Correcting the Missing Piece in Chronic Fatigue Syndrome – Part 1: Discovery

Genetic Disease Investigators; Published January 2016

Abstract

Symptoms of Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME) can involve the central nervous system (cognition, executive function, short-term memory), the peripheral nervous system (muscle weakness, fatigue with exertion), and the autonomic nervous system (heart rate, blood pressure, breathing, digestion). A close analysis of 177 symptom checklists collected from CFS/ME patients over 4.5 years revealed a previously unreported commonality among patients. The majority of patients present with some level of anticholinergic syndrome – a dramatic deficiency of acetylcholine, which could be responsible for symptoms affecting the central, peripheral and autonomic nervous systems. This is the first time that low acetylcholine levels have been suggested as a cause of many disabling symptoms in CFS/ME.

Prevalence estimates of Chronic Fatigue Syndrome range from 0.5% to 3% in the United States (2-9 million sufferers), and yet effective treatment continues to elude practitioners. A syndrome similar to Chronic Fatigue Syndrome has been described as far back as the mid-18th century[1], but the medical community struggles for consensus. Indeed, even the name Chronic Fatigue Syndrome is a point of contention. Chronic Fatigue Syndrome may be called systemic exertion intolerance disease (SEID), myalgic encephalomyelitis, chronic fatigue, and immune dysfunction syndrome, among others.[2] Currently, most sources use a combined term, Chronic Fatigue Syndrome/Myalgia Encephalomyelitis (CFS/ME) to describe this disorder.

Frequency of Symptoms Occurring in Chronic Fatigue Syndrome

Symptom	Percent of patients
Easily fatigued	100
Difficulty concentrating	90
Headache	90

Sore throat	85
Tender lymph nodes	80
Muscle aches	80
Joint aches	75
Feverishness	75
Difficulty sleeping	70
Psychiatric problems	65
Allergies	55
Abdominal cramps	40
Weight loss	20
Rash	10
Rapid pulse	10
Weight gain	5
Chest pain	5
Night sweats	5

Figure 1. Straus, SE, J Infect Dis 1988; 157:405.[3]

Countless patients are clearly suffering from a constellation of debilitating symptoms, yet there is a frustrating lack of objective biomedical findings. As such, clinicians struggle to even make the diagnosis of CFS/ME, much less provide effective treatment.

There is no "typical" presentation of CFS/ME, yet there are some features common to many patients with the syndrome. Most patients are highly functioning prior to illness and experience a sudden onset of symptoms, usually after a viral illness, trauma or extreme stress. Excessive physical activity exacerbates fatigue and related symptoms.

Many patients describe certain triggers that bring about or worsen symptoms such as emotional distress, physical trauma, decreased sleep quantity/quality, infection, and standing or sitting up for an extended period.[4, 5, 6] Each of these triggers taxes the patient and is, in one form or another, an exertion. Indeed, post-exertional malaise is often included as a diagnostic criterion. Post-exertional malaise is an exacerbation of some or all of an individual's CFS/ME symptoms that occurs after physical or cognitive exertion and leads to a reduction in functional ability.[7] Exertion exacerbates fatigue, cognitive symptoms, pain, delayed recovery of muscle function, increased severity and incidence of sleep problems, and inappropriate autonomic responses.[4, 8, 9]

A large number of additional symptoms, beyond fatigue, are present in a majority of CFS/ME sufferers, and often, these symptoms can come and go. These symptoms can include sore throat, tender lymph nodes, muscle and joint pain, feverishness, insomnia, tachycardia, abdominal pain and others (see Figure 1). Attempts to locate the underlying cause(s) of such disparate symptoms have been unsuccessful to date. Some of the leading hypotheses are viral infection[3, 10] immune dysfunction,[11] endocrine/metabolic dysfunction,[12, 13] neutrally – mediated hypotension,[14,15] genetic disorders,[16, 17] disordered sleep,[18] and complicated depression.[19]

Clearly, multiple systems of the body are involved simultaneously in CFS/ME. Symptoms of CSF/ME involve the central nervous system (cognition, executive function, short-term memory), the peripheral nervous system (muscle weakness, fatigue with exertion), and the autonomic nervous system (heart rate, blood pressure, breathing, digestion).

