

# Lyndonville News

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Information and Support for the ME/CFS/FM Community

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## HHV-6 and ME/CFS

**Introduction:** This issue of the *Lyndonville News* is a summary of the latest data on HHV-6 (human herpes virus #6). As many of you know this has long been debated as having a prominent role in ME/CFS. And over the past two years there has been increased excitement because of the anticipation of the Stanford Study results. The conference was the 6<sup>th</sup> International Conference of the HHV-6 Foundation, Baltimore, MD June 19-22 2008.

### **Background:**

HHV-6 is a virus in the Herpes family, and has long been a suspect in causing or perpetuating ME/CFS. Discovered by Dr. Dharam Ablashi and Dr. Robert Gallo, it seemed to act a lot like a fellow herpes virus, including Epstein-Barr virus. It was found to cause the common childhood infection, Roseolla, and there is no vaccine effective in preventing it. HHV-6 is present in a wide range of patients and situations, and has characteristics that indicate it is a serious pathogen. Yet questions have lingered: is it the cause of ME/CFS, a cause of some cases of ME/CFS, an innocent bystander, or some mixture - a contributor to serious illness. Going into the conference I had several questions:

1. Should HHV-6 be measured in the clinical evaluation of persons with chronic fatigue, and if so, what is the best method to measure it?
2. How can active central nervous system infection with HHV-6 be measured?
3. If HHV-6 is a trigger to set off ME/CFS, what is the mechanism, and how can it be interrupted?
4. HHV-6A or HHV-6B?
5. Is there an established link between HHV-6 infection and mitochondrial disease other than a non-specific cytokine relationship?
6. Does treatment for HHV-6 improve patients with ME/CFS?

A daunting range of goals, and I will give my opinion to them at the end of this edition. A note of caution: I am presenting my hearing of these lectures and my interpretation of the data. Others might disagree, and only time will tell. Many of the lectures concerned the biology of HHV-6 and were not specific to ME/CFS. I present snippets of wonderful science that caught my attention, in no particular order.

## **Introductory Session Dr. Robert Gallo**

HHV-6 was discovered in Dr. Gallo's lab in 1986 with Dr. Dharam Ablashi very prominent in the scientific work. It was assumed initially that the virus led to some cancers by promoting gene expression of other viruses such as HIV. However while having an affinity for T cells and nerves, it is not found in tumor cells. HHV-6A, HHV-6B, and HHV-7 are extremely similar. It appears that HHV-6 is a co-factor in many illnesses because it increases inflammatory cytokines TNF $\alpha$  and IL-1 $\beta$  (Flammand et al, Virol. 1991). As will be discussed later inflammatory cytokines are felt to be important in the mechanism of symptoms of ME/CFS.

## **Overview of HHV-6 infection Dr. P Pellett**

HHV-6 is a ubiquitous virus causing Roseolla in young children, and like other herpesviruses, can re-activate with certain stresses. The problem has been to link infection with HHV-6 to specific illnesses and this has been difficult to do. In multiple sclerosis there is an increasing concentration of HHV-6 in serum, spinal fluid, and plaque; this has helped to define its role here. The key will be to find a good predictive marker that points to disease involvement of HHV-6.

## **The Role of CI-HHV-6 in congenital HHV-6 infections Dr. C. B. Hall**

Roughly 1% of newborns will have infection with HHV-6 at birth, and it has long been assumed that these infants have transplacental infection, meaning that the virus from the mothers' blood crosses the placenta to cause infection in the infant. However, one important aspect of this virus is that it can be integrated into the human genome, chromosomal integration of HHV-6 or CI-HHV-6. In this study, it turns out that 86% of those infants infected (1% of all babies) have CI-HHV-6, and the remaining 14% are transplacental. Of the CI-HHV-6, one third are variant A and two thirds are variant B. One potential problem here is that the CI-HHV-6 infants have extremely high viral loads, so much so that practically every leukocyte has virus. There is not much difference between serum titers of antibody in the two groups. The babies have been followed for a few years now and so far seem to be doing well with no obvious disease. Ongoing studies will examine this in the future.

## **A Comparison of Diagnostic Assays for characterizing infections with HHV-6 Dr. M. T. Caserta**

The problem with the measurement of HHV-6 is that it is necessary to distinguish active replication causing illness from chromosomal integration, from passive detection, meaning that at some time in the past a person has had Roseolla or exposure to HHV-6. Thus the standard tests are of very little value because they do a poor job of differentiating these states. Furthermore, antibody titres do not distinguish variant A from B. The "gold standard" or most accurate test to date, is viral replication in culture. That is, to show that the virus is actively growing and replicating in cells.

Antigenemia Assay: In this assay the products of replication are being sought. There are two big hurdles; first, there is no separation between HHV-6A and B. Secondly, this assay requires a laser scanning microscope which are expensive and difficult to find

Antigen Capture Assay: This assay is also looking for active replication, and it detects variant A and B core protein in cell free fluid. It detects both acute and convalescent infection with HHV-6 but is not positive in normal donors.

