JC Virus infection of the brain

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Learning objectives

To review the epidemiology, pathogenesis, clinic and imaging aspects of JCV infection of the brain.

Background

The most common clinical manifestation of JCV infection of the brain is PML, but others described are iPML, JCE, JCVGCN and JCM. Although AIDS is the most common predisposing factor for JCV reactivation, there is increasing incidence of JCV reactivation in non-HIV, even in patients without any immune deficiency. Imaging plays a crucial role in the diagnosis, treatment response, progression and prognosis.

Imaging findings OR Procedure details

The JC virus is a double-stranded DNA virus and a member of the Polyomaviridae family. It was first described by Astrom et al in 1958 and was first isolated from the brain of a patient with Hodgkin disease in 1971. JC virus is the cause of progressive multifocal leukoencephalopathy, which is a rare demyelinating disease that occurs in immunocompromised patients.

Epidemiology

JC virus infection is not an opportunistic infection limited to HIV and lymphoproliferative disorders. Although HIV causes the 80% of the PLM cases, there is increasing incidence of the disease in non-HIV: 13% in hematologic and oncology condition, 5% in organ transplantation, 3% in rheumatologic treatment, antibody therapy, idiopathic immune deficiency syndrome and even in patients without immunodeficiency.

Pathogenesis

JC virus causes no recognizable clinical illness at the time of initial infection, therefore the mechanism by which one is infected and the timing of the infection remain unknown.
Studies of the prevalence in healthy individuals have demonstrated JCV antibodies in 85% of adults, and that the highest rates of initial infection occur before the age of 20%\(^4\).

The infection results from close human contact, although the precise mode of transmission has not been well defined. There are several theories like the transmission via gastrointestinal tract because JCV DNA can be detected in the mucosa of the human gastrointestinal tract and in sewage\(^5\) or the transmission via respiratory tract because JCV can be detected in tonsillar tissue\(^6\).

The primary JC virus infection is associated with viremia that results in seeding of the kidney, bone marrow and probably the spleen, where a clinically latent infection is established. During periods of immunosuppresion viral infection is reactivated and JCV infected mononuclear cells\(^7\). B cells transport the virus to the central nervous system and there the JCV infects oligodendrocytes and astrocytes thanks to the serotoninergic 5HT2A receptors on glial cells\(^8\).

**Clinicopathologic syndromes**

Progressive multifocal leukoencephalopathy was the only known manifestation of JCV infection of the brain with typical histopathologic and imaging findings but without specific clinical presentations. With restoration immunity in VIH patients with HAART, there is a change in the clinical behavior and histopathologic and imaging features, and new manifestations of JCV infection have been recognized and described\(^3\).

<table>
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<th>Types of PML</th>
<th>Clinical manifestations</th>
<th>Imaging features</th>
<th>Histopathology</th>
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<td>cPML</td>
<td>Focal neurologic signs depending on the locations of the lesions</td>
<td>- Lesions in the subcortical U-fibers which are hypointense on T1W and hyperintense on T2W</td>
<td>- Demyelination</td>
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<tr>
<td></td>
<td></td>
<td>- Diffusion restriction at the margin</td>
<td>- Swollen oligodendrocytes with enlarged densely basophilic nuclei filled with eosinophilic inclusion bodies</td>
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<tr>
<td></td>
<td></td>
<td>- No enhancement</td>
<td>- Bizarre astrocytes</td>
</tr>
<tr>
<td>iPML</td>
<td>Aggravated cPML symptoms in with or without Rim enhancement</td>
<td>Similar lesions of cPML plus</td>
<td></td>
</tr>
</tbody>
</table>

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recovered immune system HIV-patients with HAART treatment

mass effect and vasogenic edema

inflammatory reaction (CD 3 infiltration)

JCVGCN

Cerebelar symptoms: ataxia and dysarthria

- Negative findings in early stage

- Isolate cerebellar atrophy with T2W hyperintensity in later stage

Isolated infection of the cerebellar granule cell neurons

JCM

Similar to viral meningitis

No specific imaging finding

Cerebrospinal fluid positive to JCV DNA

JCE

Abnormal higher central nervous system function without focal neurologic deficit

Cortical hyperintensity on T2W

Infection of the pyramidal cell neurons

Classic progressive multifocal leukoencephalopathy (cPML)

The cPML presentation begins with focal neurologic deficits that vary from patient to patient depending on the location of their lesions in the central nervous system white matter. Most commonly, patients present with hemiparesis and hemisensory defects. There may be visual problems if there is occipital lobe or optic radiation involvement, language problems if there is involvement of the dominant parietal lobe, and ataxia or dysmetria if there is cerebellar involvement. Patients may also present with cognitive deficits.

