The Chronicles of Chronic Fatigue

Chronic fatigue syndrome as an infectious disease: a review of etiological agents

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Chronic fatigue syndrome has long walked the fine line between being categorized as a mental or a physical disease. More common in women and middle-aged patients, the disease displays symptoms which include chronic fatigue, loss of concentration, musculoskeletal pain, joint pain, severe headache, and extreme exhaustion that last at least six months or longer (Mayo Clinic 2000). Because these are just symptoms (subjective self-reports of the patient) and no physical signs or definitive laboratory methods of diagnoses exist, there is often a stigma attached to whether or not the condition is of psychiatric or physical origin. Recently, however, there has been evidence linking chronic fatigue syndrome to a slew of infectious agents, prompting public health officials to reevaluate the syndrome as an infectious disease.

"Is It All In My Head?"

The name "syndrome," rather than "disease" proper, suggests that chronic fatigue is a figment of the mind; some psychiatrists go so far as to write off the clinical manifestations as simply hypochondriac in nature. In fact, the most common misdiagnoses in patients with chronic fatigue syndrome are major depression and somatoform disorders which can manifest themselves in physically similar symptoms (Fukuda, et al 1994, 953). There is currently no standard treatment available for the debilitating disease. The syndrome is typically long lived and the rate of recovery is as low as 5% of cases. As a result, it usually consumes a patient's life (CDC 2006). Because of the nonspecific symptoms and the confusion in pinpointing the origin of the fatigue, it is hard to estimate the number of affected individuals—the CDC estimates it at one million Americans with 80% of cases undiagnosed.

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Chronic fatigue syndrome has always been closely associated with psychiatric disorder. A study done at the University of Leeds found that patients who had developed chronic fatigue were nine times more likely to have suffered stressful events and difficulties in the three months before the onset of disease than were healthy subjects (Hatcher 1991, 387). Chronic fatigue syndrome patients were also more than three times as likely to suffer from depression. However, Leonard Jason, a professor of psychology at DePaul University in Chicago, when interviewed about the disease reported, "If you ask a person who is depressed, 'What would you do tomorrow if you were better?' they say, 'I don't know.' Chronic fatigue sufferers will give you a list of ten things," (Schorr 2005).

Hints of an Infectious Agent

There have been many hypotheses as to the etiology behind chronic fatigue syndrome from purely psychological notions to actual infectious agents. In recent years, however, there has been a greater push towards finding a biological cause of the syndrome for a variety of reasons. First of all, epidemics of chronic fatigue syndrome are sometimes centered about a geographic location, suggesting a common source of a microorganism, or the communicability of a microorganism. Outbreaks in Lake Tahoe, Utah; Key West, Florida; and Punta Gorda, Florida have occurred where dozens of people would acquire chronic fatigue syndrome simultaneously. Entire hospital staffs in both LA county and London, UK have also fallen victim to this syndrome (Patarca-Montero 2004). It is not just a Western affliction, as outbreaks have been documented in remote places like South Africa and tribal New Zealand.

Secondly, researchers have found evidence that suggests that in a time of high stress, a viral infection can damage the central nervous system, causing changes in the immune system which reflect the traditional symptoms of chronic fatigue. In various studies, there has been evidence of an elevated number of natural killer cells and activated CD2 cells and T8 cells. While these may be signs of chronic stress and depression, once again suggesting the psychiatric origin of the syndrome, they are also signs of recurrent viral infections (Holmes 1991, 387). In fact, most patients who suffer episodic bouts of chronic fatigue

syndrome symptoms contracted the syndrome after an acute viral infection, proposing a further connection between the illness and a virus. The most common manifestation of chronic fatigue syndrome is a cyclic reoccurrence of symptoms, making chronic viral reactivation a very likely possibility. However, one of the biggest mysteries surrounding chronic fatigue syndrome is whether a single biological origin behind the symptoms or a combination of etiologies and pathologies all together give onset of the recognized and clinically diagnosed syndrome.

Etiology: A Start

Chronic reactivation of the Epstein-Barr virus has been one of the first viral hypotheses linked to chronic fatigue syndrome because of the similarity of symptoms, primarily fatigue, and the presence of Epstein-Barr virus antibodies in the majority of patients suffering from chronic fatigue syndrome. The term "chronic Epstein-Barr virus syndrome" was actually the name of the disease used prior to 1988 because many of the first diagnosed patients lapsed into chronic fatigue syndrome after infection with the Epstein-Barr virus (Holmes 1991, 387). Though the name has changed since then, many researchers continue to investigate Epstein-Barr as the primary cause because of the virus' tendency towards reactivation, especially in immunocompromised patients.

"Many more studies must be done in determining what microorganism is the cause, combination of microorganisms is the cause, or if they are all simply opportunistic invaders in compromised patients. However, it is becoming more and more probable that there is an infectious aspect to chronic fatigue syndrome."

Enteroviruses, RNA viruses associated with debilitating diseases like polio and other neurological diseases, have also been implicated in the etiology of chronic fatigue syndrome. In a study from the UK, enteroviruses were detected in stool and muscle samples of chronic fatigue syndrome patients in much higher frequency than in samples from control groups (Cunningham et al 1990, 1399). Chronic infection of enteroviruses occurs in many fatigue syndrome patients (Yousef 1988, 146). Because the viruses are associated with diseases of muscle pain and fatigue, further research is being done to solidify the link.