LAMP Assay: This method amplifies DNA under “isothermal” conditions, making it easier to do than PCR. It will detect primary infection but not latent infection. It is not yet known if it will be of value in detecting CI-HHV-6 or reactivation, and ability to distinguish variants unknown.

RT-PCR: This PCR technique measures the reverse transcriptase, essentially looking at the messenger RNA from an active, replicating virus. Probably just as good as culture.

Quantitative PCR: This PCR assay looks to determine the number of copies present, or the viral load. There are probably 100 papers out on this, but each paper uses different primers and it is very hard to compare different assays.

In concluding, Dr. Caserta suggests a combination of assays would be most helpful to distinguish active viral infection to latent infection.

Comment: For those readers interested in ME/CFS who are not scientists, the synopsis is this: we still do not have a good easy test to distinguish variant A from B that will universally be covered by your insurance company. The tests used in research are improving, and the big question remains: if you test positive for A or B by a good research test, what are you going to do about it?

### **Early Antigens in HHV-6 Infection** Dr. L. Flammand

In this paper Dr. Flammand looks at several of the early signals given off by HHV-6 infection, some of which will probably be important to measure in the years to come. What caught my attention was his statement that the early proteins of HHV-6 infection alter mitochondrial membrane potential.

### **New Developments in Therapeutics for HHV-6 infections** Dr. MN Pritchard

In this session, Dr. Pritchard reviews the anti-virals with known activity against HHV-6. Unfortunately the three available, cidofovir, foscarnet, and gancyclovir have relatively poor ability to treat HHV-6 infections, none are specifically approved for this use, and resistance is emerging. The most optimistic statement was that these agents “may be of some use.” On the other hand there are many agents in the developmental pipeline that may have good and specific activity against HHV-6.

Comment: Do not hold your breath for these new agents. Even if we knew for sure that HHV-6 either caused ME/CFS or was an important co-factor, it will be many years before these agents come to public use, and even more years before your insurance company will allow you to have them.

### **The Association of HHV-6 in Diseases of the Nervous System** Dr. S Jacobson

In this overview, Dr. Jacobson touches on the associations between HHV-6 (particularly HHV-6A) and CNS disease. HHV-6, like other herpes viruses, is a ubiquitous agent, acquired

early in childhood, but clear relationships or associations with specific nervous system diseases are emerging. He stresses that “association is not causation.” There are four ways to demonstrate an association between a ubiquitous agent and a clinical disorder: a) immunological b) molecular analysis c) clinical and d) pathological.

In multiple sclerosis there is clearly more HHV-6 (variant A) in brain tissue and plaque than there should be. However, is it there because underlying inflammation draws the cells that go into the plaque to the area? In a disease called mesial temporal lobe epilepsy, a portion of the brain is surgically removed and is thus available for study. In seven out of seven temporal lobes studied, all had active, replicating HHV-6. The importance of this is that this form of epilepsy is not an inflammatory disease, so it leads more weight to the presence of the virus in Multiple sclerosis.

Testing can be an enormous, even insurmountable problem. In some clinical conditions, blood and spinal fluid show little HHV-6, even though the brain, on autopsy, is loaded with virus.

Comment: This last point is critical for ME/CFS. Brain biopsy is not an option, so how can we know if HHV-6 (HHV-6A) is causing a/the problem?

### **Overview of HHV-6 and Chronic Fatigue Syndrome Dr. Anthony Komaroff**

Active infection with HHV-6 is more common in ME/CFS than in matched controls. In the opening overview, Dr. Komaroff reviewed the nine studies showing increased incidence of active infection, and the two studies that did not. He mentioned the different ways to assess active infection: PCR, IgM antibodies to HHV6 early antigen, cytopathic effect in culture, and viral isolation.

### **Overview of CFS Dr. A Komaroff**

In this session Dr. Komaroff lists, in a very convincing way, the studies that are clearly abnormal in CFS. This may be an illness of different subsets, yet the data proving that it is real is incontrovertible. He reviewed the abnormal findings in CD8 cells, NK cells, Proteomics, Genomics, MRI, SPECT, autonomic nervous system, both sympathetic and parasympathetic, hypothalamic-pituitary axis, EEG, upregulation of pro-inflammatory cytokines.

In regard to HHV-6 Dr. Komaroff said that this agent is “One infectious agent capable of triggering and perpetuating CFS.”

Comment: Is it possible that there are medical care providers who do not “believe” in CFS?

### **HERV-K18 as a Risk Factor in CFS Dr. Huber**

In this very interesting talk, Dr. Huber discussed HERV (human endogenous retro virus) K18. The presence of an endogenous retrovirus is not that exciting as it is estimated that 8% of the human genome is made up of HERV's. What is interesting is that this particular one is transactivated by both EBV and  $\alpha$  interferon. What's more, the Env gene of this HERV encodes a superantigen. This latter fact is possible to become a dominant topic in the near future, as superantigens cause a massive T cell activation. Some diseases such as “toxic shock syndrome”

are known to be caused by superantigens (not the same one as we are discussing here). In this study three different groups of CFS patients were examined: Dr. Miller at Emory (interferon related), Dr. Levine in NYC (idiopathic), and recently with the EBV portion of Dubbo study. All showed a relationship leading to the conclusion that CFS risk may be related to specific HERV-K18 genotype in subsets of patients.

