

MS News Sept 26 – October 7

Multiple Sclerosis Linked to HHV-6A Virus

Oct. 5, 2005



Dr. Claude Genain of the University of California San Francisco Medical Center presented evidence at the American Neurology Association Annual Meeting this week that shows a direct link between human herpes virus 6 variant A (HHV-6A) and a multiple sclerosis-like illness. Dr. Genain injected common marmoset monkeys with HHV-6 variants A & B. Most notably, only infection with HHV-6 variant A resulted in illness. The monkeys developed lab evidence and signs of chronic autoimmune demyelination of the central nervous system, the hallmark of multiple sclerosis. This is the first time that any animal infected with HHV-6A has developed clinical pathology of the central nervous system, and the most direct evidence to date of a possible causal connection between HHV-6A and multiple sclerosis.

Dr. Genain's marmoset developed weight loss and paralysis with sensory deficits after exposure to HHV-6A. Inflammatory lesions of the central nervous system and evidence of demyelination were seen on MRI and microscope slides of the brain tissue. However, the important finding of the study was direct evidence of the presence of HHV-6 viral antigen within the nerve cells of the brain stained with an HHV-6-specific antibody.

HHV-6 variant B (HHV-6B) causes roseola, a self-limited fever and rash, in over 95% of young children by age 2. After the initial illness, HHV-6 persists indefinitely in its quiescent, latent form in the cells of the central nervous system, bone marrow and immune system. However, HHV-6 can reemerge and actively replicate later in life, producing new virus particles that can cause illness. HHV-6 can reactivate in immunosuppressed patients and cause life threatening complications, such as opportunistic infections and encephalitis, in post-transplant patients.

The quest for a theory of viruses as a causative agent for multiple sclerosis and other diseases has long eluded scientists. A direct link between infection with HHV-6A and multiple sclerosis has been lacking until now. According to Dr. Genain, "For the first time, scientists will be able to look into the biological process leading to multiple sclerosis at its very beginning, when no one suspects the disease and people have not yet experienced its symptoms." In recent years there has been a considerable degree of interest in the relationship between HHV-6A and multiple sclerosis, because HHV-6A DNA has repeatedly been found in brain tissue and the cerebrospinal fluid of affected patients, and increased levels of antibodies to viral antigens in their blood only present during replication of HHV-6A are frequently detected.

A comprehensive analysis presented by Dr. Dharam Ablashi, co-discoverer of

HHV-6 and Scientific Director of the HHV-6 Foundation, at the International Fatigue Conference on Fatigue Science held during February 2005 in Osaka, Japan, discussed all clinical studies published in the medical literature on the association between HHV-6A and multiple sclerosis.

His summary of the existing literature demonstrates that when lab methods detecting the presence of active HHV-6A infection are used, an exceptionally strong, statistically significant association between HHV-6A and both multiple sclerosis and chronic fatigue syndrome (CFS) is consistently seen. Lab methods that detect latent HHV-6A virus are not able to consistently identify either MS or CFS patients.

Having an experimental animal model linking HHV-6A infection to central nervous system pathology will open the door to new types of research investigations. The common marmoset has a well-known propensity to develop experimental autoimmune encephalitis, a chemically-induced animal model of multiple sclerosis that is commonly used when investigating the efficacy of new MS drugs. The inflammatory demyelination of nerve cells in a live primate model after exposure to the HHV-6A virus has now been demonstrated for the first time. This marmoset model will add a new dimension to the drug discovery and development process for multiple sclerosis.

Dr. Ablashi, who has published numerous medical studies demonstrating the causative role of human and primate herpes viruses in various types of lymphomas and leukemia, commented, "Nonhuman primates are genetically closest to man. Dr. Genain's pathogenic model of HHV-6A infection in the common marmoset will enhance our understanding of the role that the HHV-6A virus plays in the induction of typical MS lesions. This model will be very important in the study of the disease process, and evaluation of new molecules that can prevent active HHV-6A viral infection and the development of multiple sclerosis."

DIRECT-MS Comments – This is a very nice study that adds strong support to the interpretation that a common childhood virus such as HHV-6 can be a key factor in the initiation of MS. Of course there are other factors involved in MS with one's vitamin D status at the time of infections like HHV-6 likely also being an integral part of the start of the long "pre-clinical phase" of MS.

