INFECTIOUS VENULITIS
CHRONIC FATIGUE SYNDROME
MYALGIC ENCEPHALOMYELITIS

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HISTORY

In the spring and summer of 1975 there occurred a major, severe epidemic of a communicable, apparent viral disease at the Mercy San Juan Hospital in Carmichael, a suburb of Sacramento, California. The first two cases became ill in February; the bulk of the cases fell ill between July and November of 1975. Several cases tailed out to 1978. The epidemic spread to all departments of the Hospital. It was equally severe in all departments.

I was appointed chairman of a committee to investigate the outbreak. Fearing that some people might die, I asked that the CDC (Communicable Disease Center of Atlanta, Georgia) to become involved. An epidemic intelligence officer of the CDC spent one week in residence, and an epidemiologist from the California State Department of Health, Berkeley, came for a day.

Cultures were obtained for all known viruses, bacteria, mycoplasma, and rickettsiae, and all were found to be negative. The disease was apparently due to an unknown agent, presumably a virus.

At the time we did a literature search and found three reports of outbreaks that were called EPIDEMIC PHLEBODYNIA (EP), meaning painful veins. While the disease at the Mercy San Juan Hospital (MSJ) was somewhat similar, it included many more features than were described in EP and so at the time I did not believe it was the same disease. Additional literature search showed that the disease was very similar to EPIDEMIC NEUROMYASTHENIA/MYALGIC ENCEPHALOMYELITIS (ENM/ME). But troublingly, very few vascular features were mentioned.

I have followed these patients on a daily basis since 1975. This is the longest continual study of this type of disease that has ever been made. Because of this, I have learned all the nuances, all the signs and symptoms of the disease. Because the complaints of patients are so many and often seemingly bizarre, I often attempted to disclaim them as being real. But I learned that you patients were always right and I was always wrong. In studying this disease, one must always have an open mind. This disease teaches the physician to be humble.

One must remember what a famous French physician, Jean Martin Charcot, said many years ago; "DISEASE IS VERY OLD AND NOTHING ABOUT IT HAS CHANGED. IT IS WE WHO CHANGE AS WE LEARN TO RECOGNIZE WHAT FORMERLY HAS BEEN IMPERCEPTIBLE."

INFECTIOUS VENULITIS

Infectious venulitis (IVN) is a disease caused by an as yet unidentified virus or perhaps a combination of more than one virus. It begins with an influenza-like onset, often so severe in nature that I call it a flu-storm, with headaches, sore throat, fever, dizziness, runny nose, nausea and vomiting, muscle aching, extremity pain, and other features. Unlike ordinary flu, the flu-storm can last from weeks to over a year. Sufferers are very drowsy at times, especially during relapse that almost resembles a light coma. The extremity discomfort is often described as a burning, searing sensation. Joint pain can be severe. Numbness and tingling of the extremities is common. The cases that occur in an epidemic have spontaneous bruises that occur without any injury, and painfully swollen veins. Those who become ill from the epidemic cases might not show this - these cases are often milder, or the bruises and painful veins might have only been at the beginning and went unnoticed.

After the initial flu state leaves, the patients are still not well. They have a constant plateau of illness punctuated by unpredictable relapses. In women who menstruate, the disease is worse at this time and relapse is apt to occur. Some patients have a relatively mild flu onset, only years later to suffer a relapse that is worse than the initial illness.

The disease is frightening to patients because of its severity and its many, unusual features. Physicians are not trained to diagnose an illness that encompasses so many signs and symptoms. Two common statements patients make during the initial flu state are: "I hurt all over" and "I am going to die".

Patients who suffer from IVN have the following features:

1. ***Severe exhaustion and weakness***

The exhaustion that occurs in this disease is profound and unusual. Patients often are not even able to hold up their heads. They have a compelling need to sleep. During relapse, patients have been known to sleep around the clock for days on end. The usual sleep pattern requires many more hours than usual. Yet patients do not sleep restfully and do not awaken refreshed. In the day time they state: "I live in a fog." Strength is greatest for most early in the morning. After a short time, endurance fades and patients must obtain bed rest. Energy is at a low ebb all of the time. Patients find that they can do

small tasks in spurts, resting between times. During relapse, many can be totally helpless and unable to care for themselves. Walking at all can become impossible and patients have been forced to crawl on their hands and knees.