Central Nervous System in Chronic Fatigue Syndrome

The cognitive symptoms of CFS/ME can be every bit as debilitating as the physical symptoms. Patients report phenomena "brain fog," confusion, and the inability to concentrate.[5] Short-term memory deficits and slowed information processing are common; the latter may be experienced as a mental fatigue similar to the physical fatigue of the condition.[20, 21]

In CFS/ME, the prevalence of attention deficits may be as high as 93% and 85% for memory disturbances.[22] Three quarters of patients experience substantial difficulty finding the correct words during verbal tasks.[22] Problems remembering, difficulty expressing thoughts, difficulty paying attention, slowness of thought, absentmindedness, and difficulty understanding are orders of magnitude more common in people with CFS/ME than in healthy volunteers.[23]

Peripheral Nervous System in Chronic Fatigue Syndrome

The peripheral nervous system (which controls muscles) has been found to affect CFS/ME patients and not uncommonly, patients complain of weakness. Fulcher, et al found that patients with CFS/ME were weaker than sedentary and depressed controls, suggesting that weakness was not psychosomatic or secondary to deconditioning. Their study found that CFS/ME patients had significantly higher submaximal oxygen uptakes during exercise, and multiple regression models suggested that exercise incapacity was directly related to quadriceps muscle weakness.[24]

Autonomic Nervous System in Chronic Fatigue Syndrome

The autonomic nervous system controls bodily functions such as heart rate, blood pressure, pupil dilation, digestion, and salivation. It coordinates the activity of various organ systems without requiring conscious effort.

Many CSF/ME patients have abnormal autonomic nervous system function.[2] Orthostatic intolerance (the inability to adjust heart rate and blood pressure when changing position) is included in the updated diagnostic criteria for Chronic Fatigue Syndrome. Orthostatic intolerance includes symptoms of lightheadedness, dizziness, faintness, or syncope when vertical. Patients may present with neurally mediated hypotension, extreme pallor, nausea, irritable bowel syndrome, heart palpitations with or without cardiac arrhythmias, urinary frequency and bladder dysfunction, and exertional dyspnea and/or postural orthostatic tachycardia syndrome (POTS).[7, 25]

What anomaly can tie together disorders of peripheral, central and autonomic nervous systems?

In order to look for clues to answer this question, between June 2011 and April 2015 Genetic Disease Investigators, LLC collected symptom questionnaires from 192 individuals with CFS/ME, resulting in 177 viable checklists. Each questionnaire contained 156 potential symptoms listed alphabetically.

Not surprisingly, autonomic symptoms were common. Percentage of respondents suffering with the following autonomic symptoms included:

Symptom	%
Constipation	89
Difficulty breathing	80
Dry eyes	78
Dry mouth	76
Gastroparesis	51
Light sensitivity	88
Large pupils	47
Lack of perspiration	46
Decreased blood pressure when standing	78
Bradycardia or tachycardia	81
Increased body temperature	57
Urinary retention	48

Central nervous system symptoms were also common. The percentage of respondents suffering with the following central nervous system symptoms included:

Symptom	%
Agitation	81

Abnormal mood swings – almost bipolar presentation	41
Confusion	81
Disorientation	79
Illogical thinking	55
Difficulty concentrating	79
Memory problems	89
Brain fog	96
Easily startled	80
Irritability	84

Peripheral nervous system symptoms were also common and were reported with the following frequency:

Symptom	**%**
Extreme fatigue	100
Tremor	69
Shaking	70
Wakeful myoclonic jerks	74
Loss of coordination (ataxia)	77

Additional symptoms not currently regarded as typical for CSF/ME (yet often present in anticholinergic syndrome) were reported with the following frequency:

Symptom	%
Seeing periodic flashes of light	63
Seeing "dancing lines, spiders or insects"	42
Double vision	67
Hallucinations – auditory or visual	28
Textured surfaces bother you visually	45
Tunnel vision	36
Visual snow	54
Warping or waving of surfaces and edges	29
Sensitivity to sudden sounds	96

When viewed as a whole, the above 36 symptoms are the symptoms of Acute Anticholinergic Syndrome. This syndrome must be identified by presentation (not via blood work) because acetylcholine breaks down rapidly. These symptoms suggest, but do not prove, that the majority of patients with CFS/ME suffer from symptoms of extremely low levels of acetylcholine.