Doxycycline Could Enhance Interferon Beta 1-a (Avonex) Therapy in Remitting Relapsing MS

October 4, 2005

Interim findings from an ongoing study suggest that the addition of oral doxycycline to interferon beta 1-a (Avonex) therapy for patients with relapsing remitting multiple sclerosis (RRMS) results in statistically significant reduction of

gadolinium enhancing (Gd+) lesions compared to interferon beta 1-a monotherapy. Researchers reported these findings here on September 30th at the 21st Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS).

"We saw a great reduction in gadolinium enhancing lesions over the period of 4 months after we introduced oral doxycycline to interferon treatment with Avonex," said investigator Rhonda Brooks, Clinical Research Coordinator, Louisiana State University Medical Center, Baton Rouge, Louisiana, United States. "We are hopeful that this combination treatment will prove to greatly reduce relapse rates among these patients, who are all relapsing remitting patients," she said.

Doxycycline, a matrix metalloproteinase (MMP) inhibitor, has the potential to limit the transendothelial migration of activated leukocytes in MS, according to the researchers. "In addition," they wrote, "MMP-9, which proteolytically cleaves myelin basic protein, is also capable of cleaving interferon-beta (IFNB) perhaps contributing to relapses despite therapy," they wrote in their abstract. The purpose of the open-label, single-center study was to determine the safety, tolerability, and efficacy of daily oral doxycycline 100 mg daily in combination with 30 mcg of weekly intramuscular Avonex for MS patients with breakthrough disease.

Patients aged 18 to 55 years with a diagnosis of RRMS were eligible for the study. Eligibility also included: Expanded Disability Status Scale (EDSS) score of 1.5 to 4.5, one or more Gd+ lesions on MRI, treatment with IFNB-1a continuously for a minimum of 6 months prior to enrollment, and a relapse within 60 days of the baseline clinical visit.

Eligible subjects were evaluated monthly for 3 months while on weekly Avonex monotherapy and before initiation of doxycycline. Then they are evaluated monthly for 4 months while receiving combination therapy. Assessments include MRIs and clinical examinations. To date, 12 subjects have enrolled in the study, 6 have completed and 5 are still active. At baseline, patients' mean age was 42 years, mean duration of disease was 6.2 years, and mean duration of treatment with Avonex was 3.8 years. Mean baseline EDSS score was 3.6. During the combination treatment period, the mean number of Gd+ lesions (6.2) decreased significantly compared to the pre-treatment monotherapy period (10.3, $P = .001$). The combination of Avonex and oral doxycycline appeared to be safe and well tolerated, the researchers reported.

DIRECT-MS Comments – One trend in drug treatment is now to add an anti-biotic to one of the standard MS drugs with the hope that the combination will improve the results from not much with an MS drug alone to something noticeable with the combination. One can only speculate at the serious problems that would result from taking a strong anti-biotic over the long term. Odds are it will not be pretty.

Water channel protein implicated in relative of multiple sclerosis

Researchers have identified a molecular suspect in a disorder similar to multiple sclerosis (MS) that attacks the optic nerve and spinal cord, according to a report presented at the 130th annual meeting of the American Neurological Association in San Diego. The protein, called aquaporin-4, is a channel protein that allows water to move in and out of cells.

"Aquaporin-4 is the first specific molecule to be defined as a target for the autoimmune response in any form of MS," said author Vanda A. Lennon, MD, PhD, of the Mayo Clinic in Rochester, Minnesota. "It is also the first example of a water channel being the target of any autoimmune disorder."

Because there are many other variants of aquaporins throughout the body, Lennon suggests that these proteins might play a role in poorly understood autoimmune disorders in other organ systems.

For some time, scientists have understood that multiple sclerosis is not so much a single disease, but a category of disorders with similar damage to different parts of the nervous system. Recently, progress has been made in teasing out a particular syndrome called neuromyelitis optica (NMO), in which the body mistakenly mounts an immune attack against the optic nerve and spinal cord. Last year, Lennon and her colleagues at Mayo, along with collaborators in Japan, were able to detect a particular antibody that occurs in most people with NMO, but not in patients with "classical" MS.