Most women love to shop, but for a woman with IVN, it may be next to impossible to do so. I often suggest a wheelchair for activities such as extended shopping and other social events. Many find that they can think more clearly lying down and are able to do a limited amount of work this way - it apparently improves their brain circulation. One patient who was desperately trying to hang onto her job would dash down to her car on her breaks in order to rest lying down, to continue working.

Patients have been known to fall asleep inappropriately, at times in mid-conversation. One severely ill patient reported that at times her head would drop onto her chest while she was standing up and she would be fast asleep.

2. ***Disturbance of cognition/mentation***

Short term memory can be severely impaired. Patients cannon remember where they place items, or store them in inappropriate sites, such as putting a book in the refrigerator, etc. Calculating is difficult; checkbooks cannot be balanced. They often cannot take care of their own financial affairs. Directions are difficult to follow; road signs cannot be read. Filling out forms may be impossible. Mental work of any sort becomes difficult or impossible. Patients cannot find the right words to say - it is though the brain is no longer connected to the tongue. At times patients have told me that their brain does not send proper signals to their arms or legs and they cannot function. Women have difficulty in following cookbook recipes. Reading becomes difficult or impossible. Patients must read again and again in order to comprehend.

Overt confusion is common. Many have great difficulty in driving and get lost, even in familiar neighborhoods. Some have gotten lost on their way to my office and had to call family to come and get them. Others often report that when they are driving they suddenly realize that they don't know where they are or where they are going and can't find their way home. There are frequent mental lapses.

Panic is common and can be severe. Rarely, patients become psychotic and have hallucinations. But this is usually not a true psychosis - they know it is not real. It is unlike Alzheimer's syndrome in which patients do not seem to have an awareness of their true state.

Because of a frightening new disease that physicians cannot recognize, diagnose, or understand, and because it never seems to go away, patients

become depressed. Upon visiting physicians, this depression is recognized and blamed for the entire illness. This of course is not true - the depression is a result of the disease and does not cause the disease.

Nervous system abnormalities

Dizziness often occurs and for some patients, it is constant. They are uncoordinated and lurch about. They do not know where they are in space, often hitting door jambs and at time have falling episodes. They state that their legs just give way causing them to fall. At times falls result in severe injury. Some have fainting episodes. Small strokes are not uncommon and can be very alarming. Seizures can occur. Many are only able to drive to a limited extent; at times, not at all. Others can never drive. Patients at times have fainted while driving and awakened to find themselves in ditches, etc. Some have had definite nerve damage such as not being able to lift a leg, etc. Some have had to use canes, walkers and wheelchairs. At the worst, patients are bedconfined.

Patients drop items unexpectedly from their hands. Women often burn themselves in the kitchen. There is difficulty in performing fine movements such as writing. Blurred vision and double vision are common. Eye muscles do not work properly. Ears ring and at times there is an extremely annoying fluttering or roaring. Numbness and tingling of extremities is common. This interferes with feeling and handling objects.

The autonomic nervous system that results in flushing, blushing etc., that controls blood vessels is deranged in this disease. Sweating, flushing, icy and blue hands and feet, hot sweaty hands, red and blotchy hands are common. When patients are in relapse it is easy to tell that they are ill; pallor of the face and dark areas under the eyes, etc. But when they are not in relapse, but still sick, they are mistakenly thought to be well. One cannot place reliance upon looks.

Pain

Pain can be the most severe aspect of this disease. It affects all areas of the body; headache is usually the more severe pain and is difficult to control, even with the most potent opioids at times. With the more severe headaches, there is nausea and vomiting that at time can lead to dehydration and hospital admission. Joint pain can be severe, but the disease does not cause a destructive form of arthritis. Mild swelling of joins is common; rarely, is it severe. The joint pain is migratory - travels around. Ulcer symptoms and ulcer disease is common. Patients relate that their food doesn't digest - it just sits in the stomach. There is partial paralysis of the stomach and gastrointestinal tract - this can lead result in nausea.