Could CSF/ME patients be suffering with extremely low levels of the neurotransmitter, acetylcholine, resulting in symptoms involving the peripheral, central and autonomic nervous system?

The actions of acetylcholine in the central, peripheral, and autonomic nervous systems

To understand abnormalities in acetylcholine, one must first understand where and how it acts under normal circumstances. Acetylcholine is the neurotransmitter of

neuromuscular junctions, ganglia in the autonomic nervous system, and is present in discrete locations throughout the brain.[26]

In the central nervous system (the brain and spinal cord), acetylcholine is critical for memory formation and recall. For example, there are acetylcholine receptors in the hippocampus, Neil cortex, and amygdala — the main memory forming structures in the brain.[27] Likewise, acetylcholine is the major neurotransmitter in the basal nucleus of Meynert, which degenerates in Alzheimer's disease.[28]

Acetylcholine is integral to the proper function of the peripheral nervous system and is the main neurotransmitter at every skeletal neuromuscular junction in the body. All conscious muscular movement requires acetylcholine.

Acetylcholine is a major component of the autonomic nervous system and is required for proper vagus nerve function.

Acetylcholine and Chronic Fatigue Syndrome

As a syndrome, CFS/ME is a constellation of symptoms. It is difficult to envision a single pathological process that gives rise to all of the various symptoms. Nevertheless, abnormalities in the acetylcholine system could explain many, if not most of the symptoms of CFS/ME.

The effects of acetylcholine deficiency are understood primarily because of the actions of atropine. Atropine blocks acetylcholine receptors, thus preventing the neurotransmitter from interacting with postsynaptic neurons. Acetylcholine deficiency (brought on by atropine) causes ventricular fibrillation, tachycardia (rapid heart rate), dizziness, nausea, blurred vision, loss of balance, dilated pupils, photophobia, dry mouth, dry eyes, extreme confusion, dissociative hallucinations, and excitation in addition to unusual symptoms such as visual snow and seeing "dancing lines, spiders and insects".[29, 30]

The link between CFS/ME and acetylcholine has been subject of ongoing research with particular attention to potential autoimmune conditions that could affect acetylcholine receptors. For example, some researchers found autoantibodies against muscarinic cholinergic receptors in over half of people with CFS/ME.[31,32]

Spence, Khan, and Belch showed that patients with CFS/ME have abnormalities in the acetylcholine (cholinergic) system.[33] The researchers showed the acetylcholinesterase inhibitor, edrophonium, applied to the skin reacts abnormally in patients with chronic fatigue syndrome. The same research group has confirmed the results of their research in several papers.[34, 35, 36, 37]

Yamamoto, et al (2012) used a radioactive agent that specifically binds to muscarinic acetylcholine receptors in the brain. They report decreased levels of receptors in the brain, but normal activity of acetylcholinesterase.[38]

Taken together, these results suggest an interesting possibility that explains the disparate findings of all of these researchers: CFS/ME patients may have abnormally low levels of acetylcholine.

Could CFS/ME patients improve by boosting levels of acetylcholine?

If this hypothesis was true, one could treat many symptoms of chronic fatigue syndrome by increasing acetylcholine levels within the synapse. Indeed, researchers have attempted to do this very thing. Kawamura and co-authors report three cases in which a small dose of oral pyridostigmine, an acetylcholinesterase inhibitor which increases acetylcholine levels in synapses, improved symptoms of chronic fatigue syndrome.[39] Many patients with POTS (Postural Orthostatic Tachycardia Syndrome) have improved gastrointestinal symptoms (gastroparesis, constipation) with the use of pyridostigmine.[40]

But because pyridostigmine does not cross the blood-brain barrier, it cannot boost acetylcholine in the brain and assist with central nervous system symptoms.