This is particularly important for clinicians because specific treatment recommendations to help prevent blindness and other later symptoms, including paralysis, differ for NMO and MS .

In the present study, Lennon and colleagues have identified an aquaporin as the target molecule of the NMO antibody. "This finding is a departure from mainstream thinking about MS and related disorders, where the major focus of research in the past century has been the myelin that insulates nerve fibers, and the cell that manufactures myelin, known as the oligodendrocyte," said Lennon.

The Mayo Clinic group's work reveals that the protein targeted by the NMO antibody is not a component of myelin, or of oligodendrocytes. Aquaporin-4, which is the most abundant water channel in the brain, is instead located in a different type of cell called astrocytes.

"Aquaporin-4 is concentrated in membranes in the precise site where spinal cord inflammation is found in NMO patients," said Lennon.

The next step in this research is to use this knowledge to create an animal model that can be used to confirm the relationship between aquaporin-4 and NMO, as well as to develop new and improved therapies.

DIRECT-MS Comments – This is an interesting finding and is further evidence for a variety of self-antigens as the targets of the immune system in MS. A persons genes and the foreign proteins they are exposed to will determine what exact parts of the CNS will be under attack and what symptoms they will experience.

Vitamin D Linked With Neuromuscular Performance in the Elderly

Sept. 28, 2005

Low serum levels of vitamin D in the body may make elderly persons more susceptible to falls, Netherlands researchers reported here at the American Society of Mineral and Bone Research (ASBMR) 27th annual meeting. "Low levels of vitamin D were associated with low physical performance," said Ilse Wicherts, a doctorate student at Vu University Medical Center in Amsterdam, the Netherlands. "This study shows that neuromuscular performance in those with lower levels of vitamin D was significantly lower than those with adequate levels." These individuals already are fragile," added Ms. Wicherts, the winner of an ASBMR Young Investigator Award. "The lack of mobility places them at high risk of falls and fractures."

In the study 1,238 men and women (mean age, 75 years) by Ms. Wicherts and colleagues, a low serum level of vitamin D was associated with lower neuromuscular performance. The study was undertaken within the framework of the Longitudinal Aging Study Amsterdam (LASA). Neuromuscular performance was measured by five chair stands for muscle strength, a walking test for balance, and tandem stand testing coordination and mobility where participants must stand with one foot in front of the other. Each performance test was scored in seconds and was classified with scores from 1 to 4 according to quartiles of distribution. The total performance score for muscle strength and balance ranged from 0 to 12. The researchers used a multivariate regression analysis adjusted for age, sex, and body mass index.

Eleven percent of the participants had serum vitamin D levels less than 25 nmol/L, 37% had levels between 25 and 50 nmol/L, 33% had levels between 50 and 75 nmol/L, and 17% had levels of 75 nmol/L or above. Scores for chair stands, the walking test, and tandem stand each showed significant improvement with increased serum levels of vitamin D. Participants with vitamin D at 25 nmol/L had a performance score of 4.9 while those with vitamin D levels between 25 and 50 nmol/L had scores of 6.82 and those with levels between 50 and 75 nmol/L had scores of 8.10. Participants with vitamin D levels of 75 nmol/L or higher had performance scores of 8.72.

"There was a linear progression," Ms. Wicherts said. "The change in performance scores with increasing serum 25(OH)D was significant for all steps." When researchers adjusted for age, sex, body mass index, smoking, and alcohol consumption, the performance score increased significantly with serum vitamin D levels up to 50 nmol/L. Performance was reduced 18% if the vitamin D levels were lower than 25 nmol/L compared with participants with levels of 75 nmol/L or

higher and 5% if vitamin D levels were between 25 and 50 nmol/L after adjusting for other risk factors, Ms. Wicherts said.

"Persons with low serum vitamin D levels had a higher risk for low physical performance," Ms. "The strongest effects were found in persons with a major deficiency." "This is a very important study because it suggests that vitamin D is not only important for bone health, but is important in neuromuscular stability," said Elizabeth Shane, MD, president-elect of ASBMR. "Bone fracture is due to not only bone issues, but issues contributing to falls. "There is a two-pronged effect here that can increase the propensity for fractures in the elderly," Dr. Shane said. "Adequate Vitamin D can aid in improving muscle strength and preventing falls in this older age group."

