

Lyndonville News

Information and Support for the ME/CFS/FM Community
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Introduction

Welcome to the second edition of the *Lyndonville News*. It is with great joy that I would like to announce that we may soon have a web site where access to The *Lyndonville News* will be available at four in the morning for those of you with some extra time on your hands at that time of night. It has taken a long time but I am now convinced that everyone needs a web site assigned to them at birth. The production of the site is kindly being donated, and hopefully we will be talking more about this in the next issue.

I am somewhat confused about sending out a newsletter by e-mail. Yours may not arrive because of spam blocker technology, and you will not even know it has been sent. Pictures and graphics may not come through on the e-mail version. Some people may not have access to e-mail. Finally, some people just like to sit and read through their newsletters in the comfort of an armchair by the window. For anyone who would like a hard copy of the newsletter sent by regular mail, it is available for \$20 per year. I anticipate that there will be four to six issues per year. The e-mail version will be offered without charge.

Notes from the Farm

This is another section that I will add to the *Lyndonville News* from time to time. Sometimes after a day at the office, I like to sit on the porch and think about life. Tonight I was thinking about the advice I gave a patient who had become very ill with ME/CFS/FM. She has been unable to work for six months now, and she misses her PhD level job very much. She is single and does not own her lodging. Her private disability company has said that they will not pay her disability benefits because they do not think she is ill, basing their decision on the fact that she was recently on an airplane. I have patients with terminal cancer who have been on an airplane. She was terminated from her job because she has not been at work for over six months. In the past I have written



letters stating unambiguously that she is disabled with chronic fatigue syndrome and has no primary psychiatric disease. She asked me what she should do.

She has two options. First she can appeal the denial of benefits from her insurance company. She can get more testing to establish the biologic basis of her illness. For example she could get the 2-5' A synthetase level, the PCR for HHV6, cytokine levels of TNF, and interferons; she could get a circulating blood volume study, or orthostatic testing. She already has been found positive for the fibromyalgia tender points. She could also get some of the more expensive and newer research tests. But if she were to get them all and all of these tests were abnormal, the insurance company would still say that they will not pay her disability benefits. They would say, "there is no proof of disability". She can spend the next few years with appeals, lawyers, tests, and, if it goes to court three years from now, she may win her claim.

Her second option is to say, 'even though I have paid into the private disability policy for nearly ten years, I should cut my losses and drop it. I am too tired and sick to wage this war, and it is just not worth the fight.'

I have no advice for her. She understands the dilemma with a chilling clarity. In my opinion, the private insurance companies have decided not to honor the promises they made in their disability policies, and arbitrarily have decided to ignore the science that exists around ME/CFS/FM. I think they have concluded that they will be able to get away with it legally, and that the patients are too sick and poor to wage a prolonged legal battle. It appears to me that they will continue to follow this approach of saying that there is no such disease as ME/CFS/FM. Perhaps they will say that even if the illness exists, it is so minor or trivial that it does not cause disability in a specific individual.

I do not know what my patient is going to do. It is possible that she will go from a prestigious, well-paying job to losing everything. It is likely to take her over two years to apply and get social security benefits. She has no other means of support for the coming two years. We talked about what life would be like while living under an underpass. It is a good thing that she has not yet lost her sense of humor. I wonder how much money she paid to the disability company over the past ten years?

Tonight there are just discouraging thoughts while sitting on the porch looking out on the north pasture. It is not always discouraging or depressing, but tonight it is.

Rookie Section

Let's look at a few definitions that will be important for the next several newsletters. And the rookies should not feel bad because most of the old-timers do not know this stuff either. In the remaining sections of this newsletter and in some of the issues to follow we will be examining the possibility of the symptoms of ME/CFS/FM being caused by autoimmunity, specifically autoantibodies directed against the autonomic nervous system. This is not a new theory, but it is one that is becoming more interesting recently.

The term autoimmunity means that the body's immune system (immunity) has made a mistake and is attacking itself (auto). The form this takes is that the immune mechanism makes antibodies against normal body tissues, called autoantibodies. In ME/CFS/FM the immune system is generally overactive. People often think of the immune system here as being deficient, and in a few areas such as the natural killer cells it is deficient. But the over-riding problem in the illness is that the immune response is over-aggressive, as if the body were attacking a flu virus. This over-reactivity is one of the supporting reasons that persistent viral infection

continues to be considered as a leading candidate for the cause of ME/CFS/FM. Think of it as if the system were revved up and looking for something to attack. In autoimmunity, the normal response goes too far and the immune system ends up fighting with something that should not be attacked, healthy body tissues.

