Summary of the 6th International Conference on HHV-6 & -7

The 6th International Conference on HHV-6 & 7 was held in Baltimore, Maryland, on June 19-22, 2008. A satellite conference on Viruses in Chronic Fatigue Syndrome and Post-Viral Fatigue followed the main conference.

Biology of Human Herpesvirus-6 (HHV-6)

In order to best diagnose and treat diseases caused by a virus, it is essential to learn as much as possible about the virus—its genes and the proteins made by those genes, as well as how it infects cells and reproduces itself.

It is known that the first step by which HHV-6 infects a cell is attachment to a receptor on the surface of the cell called CD46. New research found that the CD46 receptor is located on what is called a "lipid raft", and that the raft carries the virus inside the cell where it then can make new copies of itself.

It has been unclear where, inside a cell, new viruses are assembled. One group reported that this occurs inside little "bubbles" called multivesicular bodies (MVBs). The MVBs float toward the surface of the cell and then exit the cell to go on and infect other cells.

Proteins that are unique to HHV-6 were reported (particularly one called U94), and two proteins (called IE 1 and IE2) were shown to distinguish the variants (A and B) of HHV-6.

When cells are infected by HHV-6, the virus multiplies much more rapidly if the cell is also infected with another "cousin" herpesvirus, human cytomegalovirus, or if the infected cell is placed next to a cell called a dendritic cell.

Chromosomally Integrated HHV-6 (CIHHV-6)

Most herpesviruses remain as little circles of DNA inside infected cells, separate from the DNA of the cell's chromosomes. Several years ago it was reported that HHV-6 could sometimes integrate itself into a cell's chromosomes, including the chromosomes of sperms and eggs—making it possible for HHV-6 to be inherited from a parent. At first, scientists were very skeptical of this, but subsequent studies convinced most scientists that it was true: some people had chromosomally integrated HHV-6 (CIHHV-6).

How common is CIHHV-6? Evidence presented at the conference confirmed earlier reports that CIHHV-6 is present in about 1% of people.

Does CIHHV-6 cause any medical problems? One reason to think that it could is that in the 99% of humans without CIHHV-6, only a very small number of cells are infected with HHV-6. In CIHHV-6, since the viral DNA was inherited from the sperm or egg of a parent, the viral DNA is present in *every* cell.

Nevertheless, many scientists have been skeptical that CIHHV-6 causes any medical problems. First of all, there has not been strong evidence that the complete virus is integrated into the chromosomes, or that it can produce proteins or make copies of itself—things viruses typically must do in order to cause medical mischief.

Several preliminary reports at the conference indicated that CIHHV-6 may indeed lead to the production of multiple copies of the virus, and may cause disease. One research team repeatedly measured the "viral load"—the amount of viral DNA in the blood—from a group of patients with CIHHV-6. If the virus was not capable of reproducing multiple copies of itself, then it would be expected that the viral load would remain constant over time. Instead, the research team found extremely large differences from one sampling to another, indicating that sometimes the virus was making many copies of itself, and sometimes it was not.

Even more compelling were two small studies. One study involved three patients with CIHHV-6 and chronic fatigue syndrome. The research team found that when the three patients were given the antiviral drug valganciclovir, which kills HHV-6 in laboratory ("test tube") studies, the viral load in their blood went way down, and their symptoms improved. Another study involved one patient with CIHHV-6 who suffered from acute encephalitis (inflammation of the brain, usually caused by an infection), a neurological condition called myoclonus, and loss of consciousness. The patient was given another antiviral drug that kills HHV-6, foscarnet, and completely recovered. Still, it will take randomized trials of these antiviral drugs (or others effective against HHV-6) in patients with CIHHV-6, evidence of active HHV-6 infection, and illness that could plausibly be caused by HHV-6 to prove that CIHHV-6 can cause illness.

Diagnostic Tests

Some progress was reported in diagnostic tests that distinguish active infection from inactive (latent) infection with HHV-6, tests to distinguish the A strain of the virus from the B strain, and tests to quantify the amount of virus present in a sample. Still, the field has not reached the point where all experts can agree on what the best tests are in specific clinical circumstances.

