Researchers Implicate HHV-6 Virus in Chronic Fatigue Syndrome, AIDS and Multiple Sclerosis

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Medical researchers are finding compelling evidence suggesting that one common virus may be a co-factor in the cause and progression of such devastating diseases as chronic fatigue syndrome, (CFIDS), multiple sclerosis, (MS) and AIDS. Experimental pathologists Drs. Konnie Knox and Donald Carrigan identify this viral suspect as HHV-6, (which stands for human herpesvirus 6). Drs. Knox and Carrigan direct the Greenfield, Wisconsin laboratory, Herpesvirus Diagnostics, Inc., which offers some of the most sophisticated human herpesevirus assays in the world scientific community.

Present in about 98 percent of the U.S. population, HHV-6 remains asleep and harmless in healthy people. When activated, however, HHV-6 causes a highly disregulated immune system, often resulting in severe immune suppression which increases an individual's vulnerability to severe infections, organ damage, and even death.

New viral research discoveries related to the above diseases are significant for myriad reasons: Although they've been recognized as disease syndromes for many years, CFIDS and MS have unknown causes and their respective disease progressions are poorly understood. What's more, for over a decade, researchers have been debating whether or not there are perhaps several significant co-factors involved in the evolution of HIV into AIDS.

Should active HHV-6 infection prove to be a co-factor in AIDS, MS and CFIDS, the repercussions would be enormous. First, the prevailing theory that HIV virus alone causes the damage in AIDS would be demolished, since HIV and HHV-6 were proven to ravage key cells and immune system organs together.

Second, clinically proven anti-viral drugs that effectively reduce HHV-6, such as Labucavir, which is currently being tested in FDA-approved trials, could be used to reduce HHV-6 levels in AIDS patients. In addition, drugs such as Labucavir may be used to effectively manage MS, CFIDS and other illnesses involving immune suppression.

It's also possible that the identification of active HHV-6 as a co-factor in CFIDS might lead to the designation of a marker for CFIDS, finally proving that the disease has an organic cause, or causes. Furthermore, researchers may find that CFIDS and MS are two different diseases with overlapping symptoms that share HHV-6 as a co-factor. Or, they may find that CFIDS and MS represent two different stops along one disease continuum. Additional potential repercussions

worth considering include how discovering a marker for CFIDS would affect medical insurance providers, many of which refuse to pay for CFIDS-related medical expenses or CFIDS-related disability.

CFIDS is a debilitating illness associated with persistent severe fatigue and a variety of physical and neuropsychological signs and symptoms. According to Jacob Teitelbaum, M.D., writing in his book, "From Fatigued To Fantastic," "The most predominant condition of CFIDS is that the person's fatigue has caused a persistent and substantial reduction in their activity level for at least six months." Teitelbaum, himself a CFIDS survivor, adds that recurrent infections, cognitive impairment, poor sleep, achiness, "brain fog," increased thirst and bowel disorders that have persisted or recurred during the fatigue are some of the more common symptoms presented by CFIDS patients.

In MS, the body's immune system attacks and damages the myelin sheath surrounding nerves in the central nervous system, which is housed in the brain and spinal cord. This sheath helps conduct nerve signals along pathways, and the destruction of myelin causes degradation of nerve signals, resulting in impaired functioning of systems that those nerves serve. Common symptoms of MS include blurry vision and impaired color sensitivity and contrast. Tingling, burning and numbness are felt when demyelination occurs in an area of the CNS carrying sensory information. The damage and demyelination result in plaques which are frequently visible with magnetic resonance imaging (MRI). These plaques are also evident during autopsy. Dr. Knox notes, "Dr. Peterson tells us that many of his CFIDS patients go on to develop MS. This is influencing our attempt to pinpoint the nature of the viruses involved in both syndromes." In the United States, 1 to 3 people out of a thousand suffer from MS. There is a known genetic predisposition to this illness: while Scots and Scandinavians are particularly susceptible to developing it, MS is exceedingly rare among southern Europeans and Africans.