### **A Randomized, Double Blind, Placebo-controlled Study on the Use of Valganciclovir in Patients with CFS and Elevated HHV-6 and EBV Antibodies** Dr. J.G. Montoya

This is the first report of the study since the good results from a pilot study were released a year ago January on the use of valganciclovir. This drug is a competitive inhibitor of viral DNA polymerase, and while there were no serious adverse events during this trial, it should not be considered a completely benign medication. Anyone taking it should be followed carefully for toxicities.

The entry criteria for this study were elevated levels of antibody to both EBV and HHV-6. Over 130 persons were screened, and thirty were in the study, 20 on drug and 10 on placebo. The entry antibody levels were as follows: HHV-6 IgG  $\geq$  640; EBV IgG  $\geq$  640, and EBV EA  $\geq$  160. There were many indicators used for end points, but discussion here revolved around only three: MFI-20 indicating fatigue severity, CDC SI relating to symptoms; and a global assessment of physical and cognitive functioning. The only value that improved to statistical significance was the cognitive portion of overall functioning. The other measures pointed to a positive trend but did not reach statistical significance.

Comment: A disappointing result overall, definitely not a “home-run”. Furthermore, few CFS patients have these kinds of antibody titers from standard laboratories.

### **The Dubbo Infection Outcome Study** Dr A Lloyd

This session was a further review of studies presented earlier, but clarifying new data. Essentially this study looks at “nested” case-control studies of patients followed after acute infection with Epstein-Barr virus, Ross River virus and Q fever. As was presented earlier, all three infections had similar rates of illness resolution. Roughly 5% of each had fatigue and other symptoms at one year and this decreased somewhat by year two. The severity of acute illness was the best predictor of persisting illness.

Why do some resolve and some do not? The first hypothesis is due to persistence of the infecting agent. Their studies showed no evidence of persistence of EBV, RRV or Q fever, despite an aggressive search. Interestingly, IgM and IgG antibodies were of no use predicting in any of the three. Second hypothesis is that immunity was different with antigen-specific T cells and again no differences were found. Dr. Lloyd concluded that there was no aberrant immune response.

### **Cytokines in Post-Infective Fatigue** Dr. Vollmer-Conna

This session continued the Dubbo findings from Dr. Lloyd’s talk and looked at cytokine expression as a mechanism of symptom expression. She briefly reviewed the many inconsistent cytokine studies of the past. At the beginning of the Dubbo infections IL-1 $\beta$  and Il-6 seemed to

correlate with symptom severity, particularly fatigue. However the best association with symptom persistence was increased IFN $\gamma$ , and decreased Il-10.

Comment: The cytokine data does not look convincing in explaining symptom persistence. There was a large gap between symptom severity at onset and the increased IFN $\gamma$ /decreased Il-10. But these two talks tell us a great deal about what is going on .

**Summary and Personal Comments about HHV-6 and Conference.** This summary was not presented at the conference, but represents my personal conclusions about the relationship between HHV-6 and ME/CFS. As always, every observer could come to different conclusions.

A) HHV-6 has two variants, A & B, and is a ubiquitous agent. It causes Roseolla in young children, and everybody is exposed to it at one time or another.

B) Roughly 1% of babies are born with the virus, most with it integrated into chromosomes and have high viral loads. It is not known yet if this will cause any problems. Because children do not usually develop ME/CFS until after age 10, we will have to wait another few years to get any early information on this point.

C) HHV-6, particularly HHV-6A has a strong association with many diseases of the central nervous system.

D) In ME/CFS, the only way to know if HHV-6 is important is to treat it with an effective antiviral, or prevent it with a vaccine. The antivirals currently available are only partially effective and vaccine is not available (Note- the relationship between human papillomavirus and cervical cancer was only shown when the vaccine was shown to prevent the cancer)

E) HHV-6 infects/resides in many tissues, including vascular endothelium, making it a good candidate for the variety of symptoms seen in ME/CFS.

F) HHV-6 is one of many infectious agents that can precipitate and/or perpetuate ME/CFS.

G) A trial of valgancyclovir was not very effective in reducing the fatigue and physical symptoms of ME/CFS. It did seem to help cognitive symptoms.

**Bottom Line:** Many of my patients will want to know if I will be using valgancyclovir in regular clinical practice. As of this time I do not plan to use it in patients with ME/CFS. I may consider testing some persons with RT-PCR and quantitative PCR for HHV-6, but this can be expensive and not covered by insurance.

In my practice, I plan to aggressively pursue the relationship between anaerobic threshold and mitochondrial function in some patients. For those of you hoping to hear that the valgancyclovir study was going to be the “cure”, I am sorry. But do not give up hope. One of these days.....

**My thanks** go to Andy Detwiler who financed this trip to the HHV-6 conference, paying for the airline tickets, hotels, and conference fees. For all those who are grateful for this information summarized here, please thank Andy. He wishes to encourage interested persons to get involved in one way or another. I am in complete agreement – if those interested in ME/CFS do not make it happen, it is not going to happen

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