis and release.

The authors sum up their findings in their conclusion:

> "Several lines of reasoning implicate the cholinergic system in the pathophysiology of thiamin deficiency. *In vitro* and *in vivo* acetylcholine synthesis as well as synaptic transmission are decreased in severe thiamin deficiency. Pharmacological manipulation of the tight-rope test and open-field staring behavior demonstrate the presence of a cholinergic lesion in early stages of thiamin deficiency. The importance of this lesion and

> its treatment with cholinergic drugs in other metabolic encephalopathies require further investigation, as does the precise molecular mechanism by which thiamin deficiency produces it."

Therefore, based on the connection between thiamine and acetylcholine, a thiamine deficiency can cause the same symptoms as in choline deficiency. As previously explained, dysfunctions in the cholinergic system are clearly involved in the mechanism of POTS.

Why are patients potentially deficient in specific nutrients? Diet, food sources, and food processing could all be related, as thiamine is used up more quickly with higher carbohydrate intake (many POTS patients also report intolerance to higher carbohydrate meals, as they may become very symptomatic at this time). Inadequate intake of nutrients may also be a factor. Processing of foods strips it of many nutrients. For example, when brown rice is stripped of its hull in processing to white rice, thiamine is then lost. Therefore, a high intake of white rice can lead to thiamine deficiency (and could be why the Japanese have shown an interest and pioneered much of the research on thiamine deficiency and beriberi). Stress, whether it be emotional, physical, or environmental, can also deplete one of nutrients, as many nutrients are required in higher doses during periods of stress or excessive stimulation.

Pathogenic infections can also use up the host's nutrients. Candida and other yeasts use up many host nutrients in order to grow, including thiamine and b12:[125]

> "By employing wide ranges in vitamin concentrations in biotin basal mineral synthetic medium, it was demonstrated that vitamin B12 markedly stimulated the growth of *Candida albicans*, the organism showing a partial dependency upon this vitamin. Growth inhibition by 5-fluorouracil was reversed non-competitively by vitamin B12, suggesting

[125] M.L. Littman and T.Miwatani. 1963. "Effect of water soluble vitamins and their analogues on growth of Candida albicans II. Vitamin B12, thiamine, oxythiamine, neopyrithiamine, substituted pyrimidines and thiazoles." Mycopathologia et mycologia applicata, Dec 1963 vol 21 (3-4): 289-314. Accessed January 13, 2019. https://link.springer.com/article/10.1007/BF02052582

> that B12 has a role in nucleic acid biosynthesis of the organism. Thiamine was growth stimulatory, the organism being partially dependent upon this vitamin as well."

Another study demonstrated how Candida strains may use up thiamine in response to stress:[126]

> "The current work was aimed to elucidate the role of thiamine in stress reactions of *C. albicans, C. glabrata, C. tropicalis* and *C. dubliniensis*, subjected to hydrogen peroxide treatment. As compared to *S. cerevisiae*, Candida strains exposed to oxidative stress showed: (i) a much higher dependence on exogenous thiamine; (ii) an increased demand for thiamine diphosphate (TDP) and TDP-dependent enzyme, transketolase; (iii) no changes in gene expression of selected stress markers - superoxide dismutase and catalase - depending on thiamine availability in medium; (iv) a similar decrease of reactive oxygen species (ROS) generation in the presence of thiamine."

As these nutrients are also used by pathogens for their own survival, the role of active pathogens in patients should be kept in mind when considering supplementation of these nutrients.

Hormones

Hormones may also play into the symptom mix of POTS, especially with there being a significantly higher female to male POTS population (5:1 as previously indicated), and also the majority of females with POTS being in their childbearing years.

In one study, female POTS patients reported more lightheadedness during menstruation, with a decrease in lightheadedness during their follicular phase. The study concluded: "The severity of lightheadedness was found to vary during the menstrual cycle, which may relate to

[126] Wolak, Tomasi, Kozik, Rapala-Kozik. 2015. "Characterization of thiamine uptake and utilization in Candida spp. subjected to oxidative stress." Acta Biochim Pol. 2015; 62(3): 445-55. Accessed January 13, 2019. http://www.actabp.pl/pdf/3_2015/2015_1044.pdf

changes in estrogen levels." The researchers also noted that "Patients with POTS also reported an increase in estrogen-related gynecologic disease."[127]

Also as previously discussed, the COMT enzyme helps to degrade norepinephrine in the body. Estrogen plays a role in how well COMT is working, and therefore may directly affects the levels of norepinephrine in the body:[128]