Pain and all aspects of this disease are made worse by exercise or attempting to behave normally. A patient during a better period might attempt to act normally and then find herself or himself in bed for days. A common statement is: "I pay for everything that I do."

The discomfort of these patients is made worse by the hostility that they encounter from family, friends, associates, and physicians. Disbelieving and unsupportive spouses lead to marital stress or dissolution. Children become burned out and friends do not always want to hear that a patient does not feel well. Because patients have so often been told that nothing is physically wrong with them, they begin to believe they are "crazy".

Vascular features

At the onset of their disease, many patients have unexplained bruises (without any trauma). These often sting and burn. More severe cases exhibit swollen veins, painful in nature. At times, clots have formed in veins, but usually not in the deep circulation. Small veins can suddenly rupture, with a stinging sensation, and leaving a bruise. Deep veins can remain inflamed and are not visible on the surface.

A relapsing course

Except for the mildest cases - or those who have symptoms only during a relapse - patients have a constant plateau of illness during which they are still not well, but do not appear that ill. Appearances can be deceiving. Bear in mind that many patients with cancer, heart disease, diabetes, and other severe illnesses often appear to look normal to the casual observers they are encountered at the grocery store, church, and other sites. During relapse, however, patients look unmistakable ill. Relapses can be caused by physical, emotional, or environmental stress. Again, in the menstruating woman, relapse can occur at this time and the disease is worse in general at the time of menses. Relapses can last for indefinite periods from weeks to months to years.

Laboratory studies

To this date there is/are no conclusive test or tests of abnormal findings that are in keeping with this disease, most of them involving the immune system.

An electromyogram is frequently abnormal, showing damage to nerves. The magnetic resonance brain image (MRI) often reveals evidence of demyelination - damage to the myelin sheath covering the brain. The MRI can show the same findings in other diseases as well, including multiple sclerosis. A specialized SPECT scan invariably shows impairment of brain blood circulation. A PET scan can be abnormal, indicating that the physiology, or function of the brain is impaired.

Cytokines, produced by lymphocytes, are substances we all need but in this disease, there is often an excess that causes damage or the production of some that are damaging by nature. Some cytokines are protective, and perhaps they are deficient in this disease.

Some tests commonly found are in keeping with, and support the idea of an active viral infection. Muscle biopsies are often abnormal as well as other tests for muscle disease. Muscles, however, may be damaged but do not visibly shrink or waste away.

Treatment

There is currently no treatment that can cure this disease. Treatments are geared to treating symptoms and making life more bearable and functional, as well as to modulate, or change the immune system so that it can better combat the disease, Immune modulating therapies, however, are usually expensive and insurance carriers are loathe to pay for them.

Beyond this, however, there are many things that can be done to improve comfort and well-being. One must always have a positive outlook - have a mind set that the disease will get better. This aids the immune system - and indeed, it is possible. You must re-structure your life. Accept that you have this disease and live within its limitations. It takes some experimenting to find out how much you can get by with. Be as normal as you can, but do less of everything. Rest is essential and restorative. Gentle aerobic exercises are advised to maintain muscle tone.

OUTLOOK

The general tendency is to slowly improve and the majority of you will recover much of your function, but all things are possible. Very mild cases often recover entirely. Many of you will have residual symptoms for a long time. Beyond the mild cases, most of you will continue to have some symptoms at least intermittently.

THERE ARE A NUMBER OF CONFUSING ENTITIES (CONDITIONS) THAT NEED TO BE DISCUSSED:

FIBROMYLAGIA

Fibromylagia is an inflammation of joints and musculoligamentous connections. The diagnosis rests upon finding so-call trigger points over various joints. Early on investigators stated that if one has fibromyalgia, one should exercise - it makes you feel better. Now they do not say this. It is a term that is used by Rheumatologists chiefly although now other physicians are beginning to use the term. Generally, if you are seen by a rheumatologist or internist, he or she may say that you have fibromyalgia. And indeed you have fibromyalgia. But it is one facet, one part of your illness, the chronic

fatigue syndrome. I have examined 5000 of you at this time and all but about 8 have had the chronic fatigue syndrome (infectious venulitis). The eight I mentioned had fibromyalgia that I could not categorize. It was caused by something else. The remainder of the 5000 all had your disease.