DIRECT-MS Comments – Although this study does not concern MS directly, it clearly demonstrates another good reason to maintain a high level of circulating vitamin D.

FTY720 Phase II 12-month data show sustained benefits and good tolerability in patients with relapsing multiple sclerosis

October 1, 2005

Data from the extension of a Phase II study to 12 months confirm the significant effects of FTY720, a novel oral medication, for the treatment of patients with relapsing multiple sclerosis (MS).

The data, presented at theECTRIMS/ACTRIMS[1] meeting in Thessalonica, Greece, showed that both patient groups taking FTY720 (1.25 mg and 5 mg) who had experienced a reduction in their annualized relapse rate[2] of more than 50% during the first six months of the study compared to placebo maintained this low relapse rate during the subsequent six-month extension.

In patients who switched from placebo to either the 1.25 mg or 5 mg dosing of FTY720 after six months, the annualized relapse rate was reduced by at least 70% during the second six-month study phase compared to the first six months on placebo.

More than 80% of patients who received FTY720 for up to 12 months were free from lesions showing active inflammation on magnetic resonance imaging (MRI) at month twelve irrespective of their FTY720 treatment dose (1.25 mg or 5 mg).

"We are excited by these full-year study results confirming the significant effect of oral FTY720 on reducing both clinical relapses and inflammatory disease activity that we first saw during the six-month placebo-controlled phase of the study," said chief investigator Professor Ludwig Kappos, MD, Department of Neurology

at the University Hospital in Basel, Switzerland, "We hope that the magnitude of benefits shown in Phase II will be confirmed in the larger scale Phase III study program expected to be launched soon."

Based on the positive Phase II study results, Novartis is in discussions with regulatory authorities about the FTY720 Phase III program, which is expected to be launched by the end of 2005.

Over two million people worldwide are estimated to suffer from multiple sclerosis, which is the leading cause of neurological disability in young adults[3]. MS is the most common chronic, disabling disease of the central nervous system affecting twice as many women than men.[3] MS has a significant impact on the patient's social activities, employment and overall quality of life. Currently marketed MS therapies afford an average reduction in relapse rates of 30% in two-year studies and require frequent injections ranging from daily to weekly.[4,5,6,7]

FTY720 Phase II study results[8,9]

The results are from a large Phase II study conducted at 32 centers in 11 countries (Europe and Canada). In the initial, placebo-controlled part of this study, 281 patients were randomized in equal numbers to receive either placebo, 1.25 mg or 5.0 mg FTY720 orally once-daily for six months. The study evaluated the effect of FTY720 on disease activity as measured by MRI and clinical relapses as well as its tolerability and safety. After six months, patients in the placebo group were re-randomized to receive either FTY720 1.25 mg or 5 mg blinded for an additional six months, while patients already on FTY720 continued their originally-assigned treatment. A total of 98% of the 255 patients who completed the first six months volunteered to continue in the extension phase evaluating the longer-term effects of FTY720.

In the 12-month analysis, both patient groups on FTY720 (1.25 mg and 5 mg) who had experienced a reduction in their annualized relapse rate of more than 50% during the first six months compared to placebo maintained this low relapse rate during the subsequent six-month extension. In those patients who switched from placebo to either 1.25 mg or 5 mg of FTY720 after six months, the annualized relapse rate was reduced by at least 70% during the second six-month study phase compared to the first six months on placebo.

The MRI results at 12 months showed low levels of inflammatory disease activity in all FTY720 groups. In patients who switched from placebo to FTY720, the mean number of inflammatory (Gd-enhancing) lesions on MRI (at the 12th month) was reduced by more than 80% compared to the sixth month. More than 80% of patients who received FTY720 for up to 12 months were free from lesions showing active inflammation on MRI at the 12th month irrespective of their FTY720 treatment dose (1.25 mg or 5 mg).