Findings on HHV-6's Role In Different Disease

As with the AIDS virus, the nature of HHV-6 is so complex that science's understanding of its role in various diseases is tentative, at best. Human herpesvirus 6 was first isolated in 1986 by the co-discoverer of the AIDS virus, Dr. Robert Gallo, and his research team at the National Cancer Institute. As it happened, the team's first isolate of the virus was an A variant, and it came from an AIDS patient. The virus was initially named HBLV, which stands for the human B-cell Lymphotropic Virus. Dr. Gallo, director of the Institute of Human Virology (IHV) at the University of Maryland, and his team, however, subsequently showed its high infectivity of human T cells and decided to rename it Human Herpes Virus 6 (HHV-6). Following this, two types, A and B, were further defined. In the late 1980s, researchers discovered that HHV-6B causes the common childhood illness roseola infantum, commonly referred to as roseola. This is characterized by high fevers and a reddish skin rash which lasts for a few days.

HHV-6 has been making controversial news since the spring of 1996, when Dr. Knox and Carrigan published results of their HHV-6 research in the Journal of AIDS and Human Retrovirology challenging the AIDS establishment's central tenet: that the disease is activated by one single virus, namely, HIV. The research duo, which has been publishing their HHV-6 since 1989, advanced the innovative theory that there are two viruses involved in AIDS: HIV and HHV-6, and that the two make an especially lethal combination. In a December, 1996 ABC World News Tonight report on Dr. Knox and Dr. Carrigan's research, Dr. Gallo agreed that HHV-6 is an important co-factor in the development of AIDS and specified a potential direction for AIDS treatment. "If we could inhibit HHV-6 specifically and safely for a long period of time, it is my hypothesis we would help HIV-infected people," he said then. Today, he explains: "I believe HHV-6 could be involved in promoting progression , i.e., accelerating to AIDS, but I also believe HIV alone will cause AIDS in most people, given enough time. HIV is clearly the cause of AIDS."

Noting that HHV-6 infects most of the human population,Gallo continues, "The best interpretation of current results, or at least a tenable hypothesis, is that the immune impairment of HIV leads to more active HHV-6, which in turn contributes to AIDS progression." In Dr. Gallo's view, Knox and Carrigan's research means "only that one new possible mechanism by which AIDS progression occurs may be through HHV-6." Indeed, Gallo proposed this several years ago.

One of Knox and Carrigan's current HHV-6 research studies aims to identify "a sub-population of chronic fatigue patients whose chronic illness is caused by a virus, which we happen to think is HHV-6," Knox says. "Our studies indicate that CFIDS patients have a uniquely high infection rate with the A sub-variant of the virus; we often find A in their blood. Although we haven't evaluated for B, we think it is most likely present in the blood of CFIDS people, too." The general, long range goal of their study is to provide crucial information for the justification and design of a clinical trial of an anti-viral drug effective against HHV-6 in a selected population of CFIDS patients.

Activated HHV-6 behaves in a phenomenally destructive fashion. The virus sweeps through the human body like a warlord-warlock whose armies hex and colonize the immune system and body organs with infectious artillery. Besieged by HHV-6, immune defense forces are wiped out by the armies of viral occupation. Although no one yet knows what triggers active HHV-6 infection-genetic predisposition, antibiotic use, environmental and other factors may be involved-researchers are very clear about the damage it appears to cause.

According to Dr. Knox, "We find significant amounts of HHV-6 in the brain tissue, bone marrow and lymphoid tissue of bone marrow transplants and solid organ transplant patients. We also see HHV-6B in the brain and A & B in the peripheral lymph tissue of MS patients. What's more, every

HIV-infected patient whose lymphoid organs we've looked at shows active HHV-6A & B infection." Dr. Knox makes the extraordinary assertion that, "I have no doubt that there are many patients with AIDS who are dying of HHV-6 disease that could be treated with anti-viral drugs. And that those patients would have improved health and longer lives."

According to Darryl See, M.D., an infectious disease specialist and immunologist affiliated with the University of California at Irvine, Knox and Carrigan are charting a scientifically sound and promising research course. "Their work is generated around showing end-organ damage from HHV-6 in immuno-compromised patients," he explains. "Their research path parallels what happened ten years ago with CMV in AIDS." Back then, "Most in the medical community dismissed the assertion that CMV causes end-organ disease in AIDS. Today, however, we now know that reactivated CMV causes pneumonia, retinitis, encephelitis, colitis and other problems in AIDS patients. This end-organ disease is significant," he explains, "because some viruses remain exclusively in the bloodstream, whereas others, such as HHV-6A, tend to attack immune cells and tissues such as the lungs and kidneys. Other examples of viruses which cause end organ damage include hepatitis C, which targets the liver, and influenza, which targets the lungs." HHV-6B, Dr. See says, "attacks cells of the central nervous system."