Etiology: A Step Forward

A turning point in chronic fatigue research came in 1991 when a research group found human T-lymphotropic virus (HTLV) antibodies as well as sequences resembling a HTLV-like virus in 50-60% and 72-83% of the chronic fatigue syndrome patients respectively, and close to none in the control group (DeFreitas, 2922). The statistical significance of the findings gave renewed hope to finding the microorganism behind chronic fatigue syndrome. What is alarming is that a significant portion of healthy nonsexual contacts of the patients also had antibodies to the HTLV-like virus as well as natural killer abnormalities. These results do not appear in tests run on noncontact controls. This may be evidence of the horizontal transmission of a retrovirus that may either be a trigger for chronic fatigue syndrome or a secondary infection to an immunocompromised individual. This was the first time chronic fatigue syndrome had been linked to a retrovirus which had long been hypothesized as the most probably infectious agent.

Dr. Judy Mikovits from the Whittemore Peterson Institute also found evidence of a latent retrovirus as a possible etiological source. The October 2009 issue of Science published perhaps the most convincing study to date in which researchers discovered a correlation between a xenotropic murine leukemia virus-related virus (XMRV) and chronic fatigue syndrome. In 67 of the 101 chronic fatigue syndrome patients in the preliminary study, XMRV could be found in patient blood cells. This is considerably higher than the healthy, non-patient population whose incidence of XMRV (in

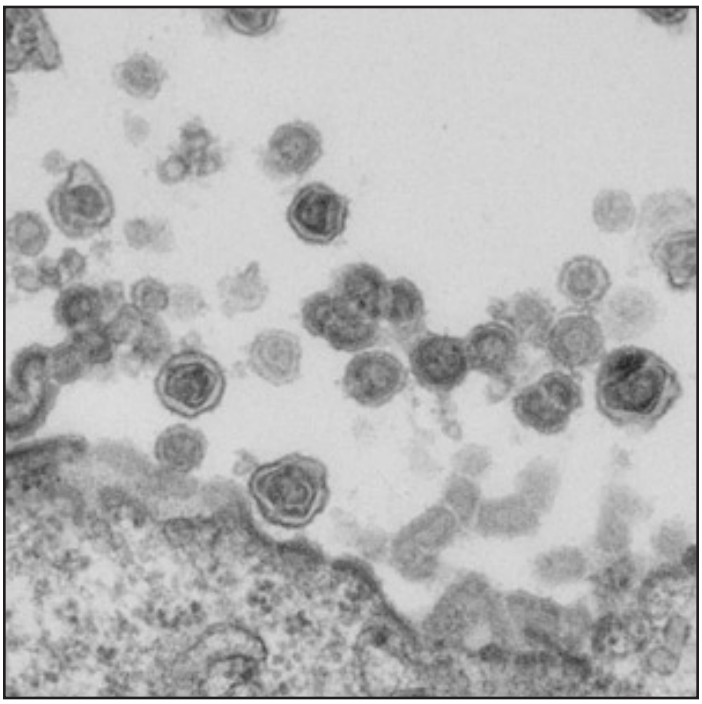

Figure 1. XMRV, the retrovirus implicated in recent studies as a factor in chronic fatigue syndrome.

the control group) was a mere 3.7% (Mikovits, 585). In a follow up study, XMRV was found in 98% of all patients with chronic fatigue syndrome (Grady 2009). The higher statistical significance of the study was groundbreaking.

While still little is known about XMRV, its relation to other known viruses that recognize and enter cells through cell surface receptors suggest that the virus may be sexually transmitted (Brower 2009, 700). Like HIV, XMRV is a retrovirus that incorporates itself into the human genome and remains latent until the host's immune system is compromised—perhaps explaining why most people are diagnosed with chronic fatigue syndrome after a stressful experience or a viral infection. If XMRV can be further substantiated as the cause of chronic fatigue syndrome, specific anti-virals can be presented as a form of treatment for the syndrome, for which none had been previously available (Mikovits 2009, 585). An etiological root can finally be established if a vaccine for the virus can prove to be effective in preventing the disease or if treatment with anti-virals shows improvement in patients.

Mikovits released a statement admitting that XMRV, though a main contributor to the syndrome, probably works in conjunction with other viruses to bring on the full spectrum of symptoms that a chronic fatigue syndrome patient experiences. This brings to light the possibility of XMRV working in synergy with any one or possibly all of the other viruses aforementioned, from Epstein-Barr to enteroviruses,

Figure 2. Chronic Fatigue Syndrome is typically long lived and the rate of recovery is as little as 5% of cases, usually consuming a patient's life

potentially tying together a body of research that is often at odds with itself in terms of reliable study results and replicability.

Light at the End of the Tunnel

A common thread throughout these studies is the possible or potential viral origins of a disease once thought to be mostly mental. Many more studies must be done to determine which microorganism or combination of microorganisms is the cause or if they are all simply opportunistic invaders in immunocompromised patients. While further research is being done on various viral agents, the discovery of retroviruses has raised concerns about how a virus may be transmitted, and the public health implications, which were long dismissed, have now resurfaced. While public health officials wait on more evidence, the breakthroughs so far have given hope to patients who have long suffered the stigma of mental disease and give promise of a definitive diagnosis and effective treatment in the near future.

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