HHV-6 in Brain Diseases

Soon after HHV-6 was discovered, it became clear that the virus could cause infection of brain cells—glial cells and neurons. That raised the possibility that HHV-6 might play a role in some brain diseases.

Encephalitis. For several years it has been clear that HHV-6 could produce encephalitis in patients with compromised immune systems (such as people placed on immune system suppressing drugs during organ transplantation, or patients with AIDS). It also has been clear that the virus can cause temporary encephalitis in young children when they are first infected with the virus.

The conference reported increasing evidence that the virus also can cause encephalitis in adults with normal immune systems. A study of adults with encephalitis of unknown cause—people who tested negative for all known causes of encephalitis—found that HHV-6 DNA could be identified in the spinal fluid of 40% of them. In one patient in whom a brain biopsy was performed, the virus was also found in the brain.

Multiple sclerosis. In multiple sclerosis (MS), the "insulation" wrapped around a nerve cell, called myelin, is damaged by an autoimmune attack (an attack by one's own immune system on some part of one's body), compromising the function of the nerve cell. In 1995, a research report suggested that HHV-6 might be one trigger of multiple sclerosis (MS). Since that time, the majority of the published papers on this subject have been consistent with the first report.

At the Conference, the following additional supportive evidence was presented: 1) antibodies (called "oligoclonal bands") specifically against HHV-6 were found in the spinal fluid of a minority of patients; 2) HHV-6 was found to cause a disease like MS in a monkey (a marmoset); 3) HHV-6 was found to damage cells called oligodendroglial precursor cells, cells that repair damage to myelin.

Epilepsy. For about 10 years doctors have recognized that when infants are first infected with HHV-6 the virus can trigger seizures. At the Barcelona Conference in 2006, preliminary evidence was presented that HHV-6 might be a trigger for temporal lobe epilepsy in adults.

At the Baltimore Conference, impressive evidence was presented by many different scientists that HHV-6 is the most common cause of seizures occurring when a child has a fever ("febrile seizures"). It also appears to be the most common cause of uncontrollable seizures in children (a condition called "status epilepticus"). It is unclear if these childhood seizures triggered by HHV-6 make the child more vulnerable to seizures or other neurological conditions in adulthood, although a study of that question is underway.

More evidence was presented that HHV-6 may trigger some cases of temporal lobe epilepsy. The strongest evidence involves brain tissue that has been surgically removed as a treatment for epilepsy. Two different research groups reported finding large amounts of the virus in that brain tissue, particularly in a region of the brain known to be involved in temporal lobe epilepsy—the CA1 region of the hippocampus. The infection primarily involved brain cells called astrocytes.

Mood disorders. A team from Japan reported that HHV-6 makes a protein called SITH-1, and that this protein appears to cause mood disorders. When, using genetic engineering, a mouse was modified in such a way that brain cells called glial cells made large amounts of SITH-1, the mice behaved in a manic (hyperactive) way.

Antibodies to SITH-1 were found circulating in the blood of *most* patients with major depression, bipolar disorder ("manic-depression"), and chronic fatigue syndrome—whereas such antibodies were not found in any adults without these conditions. In two adults with mood disorders attributed to encephalitis caused by HHV-6, unusually large amounts of the messenger RNA that makes SITH-1 were found. This preliminary study is intriguing, but much more work is needed to determine whether HHV-6, or the SITH-1 protein that it makes, are common causes of mood disorders.

Chronic fatigue syndrome. The possible role of HHV-6 in chronic fatigue syndrome (CFS) is discussed in the summary of the Viruses in Chronic Fatigue Syndrome and Post-Viral Fatigue Conference.

HHV-6 and HHV-7 Reactivation in Transplant Recipients

Many studies have shown that HHV-6 (and probably HHV-7) are often reactivated in patients whose immune systems have been suppressed by medicines (such as in organ transplantation) or by diseases (such as AIDS). New studies confirmed that: 1) such reactivated HHV-6 infection can cause encephalitis; 2) disease is reduced by white blood cells called T cells that are primed to attack HHV-6; 3) increased levels of the immune system chemical called interleukin-6 (IL-6) predict transplant patients that are more likely to develop encephalitis (and might therefore benefit from antiviral therapy).

