Progressive multi-focal leukoencephalopathy (PML)

PML is a rare AIDS-related condition of the brain, caused by the JC virus. Worldwide, more than 4 in 5 adults are exposed to this virus, but it only causes disease in people with weakened immune systems, such as AIDS, advanced cancer or bone marrow transplants.

Today, most PML cases occur in people with advanced HIV disease and very low CD4 counts. However, it occasionally appears in people with CD4s up to 500. Overall, about 1 in 20 people with AIDS will develop PML.

Because it is so rare and because it affects the brain (an organ that’s difficult to study), its diagnosis and treatment are poorly understood. In 2005 and 2006, several people with inflammatory diseases were treated with immune therapy to block inflammatory cells and developed PML. This led to renewed interest in researching this rare disease.

What are the symptoms?

Symptoms do not occur when a person is first infected with JC virus. However, when it infects the brain and begins to cause disease, the infection rapidly forms lesions.

A frightening aspect of PML is that there’s no “usual” course of disease. Whatever brain areas that are affected by the JC virus will determine how PML appears in an individual. If the virus strikes the part of the brain that controls sight, vision could be lost. If it strikes the part that controls speech or motor skills, one could lose the ability to talk or walk. There’s no way to predict where or how it will attack.

Early symptoms of PML may include weakness in one side of the body or limbs (sometimes severe), blurred or loss of vision (possibly on one side), fatigue and/or impairments in learned skills that may range from language impairments (aphasia) to memory loss, confusion, disorientation or a loss of balance. Nearly 1 in 5 people with PML disease report having seizures.

Symptoms are similar to those of other HIV-related conditions that affect the brain, including toxoplasmosis (toxo), lymphoma of the central nervous system (CNS lymphoma), AIDS dementia complex (ADC), cryptococcal meningitis, HIV encephalopathy, and cytomegalovirus (CMV) and herpes infections of the central nervous system. Therefore, it’s important to consult with an HIV neurologist.

How do you diagnose PML?

Diagnosing PML is tricky. Many HIV-related diseases in the brain can appear like one another on an MRI scan, a type of x-ray of the brain. Therefore it’s important to continue the diagnosis by doing a brain biopsy. A small hole is drilled into the skull and a piece of tissue is removed and examined. If the JC virus is found in the tissue, PML is diagnosed. A brain biopsy is considered the gold standard for diagnosing PML.

Some people who are presumed to have PML will understandably elect not to have the biopsy. Doctors may not recommend it because it’s invasive and causes discomfort. Even if a definite diagnosis of PML comes back, no therapies are very effective at treating the condition with the exception of changes in HIV treatment. You and your doctor may opt to make these changes regardless of the diagnosis.

The main benefit of a biopsy is to rule out other brain diseases. If a biopsy is not done, doctors may still recommend treating these other dis-
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eases on the off chance that the condition is treatable.

When the brain biopsy is not done, PML will be diagnosed using 3 pieces of information. This includes: 1) if the state of health is consistent with PML symptoms; 2) if JC virus DNA is present in the cerebral spinal fluid; and 3) if MRI tests show lesions mainly in the brain’s white matter. However, using HIV therapy complicates the matter. The lesions may look different, including more inflammation than what’s normally seen, when potent HIV therapy is used.

Another x-ray called a computed tomographic (CT) scan is not as sensitive as an MRI. Testing for antibodies to the JC virus in blood or urine is also not a good way to detect active virus. Up to 4 in 5 adults already have these antibodies.

How do you treat PML?

A diagnosis of PML was quite grim. The one therapy used for treating it, a toxic drug called cytosine arabinoside, is given through a shunt directly into the brain. It has shown marginal, if any, benefit and is no longer routinely used.

Before potent HIV therapy, the average time from a PML diagnosis to death was 1–3 months. Recent studies show that using aggressive HIV treatment may result in an indefinite remission of PML for some people.

Spontaneous recovery or stabilization is more likely to occur in people with CD4 counts above 200.

Potent HIV treatment

Several groups have reported symptom-free survival after a PML diagnosis of over 10 years and counting for some people using potent HIV treatment. Factors related to survival include using an HIV regimen with a protease inhibitor and changing to a new regimen after a PML diagnosis.

A more recent study shows extremely encouraging results, perhaps the best to date, with "enhanced" HIV treatment. This is when Fuzeon (enfuvirtide, T20) is added to a traditional regimen with protease inhibitors. At 6 months, the survival rate was 3 out of 4 people and the trend suggested this survival rate may hold to 1 year or more.

While there are no guidelines for HIV treatment and PML, it seems advisable to start or change to a new potent HIV regimen with a protease inhibitor. Experienced neurologists once recommended using HIV drugs that penetrate the blood-brain barrier, as in high doses of daily AZT. More recently, experts have changed their thinking about this.

More and more they believe that the benefits of HIV treatment are due to better immune responses throughout the body. This supports creating the most potent possible regimen based on resistance testing, history of HIV drug use, and cross resistance issues, because in the Fuzeon study the drug is not believed to cross the blood-brain barrier whatsoever.

Cytosine arabinoside

Cytosine arabinoside (ara-C, cytarabine, Cytosar-Ur) is currently used as chemotherapy for leukemia and cancer. For treating PML it was given through a shunt into the brain.

Side effects include nausea, consistent fevers and bone marrow toxicity. It can also harm a growing fetus. Intensive blood work is also necessary. While ara-C was once considered standard-of-care, it has fallen out of favor due to its side effects, low success rate and the superior responses seen from using potent HIV treatment.
Experimental PML treatments

CIDOFOVIR: Several studies of the CMV drug, cidofovir, first looked encouraging for treating PML. However, these studies have failed to show any benefit and so it is no longer recommended.

CORTICOSTEROIDS: There is some debate about adding corticosteroids to potent HIV treatment for treating PML. Those opposed to using them say they may further weaken the immune system. A few cases of PML has been associated with their use. Those in favor of using corticosteroids note that increased inflammation from using HIV treatment may be quieted by using these steroids and thus aid recovery.

INTERFERON THERAPY: Researchers have been interested in using both interferon-alpha and interferon-beta to treat PML. In test tube studies, both are active against the JC virus. However, studies in people have been terribly underwhelming. If there were better ways to target the therapy to the brain lesions and virus, it may be worth revisiting.

5HT2A ANTAGONISTS: This includes drugs like Remeron (mirtazapine) — a drug used for depression. Some speculate that this class of drugs might be useful in treating PML. Although anecdotal information is not terribly impressive, when added to HIV treatment this class may provide a new therapy.

OTHER POSSIBLE INTERVENTIONS: for study include interleukin-2 (IL-2), topoisomerase inhibitors (topotecan, camptothecan, etc.), adoptive cell therapy (enhancing JC virus specific cellular immunity) and RNAsi.

Some final thoughts

Many people have responded to various PML treatments. Although HIV treatment does not directly affect the JC virus, the wise use of it appears to greatly impact survival after a PML diagnosis, most likely because the immune system recovers and starts to control the JC virus.

It’s important to realize that successful PML treatment at best usually means only stabilizing or partly resolving symptoms, even when brain lesions shrink. This is different than a complete resolution of symptoms. Despite this improvement, someone with PML may face lifelong symptoms.

PML is difficult to study and its diagnosis remains a problem. A brain biopsy is quite invasive; therefore, less invasive techniques need to be developed. A spinal tap is hardly non-invasive, but it’s a far better choice to many people. Using cerebral spinal fluid (CSF) to diagnose PML may provide a medium ground, but it’s not perfect.