Treatment of HHV-6 Reactivation in CFIDS

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The human herpes virus-6 (HHV-6) is a lymphotropic and neurotropic virus which is often active in persons with CFIDS (PWCs). Gallo, et al. of the National Institutes of Health found that HHV-6 can directly target, infect and kill natural killer (NK) cells, one of the primary defenders of the immune system. *(Please see the Summer 1993 Chronicle, pg. 48, for a reprint of this study.)* Destruction of NK cells may suppress the natural antiviral immunity of the host and may be one explanation of the defective NK cell activity found in many PWCs.

Implications for Treatment

This phenomenon may shed some light on possible treatment regimens for NK cell functional deficiencies. While the exact significance/relevance of the HHV-6 virus to PWCs with neurological and cognitive disorders is unclear at this time, the neurotropic properties of HHV-6 raise many questions. One interesting preliminary finding from our recent study of early antigen (EA) to HHV-6 is that those PWCs who had the highest titers of EA to HHV-6 also appeared to have significant neurological/cognitive changes. It is interesting to theorize that perhaps some of the cognitive changes and blood flow disturbances that have been shown may be secondary to a viral immune complex causing either a vasculitis and/or a neuritis of the central nervous system.

> ***"It appears that those patients who are positive for early antigen (EA) to HHV-6 have more significant cognitive and/or neurological changes and lower NK cell functional activity than those patients who are negative to EA HHV-6."***

HHV-6 Prevalence Higher Than Reported

In general, the consensus among physicians specializing in CFIDS has been that HHV-6 reactivation may play a part in 10 to 15 percent of patients with CFIDS. However, preliminary data from our study, conducted in association with Specialty Labs, Inc. of Santa Monica, CA, shows that the prevalence of HHV-6 reactivation appears to be considerably higher than most physicians would have expected. Of 40 patients sampled, 20 were positive for EA to the HHV-6 virus. These patients also had significantly lower NK cell function than either the controls or the 20 CFIDS patients who were EA negative. This data, if it continues to hold up with further study (we have expanded the study now to almost 100 patients with CFIDS), has rather significant ramifications for the diagnosis and treatment of CFIDS. First, it gives us a cost-effective manner of determining whether or not the patient has HHV-6 reactivation, based upon the work of Dr. Ablashi, et al. presented at the International CFS/CFIDS/ME Conference in October 1992. This study, *Kutapressin Inhibits In Vitro Infection of Human Herpes Virus-6*, showed that Kutapressin was able to block HHV-6 infection of HSB2 cells *in vitro* without being toxic to the cells. Kutapressin was established to be a potent inhibitor of HHV-6 infection, although its inhibitory mechanism is currently unknown.

Another interesting preliminary finding of our HHV-6 study is that there appears to be a segment of the CFIDS patients tested who do not sero-convert; that is, they do not become IgM negative with elevation of IgG, even after having HHV-6 infection for several months. This phenomenon has also been seen in Epstein-Barr Virus (EBV) reactivation. This group does not sero-convert and remains EA positive and/or IgM positive for prolonged periods of time — 2 to 4 years. The mechanism for this is uncertain; it may be an inborn conversion problem (genetic) or possibly an acquired conversion problem secondary to enzyme deficiency and/or the viral infection itself.

Essentially, our study has shown that 50 percent of 40 CFIDS patients tested positive for EA to HHV-6. It appears that those patients who are positive for early

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antigen to HHV-6 have more significant cognitive and/or neurological changes and lower NK cell functional activity than those patients who are negative to EA HHV-6. This may have important ramifications for the diagnosis and treatment of CFIDS, in that if a patient is EA positive for HHV-6, the physician should consider instituting Kutapressin antiviral therapy. It is my opinion that the data we have seen is not an indication that HHV-6 is the cause of CFIDS, but that HHV-6 may be an important player along with other viruses in a reactivation phenomenon secondary to immune dysfunction. This data also shows that HHV-6 may play an important role in the NK cell dysfunction often associated with CFIDS. Furthermore, this may give additional information to the physician who has not instituted Kutapressin therapy because the patient has appeared to be seronegative for EBV, cytomegalovirus (CMV) and herpes simplex virus (HSV). I believe that when a patient is identified as HHV-6 EA positive, they should be aggressively treated.