Acting on the evidence of low acetylcholine levels as exhibited by symptomology, Genetic Disease Investigators, LLC began to search for a compound that could cross the blood-brain barrier and boost acetylcholine in the central nervous system as well as effectively replace acetylcholine in the autonomic nervous system and the peripheral nervous system.

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Correcting the Missing Piece in Chronic Fatigue Syndrome – Part 2: Treatment

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Abstract

After discovering the majority of patients with CFS/ME appeared to suffer with anticholinergic syndrome, attempts to formulate a compound to boost acetylcholine in the central, peripheral, and autonomic nervous system began. Objective measure of success included the ability of the compound to trigger the postganglionic vagus nerve, resulting in a bowel movement. Out of 27 patients studied, 88% reported a bowel movement within 90 minutes of ingesting the patented compound (Parasym Plus™). A dramatic increase in mental/physical energy was reported by 93%. Parasym Plus™ can be effective in reversing many symptoms of CFS/ME.

Genetic Disease Investigators conducted an analysis of signs and symptoms reported by 177 patients with Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME). Results revealed that the majority of patients suffered with symptoms and signs of anticholinergic syndrome (low acetylcholine levels). Symptoms involved abnormalities in the autonomic nervous system, the central nervous system and the peripheral nervous system. Research then turned to why acetylcholine levels were low, and importantly, to explore the possibility of providing patients immediate relief by increasing levels of acetylcholine. If successful, many symptoms of autonomic dysfunction (orthostatic intolerance, tachycardia, gastroparesis, poor digestion, poor gall bladder function and others), central nervous system dysfunction (brain fog, cognitive decline, mood swings, irritability and others) and peripheral nervous system symptoms (extreme fatigue, tremor, loss of coordination and others) could potentially be alleviated.
Because acetylcholine is required for multiple nervous systems of the body, a replacement compound needs to be available in the brain (central nervous system), the muscles (peripheral nervous system) and the organs (autonomic nervous system).

> *Because acetylcholine itself is not a drug (it is broken down immediately by the body), a replacement compound needed to be created that was easily and safely absorbed by the body.*

Additional goals for this compound were as follows:

1. The ingredients needed to assimilate in the body rapidly in order to stimulate the (postganglionic) vagus nerve to assist with all aspects of digestion (autonomic nervous system). Such vagus nerve stimulation could also improve immune system function and decrease systemic inflammation.
2. The levels of acetylcholine needed to increase in the central nervous system (brain) to help alleviate symptoms of "brain fog", cognitive decline and poor short-term memory. To accomplish this, all ingredients needed to cross the blood-brain barrier.
3. The ingredients could not activate histamine-producing cells (or any aspect of inflammation).
4. The ingredients needed to be within what the FDA has already determined to be safe.
5. The combination of ingredients needed to be effective regardless of genetic defects involving the production of acetylcholine, should such defects be present.

The vagus nerve in CFS/ME

The vagus nerve (part of the autonomic nervous system) controls most aspects of digestion, inflammation and immune function, and because abnormalities in all of these conditions are considered significant contributors of symptoms in CFS/ME, focus on vagus nerve response was a critical aspect of research. The ability of the compound to trigger the (postganglionic) portion of the vagus nerve was an essential goal.