At their most basic level, the new findings on HHV-6 and related viruses signify that viral co-conspirators in several devastating diseases may behave far more enigmatically and treacherously than previously believed. Dr. Gallo maintains, "There are too many mysteries surrounding HHV-6. It's too common a virus and the full extent of its involvement in various diseases is not being probed." HHV-6, Gallo asserts, is understudied worldwide, and "the virus merits a serious push in terms of research funding…we need to prove its pathogenetic role in disease and we need to develop an inhibitor." IHV researchers such as Dr. Paula Secchiero have been studying HHV-6; Secchiero's grant application for HHV-6 research was turned down by the National Institutes of Health. Gallo's goal is to team up with a pharmaceutical company to develop an HHV-6 inhibitor. "We can provide the molecular biology research, the virology and animal models, " says Gallo. "The core of the apple of this virus is to develop an inhibitor."

Knox and Carrigan theorize that in diseases such as AIDS, MS and CFIDS, HHV-6 may be the ringleader of a viral gang whose members most likely include HHV-7, cytomegalovirus (CMV), Epstein-Barr (EBV) and HHV-8. These viral gangsters may converse and influence each other to the point where "they're making each other act up and disregulate the immune system, sometimes so much that the host becomes terribly immune-compromised, such as you see in AIDS patients, organ transplant patients and chronic fatigue patients," says Knox. "We know that HHV-6 is commonly found in people who have profoundly suppressed immune systems, such as organ transplant recipients. And we think that HHV-6A may be activated in CFIDS patients." Knox ventures, "This could help explain why those with CFIDS and MS get so many infections and experience prolonged bouts of exhaustion and sleep disturbances."

Because a disease marker for CFIDS has yet to be discovered, many in the medical community believe it to be neuropsychiatric in origin, "which is exactly how MS was viewed until the early 1960s," Knox observes. Given that it's been published in the medical literature that 20 to 25 per cent of the MRI scans of MS and CFIDS patients show similar kinds of demyelination and decreased blood flow in the same areas of the brain, this prevailing opinion on CFIDS seems both unfair an uninformed. "The syndromes of MS and CFIDS share so many similarities," Knox says. "And we know from looking at the viral loads of HHV-6 in CFIDS patients that these people are profoundly, physically ill. Their blood is so loaded with HHV-6 that we know they are not malingerers." Knox concludes, "The widely held belief that CFIDS is neuropsychiatric in origin may be one reason why we've hard a tough time getting funding for studies into HHV-6's role in CFIDS."

Admittedly, the research on HHV-6's potential role in CFIDS, AIDS and MS is fairly preliminary. But leading researchers and clinicians such as Darryl See, M.D. agree that "it's impeccably performed and by authoritative, top-drawer researchers. It's baffling why so little government and other institutional funding is allocated towards HHV-6 research. There's no plausible reason," See asserts, "why the federal government passes on funding for HHV-6 research."

Knox and Carrigan have published papers on HHV-6 and its role in the bone marrow and organ transplant population, as well as AIDS, MS and pediatric AIDS patients. Their articles routinely appear in pre-eminent peer-reviewed medical journals such as Blood, the Journal of Infectious Disease, The Lancet, the New England Journal of Medicine; Neurology, and Transplantation. Such stellar credits indicate that their peers deem their scientific approach as impeccable. Despite their formidable credentials, federal sources have consistently denied Knox and Carrigan's grant applications for HHV-6 research studies. None of their published research on HHV-6 received federal funds, although the National MS Society gave them a small grant for a study.

"The medical establishment never faults our science," Knox explains, "but some sectors simply refuse to believe our concept that everyone carries HHV-6 within them, and that sometimes the virus reactivates, which can lead to disease and even death." Knox reports that certain individuals working at organizations which have rejected their grant proposals have justified their refusals by challenging her and Carrigan. "Well if everybody's infected," they ask, "then why doesn't everyone develop bone marrow suppression?"

According to Dr. Gallo, discussing HHV-6 in such simplistic terms "…is really misguided. After all," he explains, "the whole world is infected with Epstein-Barr virus, which can cause lymphomas and nasopharyngeal cancer, among other disorders. But relatively few people develop these, owing to genetic and other factors." Dr. Knox says, " We know that not everyone with HHV-6 has an active infection, and some HHV-6 infections cause greater physical damage than others. In short, the conformist nature of AIDS and other disease research is significantly impeding medical progress."