In other words, fibromyalgia is just one part of your disease. Some of you have it mildly, some of you, severely, Generally I believe that those who label this disease fibromyalgia are akin to the seven blind men with the elephant; they only see the trunk or the tail - and miss all the rest that is going on with you. Many of you fulfill all of the criteria for fibromyalgia and in addition to the chronic fatigue syndrome and/or infectious venulitis.

Fibromyalgia can also occur with many other illnesses including cancer, Lyme disease, rheumatoid arthritis, lupus erythematosus, to mention just a few. Other viral diseases can cause fibromyalgia, but unlike your disease, it does not last very long, nor does it keep coming back.

SICK BUILDING SYNDROME

I have examined many of those labeled as having this. I find the disease identical to the chronic fatigue syndrome. There is no difference - it is the same disease. Also, these people without exception show the same laboratory features. I will comment later on causes.

GULF WAR SYNDROME

At this writing, I have examined two patients with this label and also, find them to have the chronic fatigue syndrome. From the histories that they gave, it also is a communicable disease, as is the chronic fatigue syndrome. They are already carrying, or had been simultaneously exposed to a viral agent that caused disease when they were exposed to an environmental toxin or pollutant.

EPSTEIN-BARR VIRUS DISEASE (EBV)

This is an outmoded term, but one that physicians who are not up to-date (and they are many) still cling to. No expert, including me, believes that chronic fatigue syndrome (CFS) is caused by EBV. Whether it plays a lesser role, along with other viruses, cannot now be determined. But it is not the cause of your disease. It is reactivated by CFS, along with other common viruses.

SUMMARY

The chronic fatigue syndrome first occurred in modern times at the Los Angeles County Hospital in 1934. It occurred in the midst of a poliomyelitis epidemic. Several astute physicians recognized that there was a new disease present. Gilliam, who wrote a large research paper accurately described CFS

but did not name it. In the fifties there was an epidemic in Iceland, also associated with a polio outbreak - but again, recognized to be a new disease. It was found that patients who developed CFS became immune to polio. CFS has occurred more or less world-wide. Epidemics have been described in closed, contained populations such as schools, military barracks, convents, monasteries, and especially hospitals.

What I call infectious venulitis, that occurred in severe epidemic form in 1975 in suburban Sacramento, is a variant of the chronic fatigue syndrome. Until 1988, it was called epidemic neuromyasthenia (ENM). Those in the United Kingdom call it myalgic encephalomyelitis (ME), a term that is still in vogue, although chronic fatigue syndrome is starting to be used there interchangeably. I believe that the pathophysiology - the damage - is to the vascular system. Pellew & Miles who studied an epidemic in Aidelaide, Australia in the 50's and inoculated monkeys with material from patients described damage to the vascular system. Gilliam and others found involvement of the vascular system in the Los Angeles outbreak also. I find evidence of involvement of the vascular system in the chronic fatigue syndrome, although generally not so striking as infectious venulitis.

In the 50's and 60's, three different epidemics of a painful vein disease occurred in this country and were published in the medical literature. It was called epidemic phlebodynia (painful veins). It had many features of what I call infectious venulitis and the chronic fatigue syndrome. I believe it was a milder form of infectious venulitis. (Infectious venulitis has a more complete expression). It has not been reported since the 1960's.

In 1984 I visited New Zealand at the request of medical staff at the University of Otago in Dunedin, the South Island because of a widespread epidemic in both North and South islands of New Zealand. It was called myalgic encephalomyelitis (ME) or Tapanui Flu, after the small area where it was first discovered. I spoke to large groups of people and appeared on national radio and TV. I was able to examine patients there and showed medical staff my methods of examination. It was then I found what I was calling infectious venulitis (INV) was the same as ME, and thus also, ENM.

Also in 1984 I presented a research paper at the INTERSCIENCE CONFERENCE FOR ANTIBIOTICS AND CHEMOTHERAPY, a forum where much original research is aired world-wide. This was in Washington, D.C.. An abstract of this presentation is published in their proceedings of that year.