A Multidimensional Approach

At our clinic in Michigan, we take a multidimensional approach to the treatment of CFIDS. CFIDS is an extremely complex disease process, requiring complex and innovative therapy. Our treatment of patients with chronically reactivated HHV-6 (EA positive), is as follows:

1) Kutapressin:

We begin with Kutapressin, two cc. daily. Most PWCs are familiar with Kutapressin based on the work done by Drs. Steinbach and Hermann. *(Eds. note: The investigation of the use of Kutapressin in CFIDS by Drs. Hermann and Steinbach was first reported in the February 1988 issue of The CFIDS Chronicle. Please see the articles in the Summer '93 Chronicle, pg. 72, and the Spring/Summer 1990 issue, pg. 25 for recent summaries of their work.)* Kutapressin is a brand name of porcine liver extract and polypeptides originally developed during the late 1940s. It has been used in the past for inflammatory reactions of the skin and also for treatment of herpes zoster infections. The exact mechanism of Kutapressin is not well known; it is felt that perhaps the polypeptides derived from the porcine liver may potentiate lymphokines which may then have an effect on immune function. It is unknown whether Kutapressin acts by competitively inhibiting lymphokine receptors or whether it reactivates receptors enabling it to reverse the deleterious effects of an upregulated immune system.

Kutapressin is an extremely well-tolerated medication with minimal side effects. At our clinic we have not had any patients who have not tolerated Kutapressin except for one patient who was allergic to pork (this is a contraindication). Kutapressin is given by injection, either intramuscular or subcutaneous. The cost of Kutapressin is somewhat prohibitive; at the time of writing, it is approximately $85 per vial. However, in the state of Michigan, we have had success in having Blue Cross/Blue Shield and several other major insurers cover Kutapressin. Usually, the effects take several weeks to develop and our initial trial lasts for 90 to 120 days. If the patient does not improve, we reevaluate the diagnosis of viral activation and, if we feel the patient is truly virally activated, we increase the dosage to four cc. daily.

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Therefore, I believe a clinical trial of Kutapressin is warranted in any patient who is HHV-6 EA positive. (I am unaware of any other medications that have activity against HHV-6, except Ampligen, which is not available.) Once we have Kutapressin on board, we look for ways to improve the patient's overall immune function.

2) Reducing Load:

Our second phase of attack is to attempt to take the load off the immune system, and allow it to regulate itself more effectively. This, in theory, should permit better antiviral activity. Since so little is known about what causes the immune system to become deficient, treatment is somewhat speculative. However, at our clinic we take a look at several different variables.

a) Cigarette smoking. I believe it is imperative that PWCs quit smoking. Smoking increases production of free radicals and carbon monoxide and decreases oxygen absorption, all of which lower immune function.

b) Resolution of overlying systemic candida infections. This is very controversial in the general medical community and indeed in the CFIDS community. However, Iwata, et al. have shown that certain types of candida albicans produce a toxin which may lower NK cell functional activity and/or suppress cell mediated immunity. Current studies at our clinic (preliminary data) have shown a large percentage of our PWCs have significantly elevated anticandida antibody titers. We can verify overgrowth of candida on physical exam or with other laboratory measures such as the in-depth stool analysis. Candida overgrowth is treated with a basic anticandida diet along with one of several medications, such as Nystatin, Diflucan or Sporanox. We also use replacement therapy of beneficial bowel bacteria with Vital-Plex™, a balanced flora replacement formula. One of the possible etiologies for the rather consistent observation that PWCs have absorption difficulties may be overgrowth of candida (and lack of normal bowel flora); therefore it makes sense to reduce the candida load and replace the patient's normal flora. Additionally, many PWCs have had long courses of wide-spectrum antibiotics either for true or perceived bacterial infections which may be responsible for overgrowth of candida in the bowel. When we isolate an overgrowth phenomenon, we treat it.

3) Improving Overall Immune Function:

Ester C: Several recent studies have shown that Ester C has a greater ability to improve lymphocyte activity levels, penetrate the white blood cells and stay in them longer than regular Vitamin C. Our usual dose is between 1 and 5 grams daily. Since Ester C is buffered, it generally is tolerated well in the gastrointestinal tract and we have had very few significant side effects.

Summary

Based on our preliminary data, HHV-6 reactivation may play a significant role in the disease process of CFIDS. Pending results of further study, I feel that HHV-6 reactivation should be a consideration in all PWCs. If these patients are found to have HHV-6 reactivation, aggressive therapy with Kutapressin is indicated. This is based on *in vitro* data presented by Dr. Ablashi and the fact that no other available medications are known to have effect against HHV-6. Our basic Kutapressin therapy is two cc. daily, progressing to four cc. if no effect is seen. As we feel that this HHV-6 infection is indeed a viral reactivation, aggressive rehabilitation of the patients' immune system is indicated, concomitant with Kutapressin therapy.