FTY720 appeared to be well tolerated, with 91% of patients who entered the extension phase completing the 12th month on the study drug. There were no

unexpected safety findings during the extension as compared to the six-month placebo-controlled phase. The most frequently reported adverse events in patients treated up to twelve months were non-serious infections (colds, influenza), headache, diarrhoea and nausea.

About FTY720

Oral FTY720 has a novel mode of action different from all available therapies. It reversibly sequesters lymphocytes away from blood and susceptible target organs such as the central nervous system (CNS), thereby reducing neuroinflammation in MS. FTY720 has been developed by Novartis Pharma and licensed from Mitsubishi Pharma Corporation.

DIRECT-MS Comments – The fact that this drug is taken orally and seems to have the same efficacy as the current injectable drugs, it would be nice if the pivotal Phase III trial demonstrates equivalent results. The side effects are somewhat worrisome.

New immune cell found to be a key to inflammatory diseases

Sept 30/05

The molecular roots of inflammatory and autoimmune diseases such as asthma, arthritis, and multiple sclerosis (MS) have been discovered by a team of researchers led by The University of Texas M. D. Anderson Cancer Center. They say their findings may point to ways to effectively treat these diseases - if not stop them before they start.

In a lead article in the November issue of Nature Immunology (released online on Oct. 2), the scientists report finding a novel type of "T helper" cell they say is the culprit for initiating chronic inflammation and autoimmunity in a variety of body tissues. This newly described T cell - which they call inflammatory TH cells (or THi) - produces interleukin 17 (IL-17), a potent cytokine that researchers have already linked to an immune system gone awry.

"We suspected that IL -17 is a player in autoimmune and inflammatory diseases, but we didn't understand where IL-17 came from before this finding," says the study's lead investigator, Chen Dong, Ph.D., an associate professor in the Department of Immunology.

"Now we have discovered the source of IL -17 and also have solidly demonstrated that these are the crucial cells that regulate tissue inflammation in autoimmune disease and asthma," he says. "These findings suggest that shutting down the activity of these THi cells might stop chronic inflammatory diseases from developing in the first place."

He adds that while such drugs are years away from development and clinical trials, agents that block IL-17 could represent an effective treatment, based on these results.

Dong and four other M. D. Anderson researchers collaborated with scientists from the University of Washington, the Institute for Systems Biology in Seattle and Johns Hopkins School of Medicine.

While the findings have no immediate relevance to the field of oncology, it is known that cancer can arise from inflammatory processes. Further understanding of how the immune system functions, and how it can go awry, is important, Dong says.

T cells are white blood cells that play a variety of roles in the immune system, including the identification of foreign molecules in the body, such as bacteria and viruses, and the activation and deactivation of other immune cells.

T helper cells are specific T cells that have receptors that recognize and bind to fragments (known as antigens) of the invaders that already have been displayed on the surface of other immune system cells. (These T helper cells are also called CD4 T cells since they express CD4 molecules.) Once the antigen has been bound, these T helper cells become activated, and they morph into "effector" cells which then boost an immune response by secreting "cytokine" molecules such as interleukins and interferons.

Before this study, two such different types of effector T helper cells had been known - type 1 (TH1), linked to the body's response to microbial infection, and type 2 (TH2), which plays a crucial function in production of B cell antibodies and also is associated with development of allergies.

Although TH1 and TH2 are known to produce powerful cytokines - such as interferon-gamma (IFN-g) and allergy-associated interleukin 4 (IL-4), respectively - they are not inflammatory or associated with production of IL-17, which sets off an errant immune response that results in tissue inflammation.

Researchers could not understand the origins of such an inflammatory response in body tissues. The only clue they had was that excess IL-17 molecules are found in arthritic joints, in lungs swollen by asthma and in brain cells that lead to nerve degeneration and the onset of MS. "But we didn't know which T cells were responsible for secreting IL-17," Dong says. To find out where IL-17 came from, the researchers designed a series of cell culture studies and mouse experiments. In brief, they "educated" T helper cells to become IL-17 producing cells. They found that IL-17 is triggered by a unique set of signals that now define this new "lineage" of T helper cells. "They are completely different from TH1 and TH2 effector cells," says Dong. They then used a mouse model of MS and demonstrated that they could stop development of the disease with an antibody

agent that blocked IL-17. Finally, they developed a transgenic mouse model of asthma and found that, by producing excessive IL -17 in the lung, they were able to produce asthmalike symptoms.