As Knox puts it, “AIDS research primarily studies HIV and not the disease, and HHV-6’s candidacy as a co-factor in AIDS is a radical departure from the prevailing medical model of the disease.” When one considers these assertions, along with the fact that AIDS research is a billion dollar industry underwritten by various government, academic, corporate and private entities, it’s easier to imagine why the scientific establishment may hesitate to fund HHV-6-related AIDS research. As it happens, every year in the United States, the U.S. government spends approximately $40 million on clinical MS research. The U.S. government spends approximately $12 million on CFIDS research annually and very few new concepts of the disease have been generated. There are, however, some mitigating factors which help account for this situation.

Unlike MS, AIDS and other diseases, no tissue banks exist for CFIDS, which makes studying HHV-6 in CFIDS especially challenging. Knox explains, “If we can understand how HHV-6 may be causing damage in the CFIDS, MS or AIDS patient populations, then that information can be extrapolated into other patient populations of immune-compromised people. Exploring how HHV-6 causes brain damage in MS patients, for instance, may help us understand how it may be affecting the central nervous system in CFIDS patients.” Another factor complicating HHV-6 research is that culturing HHV-6A in the lab is as difficult as integrating a pack of passive-aggressive pit bulls into a litter of labradors. In the words of Dr. Knox, “HHV-6A is so tuned in to the cell that it infects that it either doesn’t grow, or it kills everything. It’s just really a monster. The B variant is easier to grow in cell culture.”

Knox and Carrigan are conducting their current CFIDS-HHV-6 research with Dr. Daniel Peterson of Sierra Internal Medicine in Incline, Nevada, and Dr. Anthony Komaroff, Chief of the General Medicine Division at Brigham & Womens Hospital in Boston, Massachusetts. Peterson and Komaroff are supplying blood samples from their chronic fatigue patients. Knox and Carrigan are saving serum and blood cells on every sample that comes in. One useful by-product of their study is that they are developing a new blood test which they feel is more sensitive in detecting active HHV-6 in CFIDS patients that is tissue-based. “We can’t expect to be getting biopsies from too many CFIDS patients,” Knox notes. Although they are finding active HHV-6A & B in MS, AIDS, CFIDS and the transplant population, (in which B happens to be very active), the duo admits that, “We’re just beginning to understand how these viruses interact.”

Before starting their current study, Knox and Carrigan performed preliminary research to test the blood of eight CFIDS patients for HHV-6 in the winter of 1997. This was funded by the Santa Barbara, CA. nutritional supplement company, Pro Health, Inc., and its subsidiary, The CFIDS & FM Health Resource, which publishes Healthwatch. “This preliminary study found that six of eight CFIDS patient blood samples tested for active HHV-6 A & B infection, whereas none of the six healthy controls tested positive for active HHV-6,” says Knox. The CFIDS blood samples came from patients who had had CFIDS for five years or more, so these were very ill, disabled patients. “We wanted to study blood from longterm CFIDS patients,” Knox says, “because we

wanted to look at the blood and viral loads of those who had been grappling with severe illness for an extended period of time."

Pro Health's CFIDS & FM Health Resource also raised funds for Knox and Carrigan's controlled, double-blind study presently underway, which involves twenty patients and twenty controls. "Our results will be published in the medical literature in 1998," says Knox. A grant application for funds to complete the study is pending at the CFIDS Association of America. "We need $55,000 in order to complete the study," says Knox, "and Drs. Peterson and Komaroff need $2,500 a piece."

Drs. Knox and Carrigan's grant application for this study has been evaluated by the CFIDS Association of America. Pro Health and The CFIDS & FM Health Resource, however have maintained full responsibility for funding this $100,000-plus project. Their colleagues are rooting for them to receive further funding. "We are now in the position," Dr. See says, "where we are seeing scientific data to support the claim that both HHV-6 strains reactivate in immuno-compromised patients and cause disregulated immune function and end-organ damage in tissues." Funding entities and researchers alike need to pay serious attention to HHV-6, says Dr. Gallo. "I'd like to see one hundred decent labs, each funded in excess of $100,000 for basic clinical studies," he says. "I think HHV-6 could be one of the more specific factors helping AIDS develop… Although I wonder whether chronic fatigue is perhaps one, two or three different diseases, each with different etiologies, further research into the role of HHV-6 in chronic fatigue patients will help deepen our insights into this syndrome and maybe lead to a true understanding of how it develops."