In 1985 two scientific papers were published on so-called Epstein-Barr virus disease. At the same time, an epidemic of a strange, viral-like disease took place at North Lake Tahoe in Incline Village. Researchers there, who had

read these two papers promptly called it chronic EB virus disease. When this occurred I had misgivings and did not believe that this was the case. Virtually the only manifestation of EB virus is infectious mononucleosis with rare exception. Other types exist but they occur in severely immune deficient individuals. The reason I did not believe it because among my patients with IVN, whom I had followed daily since 1975 - some had developed infectious mononucleosis well after the onset of IVN. I witnessed the infectious mononucleosis to come and go, but IVN remained and remains the same to this day. I had reasoned that the disease at Lake Tahoe was either the same disease as IVN or a variant of the same disease. And if this was so, it could not be due to the Epstein-Barr virus. Finally, all experts in the field across the country came to the same realization - the disease was not due to EB virus.

In 1986, the National Cancer Institute of the NIH discovered a new human virus that they first named HBLV and then renamed HHV6 for human herpes virus number 6. There was an immediate flurry of activity and claims that this was the cause of the Incline Village outbreak and the cause of CFS. But this did not prove to be the case epidemiologically and this theory has been largely discarded at this time. It is possible that HHV6 plays some ancillary role, along with other viruses. Since then HHV7 and HHV8 have been discovered - two human viruses without a disease discovered thus far. There are now thus 8 Herpes viruses; chicken pox/shingles (the same virus), Herpes simplex-fever blisters & genital herpes, cytomegalovirus (CMV), Epstein-Barr virus (infectious mononucleosis), HHV6, HHV7, and HHV8.

In 1988 the Centers for Disease Control (CDC) of Atlanta, Georgia's (formerly called the Communicable Disease Center), convened a symposium featuring many prominent researchers of this disease from across the country. The name chronic fatigue syndrome was coined and criteria were changed and simplified somewhat.

How is chronic fatigue syndrome/myalgic encephalomyelitis different from IVN? I believe it is the same disease. Although no vascular features are mentioned in CFS, there are allusions to vascular involvement in ME. I believe thus far researchers on CFS have failed to note them - they are there. Many of you whom I have examined exhibit the same features as my original patients of 1975 with very evident vascular features. In all of you I find inflammation of deep veins.

My original 1975 cases, with the passage of time, have less evidence of superficial vascular involvement and now resemble most of you. Aside from that, you fulfill all the criteria for CFS. But unlike the official diagnosis of CFS, I also use a very specific physical exam to make the diagnosis.

So what causes IVN/CFS/ME? A specific viral agent has not yet been identified. It does not appear to be anything common. It could be a viral agent very difficult to cultivate. It could be what is called a partial virus. Could it be due to two viruses? As yet there has been no association with the retrovirus that has been proven. The previous finding of a retrovirus has not been able to be repeated by experiments and is invalid. But suppose that all, or nearly all of us, carry an unknown retrovirus in our genes. And then another viral agent infects and the two in combination produce the disease? Or could this illness be due to a virus that escapes immune surveillance. This is, that our immune system is unable to detect it as a foreign invader?

There is a very interesting illness called the post-polio syndrome. Patients who have had polio 20-30 years before acquire an illness that closely resembles CFS. I have examined some of these people and cannot tell the difference. Could this syndrome be due to a mutant polio virus that escapes immune detection? Earlier I said that the early epidemics of ME/ENM/CFS were always in association with a polio outbreak. And that those who came down with ME/ENM/CFS were immune to polio.

There are those who believe that CFS can be caused by different things such as stress including injuries, operations, childbirth, and exposure to toxins (here is where the sick building syndrome comes in). I myself believe that there is always a virus in residence. I believe that these various stresses can precipitate the virus to cause CFS in individuals who are already carrying it or are exposed to it at the same time as the given stress.

The general tendency in this disease is for gradual improvement but anything is possible. Beyond the mild cases who might totally recover, most of you will have some symptoms lifelong.

It is very important for you to have a firm diagnosis. If you know what you are up against, it is half the battle won.

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