Rheumatoid arthritis is an autoimmune disease. The body's immune system messes up and starts attacking healthy joint tissue. This causes the swelling and pain of rheumatoid arthritis. Lupus and multiple sclerosis are also autoimmune diseases, and there are many others. To make a diagnosis of autoimmune disease, it is necessary to isolate an auto-antibody and show that it is causing the symptoms of an illness.

Section for the Old-timers

Over the coming months to years we will be returning to a discussion of the autonomic nervous system in our discussion of ME/CFS/FM. So I thought it would be a good idea to outline a little of the structure or organization.

First there are two types of human nervous system. The motor or voluntary system and the autonomic (or automatic) system. The autonomic system is composed of two parts: central and peripheral. The central autonomic system is composed of the 'primitive' parts of the brain and upper spinal cord that control heart rate, blood pressure, body temperature, pain sensation, sweating, appetite, and so on. The peripheral autonomic nervous system (ANS) consists of the nerves going to the intestines, bladder, sweat gland, adrenal glands, heart and so on.

There are two big divisions of the central and peripheral autonomic nervous system, adrenergic and cholinergic. The adrenergic system (sympathetic nervous system) is the 'fight or flight' response. It is run by adrenalin (epinephrine, noradrenalin) and mobilizes the body automatically for an emergency like running away from a saber tooth tiger. The cholinergic system (parasympathetic nervous system) is run by acetylcholine (ACh) and this controls more subtle aspects like sweating, sleep, pupil dilatation, concentration, intestine function and so on.

Just to make life really complicated, the cholinergic system is divided into two parts, the nicotinic and muscarinic system. Each neurotransmitter (chemical which transmits the impulse across nerve junctions) has one or more receptors. If it cheers any of you up, I saw this in medical school and said that there was no way this was ever going to be important, so I never learned it. So the last five years....

Case Reports

Amy T is a young lady who became ill while coming out of a movie theater nine years ago. It is one of those things she remembers. At the time, however, she assumed it was a minor infection: sore throat, fever, swollen glands and flu-like aching. For a few days she rested in bed and then saw her doctor who agreed it was a minor virus. A few days later the mononucleosis test was run and it was positive. Ah.... plan on two weeks of rest, fluids, and chicken soup.

Amy remained ill for the next two weeks and then she got really sick. She said it was like being hit by a Mack truck. The exhaustion and weakness were severe. Whereas before she was sick, now she was really sick. Tests were run, and six months later she began to improve slightly. She was diagnosed with chronic fatigue syndrome. Now, eight years later she is doing pretty well, but the symptoms continue.

Amy's story is pretty characteristic of the acute onset of ME/CFS/FM. But there is a clinical detail hidden which is an important piece of the puzzle. Here is the issue:

One theory of the symptoms of CFS states that the cytokines (tumor necrosis factor, interleukin, interferons) which are stimulated by the initial infection get stuck in the "on" position and continue to produce symptoms for the indefinite future. A second theory says that an infection, (in this case mononucleosis) starts and ongoing viral activity continues for years because some defect in the immune system prevents the eradication of the infection. Amy's story, (which is true, by the way) proves both of these theories false.

Coming out of the movie theater she became ill with mononucleosis. The cytokines began to be produced at that time. However it was just the ordinary illness – fever, sore throat, tiredness, muscle aching, and swollen glands. The "essence" of ME/CFS/FM, which is the "hit by a Mack truck", started suddenly two weeks later. It could not have been the cytokines because they had been circulating for the initial two to three weeks of the illness. Something new had occurred at the two week point, the "hit by a truck" phenomenon.

Furthermore, it could not be the viral infection. The mono infection had been underway for two weeks before the worsening occurred. Therefore it was not a result of viral persistence, it was something new. There must be some other mechanism.

The logical explanation for me is that the mononucleosis began a process that became apparent at the two week mark. The model I like best is that the body developed an autoantibody to a part of the autonomic nervous system that was the phenomenon of "being hit by a truck." There is an illness called Guillan-Barre syndrome that is quite parallel except that the auto-antibodies developed are against the motor system and thus cause a true paralysis. The paralysis starts at the feet and moves up the body. Usually it improves and the person gets better. The Guillan-Barrre syndrome is an autoimmune disease and is not ME/CFS/FM.