HHV-6 in Drug-Induced Hypersensitivity Syndrome

Investigators reported that HHV-6, HHV-7 and other herpesviruses are often reactivated during an unusual and severe type of drug allergy, variably called either DIHS or DRESS. The illness involves many different organs (often the brain and the liver), frequently leads to high numbers of white blood cells called eosinophils, and is sometimes followed by the development of type 1 diabetes or autoimmune thyroid disease (thyroiditis). HHV-6 was found in diseased tissues, including brain and liver, suggesting that—once reactivated by the allergic reaction—the virus might have contributed to the disease.

Another report found that several of the medicines that most often trigger the severe allergic syndrome also cause reactivation of HHV-6, suggesting that reactivation of the virus might even be a primary, rather than a secondary, cause of the illness.

HHV-6 and HHV-7 in Cancer

Several herpesviruses—particularly Epstein-Barr virus—have been found to cause some kinds of human cancer. The first step in suspecting a possible role for a virus in causing cancer is to find the virus inside the cells that are cancerous—but not in most of the noncancerous cells nearby. Research groups reported finding HHV-6 in cells of non-Hodgkin's lymphoma, Hodgkin's lymphoma, brain tumors called gliomas and in cells from cancer of the cervix. In several of these reports, there was a greater amount of virus in the more malignant cells. While these reports could indicate that HHV-6 is a factor (or co-factor, along with other cancer-causing viruses) in causing these cancers, it also could be an "innocent bystander", attracted to the cancerous tissue but not really making the tissue turn cancerous.

Heart Diseases

Two possibly-related diseases of heart muscle, myocarditis and dilated cardiomyopathy, have no known cause. Several research teams reported that HHV-6 (and several other viruses) could be found in the heart muscle of patients with these diseases, but only rarely in healthy heart muscle. These patients often also had evidence of reactivated HHV-6 infection in white blood cells. In one patient treated with an antiviral drug effective against HHV-6, the pumping power of the heart muscle improved, suggesting that the viral infection might be causally related to the heart muscle disease.

Even more provocative, one group reported that HHV-6 can infect the inner lining (called the endothelium) of the arteries of the heart (the coronary arteries). Furthermore, they found that HHV-6 infection causes inflammation in the wall of the artery. A second group compared patients with myocarditis that was associated with HHV-6 to those with myocarditis not associated with HHV-6. There was a greater tendency in the first group for the coronary arteries to go into spasm.

Together, these results suggest the possibility that patients with myocarditis caused by HHV-6 may also have HHV-6 infection of the lining of their coronary arteries. That, in turn, could mean that HHV-6 may play a role in causing or worsening coronary artery disease—the most important cause of premature death in adults. While at this time a role for HHV-6 in coronary artery disease is just a remote possibility, there is some evidence that its "cousin" herpesvirus—human cytomegalovirus—may play a role in coronary artery disease. There also is strong

evidence that a related herpesvirus, Marek's disease virus, causes coronary artery disease in birds.

Treatments for HHV-6

Several antiviral drugs—some already available to treat other viruses and some still experimental—appear to be very effective against HHV-6 in laboratory testing. Whether these drugs will work when used in people with illnesses caused by HHV-6, and whether they will produce side effects, remains to be seen.

Summary

When HHV-6 was discovered 20 years ago, its remarkable ability to infect a wide variety of cells suggested the possibility that it might be capable of triggering a wide variety of diseases. At this conference, the expanding spectrum of diseases associated with HHV-6 (and, in some cases, HHV-7) was remarkable. While none of these disease associations has been proven, in every instance the evidence in favor of the association of HHV-6 and the disease was stronger than it had been in the past, and no previously-suggested association was contradicted by newer and better information.

This makes it imperative that a greater effort be made to improve diagnostic testing and expand available treatments.