Dong says the researchers hypothesize that these newly discovered THi cells travel to selected body tissues and release IL -17. This action, in turn, stimulates expression of "chemokines," which results in a rush of inflammatory cells into the tissue. Thus a chronic inflammatory reaction is set up, he says.

The scientists don't know what initially sets off activation of the newly discovered T helper cell in diseases such as arthritis and asthma, Dong says. "We don't know why these dangerous helper T cells are activated in the patients, but we now know how they function, and that should take us a long way to understanding and treating these and other inflammatory and autoimmune diseases

Biogen, Elan seek return of multiple sclerosis drug

Sept 26

Biogen Idec Inc and Elan Corp. on Monday said they have submitted new safety data to U.S. regulators on their drug Tysabri, in hopes of getting the withdrawn multiple sclerosis treatment back on the market.

The companies, which withdrew the injectable medicine in February, said they have asked the U.S. Food and Drug Administration to review the additional safety data within the next six months. That compares with the standard review period of 10 months.

Biogen Idec and Irish drugmaker Elan voluntarily suspended sales of Tysabri after one multiple sclerosis patient died following treatment with it in combination with Biogen Idec's widely used Avonex drug.

The patient died from a brain disorder known as progressive multifocal leukoencephalopathy (PML) and another patient at the time was suspected of having the condition, which is caused by a virus. Another case was identified in March, and two of the three patients have died.

The appearance of the rare disorder raised the question of whether Tysabri was making patients more susceptible to the so-called JV virus which causes it.

The drug was deemed a potential blockbuster when it was launched in November 2004 because clinical data suggested it was far more effective than existing treatments for multiple sclerosis, including Avonex.

The new data involves more than 3,000 patients with multiple sclerosis, Crohn's disease and rheumatoid arthritis that have taken Tysabri in past trials.

Some patients in the two late-stage multiple sclerosis trials took Tysabri by itself, while others took it in combination with Avonex.

DIRECT- MS Comments – It is not surprising that Biogen and Elan are trying to bring Tysabri back despite its nasty side effect of promoting PML, a potentially

fatal brain disease. Their companies depend on the success of this drug for survival and when it comes to patient survival versus company survival it is not hard to predict which one the companies will choose. What happens with Tysabri will determine if the FDA is a regulatory agency that places patient safety above all else or is a handmaiden for the pharmaceutical industry.

Study Shows Glycominds Test May Predict Active Multiple Sclerosis

Sept.28, 2005

Prof. Mark Freedman of the University of Ottawa will present at the conference the initial results of a landmark study that successfully predicted the level of disease activity in multiple sclerosis (MS) patients using technology developed by Glycominds Ltd.

For the first time researchers have shown that it is possible to predict, using a blood test, whether or not a patient will imminently develop an active form of MS, after the first neurological event.

"Neurologists have been struggling with a decision to initiate or not disease modifying therapy after only a single attack of what might be MS," said Prof. Mark Freedman, the principal investigator of the study known as PRACTIMS (Prognosis and Response of Anti-Carbohydrate Titer In MS). "Knowing at this earliest time point that a patient is destined to develop active disease would greatly assist this decision," he added.

The MS predictor test is a simple blood test based on novel biomarkers to indicate the likely course of a patient's condition.

The study results show that the Glycominds technology was able to correctly predict the future course of the disease in patients, on the basis of retrospective blood samples taken from 90 patients after their first neurological event.

The Glycominds test correctly identified in advance the 36 percent of patients who later on suffered additional clinical events in the two year period following their first symptoms.

Currently, doctors are unable to tell if a patient who has suffered a single neurological event will develop a mild or active form of the devastating disease. Consequently many people who do not require treatment, find themselves on life-long therapy regimens which may be expensive, cause adverse side effects and leave them in a perpetual state of anxiety. At the same time, many MS patients do not receive the more aggressive therapeutic intervention they may require because doctors are uncertain of their level of disease activity.

"Glycominds next plans to validate externally these results on thousands of retroactive patient samples and to bring this product to market during 2006," said Avinoam Dukler, CEO of Glycominds.