The vagus nerve controls most aspects of proper digestion including peristalsis of the food down the esophagus and through the intestines, opening of the pyloric valve at the base of the stomach (allowing food to pass into the intestines), the proper production of stomach acid required for digestion (and the absorption of numerous vitamins), the release of bile by the gall bladder, the release of digestive enzymes by the pancreas, and the opening of the Sphincter of Oddi (allowing the release of bile and pancreatic enzymes into the intestines). Many patients with CFS/ME suffer with delayed gastric emptying/gastroparesis/constipation, and other manifestations of gut dysfunction and irritable bowel syndrome (IBS).[1, 2] Gut inflammation has been proposed to be a significant contributor of symptoms in this population.[3]

Immune system function has also been found to be adversely affected in CFS/ME.[4,5] Studies have found evidence of dramatic disturbances of immunity, including alteration in cytokine profiles in CFS/ME patients.[6, 7] Numerous aspects of cellular immunity have been found to be abnormal and are considered to be a key component to the disease.[8,9] Proper functioning of the vagus nerve is critical for normal immune system function because the vagus nerve controls the function of the spleen, a key organ in both innate and adaptive immunity.[10,11]

As the cholinergic anti-inflammatory pathway of the body, proper triggering of the vagus nerve can also decrease systemic inflammation.[12,13,14] The vagus nerve helps control inflammation both through its innervation of the spleen and through its control of inflammatory cells.[15] These inflammatory cells contain alpha-7 subunit containing nicotinic acetylcholine receptors which, when properly stimulated by the vagus nerve, control the release of inflammatory cytokines. This control links the inflammatory reflex to immunity, and proper functioning is critical to control abnormal inflammation often found in CFS/ME. Disorders of the inflammatory pathway can exhibit as neuroinflammation, cardiovascular disorders and gut inflammation in CFS/ME and appear to be a critical component to symptoms of illness.[2, 16, 17]

Results of Treatment Trials

When eliciting response to treatment, objective measures are preferable to subjective responses. The objective finding of a bowel movement within 90 minutes of ingesting the compound (repeatable over two consecutive days) was considered an objective, positive response (indicating vagus nerve stimulation). Subjective responses (improvement in cognition, mental and physical energy) were also collected.

Twenty-seven (27) patients with CFS/ME volunteered to participate in treatment trials of the compound (now known as “Parasym Plus™”). All patients were over the age of 12 and were not taking Adderall, opioids, cholinergic or anticholinergic medications (medications which could mask the vagus nerve response). Patients were instructed to take the compound on an empty stomach, preferably in the morning prior to eating.

# of patients tested	**27**	**Percent**
Female *n*	25	93%
Age *y*	32 +/- 13	

Positive for bowel movements within 90 minutes	24	88%
Increase in mental/physical energy	25	93%

Response of patient testing was dramatic. Twenty-four (24) out of 27 patients reported a bowel movement within 90 minutes of taking the ingredient mix, despite long-standing constipation/gastroparesis. This response was repeatable (occurring two consecutive days, at a minimum). Additionally, 25 out of 27 patients reported a significant improvement in both physical and mental energy.

Although preliminary, such dramatic response suggests that the majority of patients with CFS/ME may indeed be suffering with low levels of acetylcholine, contributing to illness. Perhaps more importantly, this demonstrates that effectively replacing the acetylcholine appears to alleviate many symptoms of illness.

These findings also suggest alternative explanations for many cases of POTS – Postural Orthostatic Tachycardia Syndrome, a commonly overlapping condition with CFS/ME. Currently, research has considered abnormal receptors of the autonomic nervous system (acetylcholine receptors) as a cause of autonomic dysfunction in POTS and CFS/ME. As stated by Loebel, et al, "autonomic dysregulation in CFS/ME points to an autoimmune disease directed against the neurotransmitter receptors".[18] Such abnormalities can be found in autoimmune autonomic gangliopathy and research has delved deeply into the search for obscure autoimmune conditions that may be affecting these patients.[19, 20, 21]

Instead, this new research indicates that rather than a disorder affecting (acetylcholine) receptors, the majority of these patients may be suffering with a neurotransmitter problem (low acetylcholine levels).

The research of Genetic Disease Investigators, LLC continues to investigate the cause of acetylcholine decline, and to determine if the (initial) decrease of acetylcholine could be the cause of changes to the receptors found in some patients. Meanwhile, boosting acetylcholine levels while simultaneously stimulating the postganglionic portion of the vagus nerve (with patented Parasym Plus™) is effectively reversing numerous symptoms of CFS/ME.

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