> "Alterations in transporter activity by female sex steroids may be organ specific. For example, inhibiting the transporter resulted in a greater increase in blood pressure during the follicular than luteal phase of the menstrual cycle but heart rate and cardiac output increased to a greater extent in the luteal compared to follicular phase. Changes in the activity of NET transporter are implicated in orthostatic intolerance including POTS which occurs more frequently in young women than young men and may be associated with a coding mutation of the NET gene.
>
> Evidence also suggests that estradiol and the catecholestrogens affect norepinephrine disposition via non-neuronal degradation in the vascular smooth muscle. The enzyme catechol-O-methyltransferase (COMT) in the vascular smooth muscle degrades norepinephrine to normetanephrine. Additionally, this enzyme also metabolizes the catecholestrogens to methyloxyestrogens. Thus, the catecholestrogens appear to competitively bind to COMT and inhibit the methylation of catecholamines in the liver, in canine adrenergic nerve endings and the rat heart. Consequently, when catecholestrogens are high, the concentration of norepinephrine in the synaptic cleft may increase, with the net effect of prolonging the impact of an adrenergic neuronal signal on both pre- and post-junctional adrenergic receptors and perhaps increasing the amount of norepinephrine which can be removed by the capillaries. In this context, plasma levels of norepinephrine are greater during the luteal phase (estrogen and progesterone high) compared to the early follicular phase of the menstrual cycle in young healthy women."

> "The influence of the female sex hormones on the adrenergic receptors can further be emphasized by evidence which shows that young women appear to have an attenuated forearm vasoconstrictor response to norepinephrine infusion during the luteal phase (high estradiol) vs. the early follicular phase (low estradiol) of their menstrual cycle."

---

[127] Peggs, Nguyen, Enayat, Keller, Al-Hendy, Raj. 2012. "Gynecologic disorders and menstrual cycle lightheadedness in postural tachycardia syndrome." Int J Gynaecol Obstet. 2012 Sep; 118(3):242-6. Accessed January 19, 2019. https://www.ncbi.nlm.nih.gov/pubmed/22721633

[128] Hart, Charkoudian, Miller. 2010. "Sex, Hormones and Neuroeffector Mechanisms." Acta Physiol. 2011 Sep; 203(1):155-165. Accessed January 19, 2019. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3025263/

> "In young women, sympathetic nerve activity actually increased during the luteal phase (when estrogen and progesterone are elevated) compared to the early follicular phase when both hormones are low suggesting that progesterone may also have an effect on central sympathetic outflow. Future studies should therefore consider both the separate and interactive effects of estrogen and progesterone on the function of central autonomic nuclei."

Therefore, it may also be beneficial to assess sex hormones, including estrogen and progesterone, in POTS patients.

Conclusion

Currently, the traditional medical community attempts to treat POTS patients simply by targeting symptoms. However, this does not treat the cause of POTS, and therefore, is not sufficient to bring a POTS patient back to homeostasis, or optimal functioning.

However, by viewing the body as a "whole system," and by assessing and addressing possible root causes, we may be able to determine the plausible root causes of POTS for a particular patient and help them achieve remission from POTS symptoms. Based on the research presented, some areas we may wish to explore with POTS patients include: nutrient deficiencies, excesses or toxicities, pathogens, and stressors.

Deficiencies may include a deficiency of vitamins, minerals, or other nutrients (including B12, Iron, Vitamin D, and Thiamine or Vitamin B1). This area may also include a deficiency of contact with substances required for health, including sunlight, fresh air, and clean water and hydration, cleanliness habits, exercise and movement, or a lack of refreshing sleep.

An excess or toxicity of substances may include contact with, or a buildup of, toxins including heavy metals, toxic gasses or chemicals, unhealthy or inappropriate foods or alcohol, or even toxicity from too much of a certain nutrient or type of food.

Pathogenic influences may include pathogenic bacteria, viruses, yeasts or fungi, or exposure to mold mycotoxins, which could be contributing to stress on and imbalance of the immune system, hormonal imbalances, neurotransmitter and other chemical imbalances, toxic byproducts, and nutrient depletion.

Stressors may include environmental or emotional stressors, such as chronic stress from harmful or "toxic" relationships, overwork or over-exercise, emotional trauma, an unclean or stressful environment, or simply an inability to adequately cope or manage daily stressors.

If genetic influences appear to be involved, the emerging importance of epigenetic factors on gene expression should be considered. As Dr. Lonsdale has stated:[129] "The basic root of any disease could well be derived from three phenomena: genetic stressors, environmental stressors, and nutritional liabilities. To the extent those stressors can be effectively managed determines health. It is of course true that a genetic cause, the stress of an injury, or starvation may dominate, but the other two circles are always potentially present. The new science of epigenetics completely alters our previous concept that genes represent a fixed blueprint. We now know that they can be influenced by lifestyle and the quality of nutrition. Many common diseases can only be understood by considering all three components."

[129] Derrick Lonsdale and Chandler Marrs. *Thiamine Deficiency Disease, Dysautonomia, and High Calorie Malnutrition*. London, United Kingdom: Academic Press, 2017.

In summary, by following the standard Naturopathic or Holistic framework of viewing the body as a whole, instead of attempting to separate out and treat individual body systems, we may be able to help the patient successfully bring their body back into balance and regain a normal and optimal life.