If ME/CFS/FM were an autoimmune disease stimulated by an acute infection, we do not know what the auto-antibody is. But this is an exciting area of research because there are now several auto-antibodies on the horizon. For now, with Amy's case, we can just speculate about this potential mechanism. But it may be that in a relatively short period of time we will be able to measure certain auto-antibodies, and make a diagnosis of "autoimmune dysautonomia" following mononucleosis. And hopefully we will then have specific treatments which can reverse the process. For reasons that I have never understood, people seem to think that I am an optimist.

It would be interesting to approach the question, the biphasic onset, with a questionnaire. Maybe this would be a good project for the Lyndonville Research Group. But it is because of this possibility that I have chosen to review a paper on autonomic autoimmunity in the next section.

Literature Review

Article #1: Tanaka S, Kuratsune H, Hidaka Y, Hakariya Y, Tatsumi K, Takano T, et al. Auto-antibodies against muscarinic cholinergic receptor in chronic fatigue syndrome. *International Journal of Molecular Medicine*. 2003;12:225-230.

In this study, the authors examined blood samples of 60 patients with chronic fatigue syndrome (CFS), 33 patients with known autoimmune disease and 30 healthy control persons for autoantibodies to four different neurotransmitter receptors. The one autoantibody most positive in this study was to the recombinant human muscarinic cholinergic receptor 1 (CHRM1), with 53.3% of the CFS patients positive. Of those with known autoimmune disease, 15.2% were

positive, and there were no healthy controls positive. Because the symptoms of CFS could be due to impaired cholinergic neurotransmission, this finding is extremely interesting. This particular neurotransmitter receptor, CHRM1, is in the brain and may be central to the symptoms of CFS. The authors state, “positive reactions against CHRM1 in CFS patients may play an important role in the clinical characteristics of CFS.”

Also of interest were the results of the testing for autoantibodies against the *mu*-opoid receptor (OPRM1), and 15% of CFS patients were positive against none of the controls. Given the prevalence of severe pain in CFS, this needs to be looked at more carefully in future studies.

Comment: I am very surprised that this study has not received more attention. If a patient with fatigue and weakness tested positive for the acetylcholine receptor autoantibodies at the neuromuscular junction, the diagnosis would be established as Myasthenia gravis. Here we have over half of a group of CFS patients who appear to have an autoimmune cholinergic dysautonomia. This study should be replicated by other groups as soon as possible.

Article #2: Vernino S, Low P, VA L. Experimental autoimmune autonomic neuropathy. J Neurophysiol 2003;90:2053-2059.

Autoantibodies to neuronal ganglionic nicotinic receptor have been found in patients with autoimmune autonomic neuropathy (AAN). In this paper the authors developed an animal model of autonomic failure by immunizing rabbits with a portion of the ganglionic receptor. Following this the animals developed autoantibodies to the receptor and then developed dysautonomia, confirmed by examination of the nerve structure. This model suggests that AAN in humans is a disorder of ganglionic cholinergic synaptic transmission caused by nAChR antibodies.

Comment: One of the most important questions in the subject of autoantibodies is whether the autoantibody found has any relevance to the illness being studied. For example, antithyroid peroxidase antibodies (autoantibodies against a component of thyroid tissue) are found in 5% to 10% of healthy individuals. Therefore by finding this particular autoantibody, it does not automatically follow that the autoantibody has caused a disease. However in this study they provide some evidence that autonomic failure, and in particular autoimmune autonomic neuropathy or AAN, can be caused by autoantibodies to the acetylcholine receptor.

It would be of great interest to know if patients with CFS have autoantibodies directed against parts of the autonomic nervous system as the cause of their illness, as is described in the first article. This is one of those simple studies that would give us an enormous amount of information. Imagine if one one hundredth of the money spent on psychiatric studies had been spent on medical studies like this where we would be.

So much for autoimmunity for now. It is a subject we will be returning to over and over in the future because I feel it must be tied into the mechanism of the illness. I apologize for the complexity of the subject, and will work to make the next newsletter easier to read. Please send me your comments.

Also, please send clinical questions that I can attempt to address. The questions should be of a general nature and not personal.

General Disclaimer Any medical advice that is presented in the *Lyndonville News* is generic and for general informational purposes only. ME/CFS/FM is an extremely complex illness and any advice may not be appropriate for an individual with this illness. Therefore, should you be interested or wish to pursue any of the ideas presented here, please discuss them with your personal physician.