Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) is a virus infection of the brain that can cause serious disability or death.

The virus causing PML is named the JC virus after John Cunningham, a patient who had PML. This virus is often caught early in life and usually causes no or minimal symptoms initially. Once a person has the JC virus it remains in the kidneys or bone marrow for the rest of that person’s life. From time to time, the virus can reactivate and enter the bloodstream. This reactivated virus is quickly controlled by the immune system. Though about 55% of adults have the JC virus, it does not cause any known diseases in those with normal immune systems.

If the immune system is unable to control the virus when it is in the bloodstream, the virus can spread to the brain. In the brain, the virus is able to infect oligodendrocytes, which are the cells that make myelin that surrounds the nerves. The oligodendrocytes and the myelin they make are also the cells attacked by multiple sclerosis, but the JC virus does not play a role in causing MS. There are a number of diseases that can affect the immune system and lead to PML such as AIDS and diseases of the immune system. In addition, a number of medications can suppress the immune system, increasing the risk of getting PML. These medications include chemotherapy medications as well as several medications that are used for autoimmune diseases. In multiple sclerosis, Tysabri has been found to have an increased risk of PML.

PML causes neurological symptoms such as change in behavior, decreased vision, weakness, numbness, cognitive impairment or other symptoms. The symptoms depend on which area of the brain becomes infected with the virus. These symptoms may initially mimic the symptoms of MS relapse, but generally evolve more slowly, and do not respond to steroid treatment.

Diagnosing PML: PML has a characteristic pattern on MRI, so the first step in the diagnosis is to obtain an urgent MRI image. If PML is still suspected after the MRI, then a lumbar puncture (spinal tap) is required to confirm the diagnosis. The spinal fluid must be sent to one of a few laboratories that specialize in identifying PML in MS patients. Most commercial laboratories do not have tests that are sensitive enough to pick up the virus in these cases.

Treating PML: The only way to control the JC virus infection is to restore the immune system. In patients treated with Tysabri, this requires removing the medication from the bloodstream with plasma exchange. This involves removing plasma from the blood with a machine, replacing that plasma and returning it to the body. This takes approximately 4 hours of treatment every other day for three treatments. Care must be used to control the immune system when it recovers to avoid the Immune Reconstitution Inflammatory Syndrome (IRIS).
Outcomes of PML: In PML associated with Tysabri, about 25% of cases are fatal. Of the people who survive, 48% are unable to care for themselves and 36% are unable to work. Only 16% have normal activity though this may require greater effort than before.

Measuring the risk of getting PML: The risk of getting PML with Tysabri depends on a number of risk factors. The most important of these is a blood test that measures antibodies to the JC virus. If antibodies are absent it implies that the person has never been infected with the virus and thus has a very low risk of PML.

- If the JC virus antibody test is negative, the risk of getting PML with Tysabri is 1 in 10,000 or less. The risk is low whether a patient has received immunosuppressive medications or not.

- If the JC virus antibody test is positive, the risk of PML then depends on how long one has been on Tysabri, AND whether they were exposed to immunosuppressant medications in the past. In addition, the risk may depend on how high the titer of JC virus antibody is (see next page).

Previous use of immunosuppressive medications increases the risk of PML, including mitoxantrone (Novantrone), azathioprine (Imuran), cyclophosphamide (Cytoxan) and others. Note that injectable medications used to treat MS (interferons and Copaxone) are not immunosuppressives. At this time, it is unknown whether oral MS medications are immunosuppressants in this context.
What is your risk of developing PML?

RISK FACTOR: Time level in the level of antibodies to your blood

- 1 in 33,000
- 1 in 1,625
- 1 in 739
- 1 in 333
- 1 in 200
- 1 in 123
- 1 in 87
- 1 in 55

RISK FACTOR: Treatment with interferon for at least 4 years
- 1 in 2,000
- 1 in 739
- 1 in 333
- 1 in 200
- 1 in 123
- 1 in 87
- 1 in 55

RISK FACTOR: Previous treatment with immunosuppressants
- 1 in 10,000
- 1 in 739
- 1 in 333
- 1 in 200
- 1 in 123
- 1 in 87
- 1 in 55

What is your JC virus status?

Positive
- Previous treatment with immunosuppressants
- Previous treatment with interferon

Negative
- No previous treatment

PML risk
- Low PML risk
- High PML risk