The principal histopathological feature is demyelination, at the beginning are foci and then they coalesce into larger areas. Characteristic histopathologic findings are swollen oligodendrocytes with enlarge densely basophilic nuclei filled with eosinophilic inclusion bodies, they are located at the periphery of the lesions. There are also bizarre astrocytes, which are enlarged and contain multilobulated hyperchromatic nuclei.

Inflammatory progressive multifocal leukoencephalopathy (iPML)

More commonly iPML develops in HIV-positive patients who recover the immune system due to the treatment with HAART. iPML may rarely be the presenting in non-HIV patients.
PML lesions are accompanied by inflammatory reaction, and histopathologically it can be seen perivascular mononuclear infiltrates, mostly of CD3 T-cells, monocytes, or macrophages and B-lymphocytes, CD4 T-cells, and plasma cells.

**JC virus cerebellar granule cell neuronopathy (JCVGCN)**

Posterior fossa involvement, typically the middle cerebellar peduncles and adjacent pons or hemispheres, is frequent in cPML and iPML. But there is another cerebellar JC virus manifestation, which infects only the cerebellar granule cell neurons. The tropism for these cells is believed to be due to a unique mutation of the VP1 gene of the virus. Patients present isolated cerebellar symptoms like ataxia and dysarthria.

**JC virus meningitis (JCM)**

Cerebrospinal fluid testing for JCV is not a routinely performed in patients with clinical symptoms of viral meningitis, but Blake et al first described JCV associated with meningoencephalitis in an immunocompetent girl in 1992.

**JC virus encephalopathy (JCE)**

JC virus infects the cortical pyramidal neurons and astrocytes located in the cortical gray matter and gray-white junction. Patients have abnormality of higher central nervous system functions with no focal neurologic deficit.

**Diagnosis**

The gold standard for diagnosis of progressive multifocal leukoencephalopathy is the brain biopsy, which has a sensitivity of 64% to 96% and a specificity of 100%, with estimated associated procedural complication in 2.9% and morbidity in 8.4%.

Some patients may not tolerate brain biopsy or lesion is inaccessible. As an alternative the diagnosis of progressive multifocal leukoencephalopathy can be established by imaging or detecting the JCV DNA in the cerebrospinal fluid with polymerase chain reaction. PCR had a sensitivity of 72% to 92% and a specificity of 92% to 100% before HAART. It is common to have negative PCR results in patients with AIDS with symptoms and imaging features indistinguishable from progressive multifocal leukoencephalopathy. The explanation is that the immune restoration is associated with decreased viral replication.

Progressive multifocal leukoencephalopathy is classified in definitive or presumptive based on biopsy, PCR and imaging.
<table>
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<tr>
<th>Diagnosis</th>
<th>Typical symptoms</th>
<th>Typical imaging</th>
<th>PCR</th>
<th>Typical histopathology</th>
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</thead>
<tbody>
<tr>
<td>Definitive</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Definitive</td>
<td>+</td>
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<tr>
<td>Presumptive</td>
<td>+</td>
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**Imaging**

Imaging plays a crucial role in the diagnosis and follow-up of JC virus infection, and the technique of choice is the magnetic resonance. CT finding is a focal nonenhancing white matter hypoattenuation without mass effect.

**Classic progressive multifocal leukoencephalopathy (cPML)**

Typically progressive multifocal leukoencephalopathy is a confluent, bilateral but asymmetric, supratentorial white matter disease (Fig 1). Lesions start in the subcortical U-fibers (Fig 2), and then move into deeper white matter in the centrum semiovale and periventricular regions. Internal capsule, external capsule and corpus callosum are rare involvement. The parietal lobe is most commonly affected, followed by the frontal lobe.

White matter of the posterior fossa is the second most common area of involvement (Fig 3). Typically the disease involves the middle cerebellar peduncle and adjacent pons and cerebellum.

Spinal cord involvement is exceedingly rare.

Progressive multifocal leukoencephalopathy may involve grey matter, usually grey matter lesions are associated with white matter involvement. The thalamus is the most common area, followed by the basal ganglia.

**Imaging appearances**

Progressive multifocal leukoencephalopathy lesions are characteristically hypointense on T1W (Fig 1 and Fig 3), this low signal intensity is a differentiating feature from HIV encephalopathy. Less commonly lesions may be T1 isointense. In some lesions there is an incomplete hyperintense rim on precontrast T1W sequences (Fig 1), it may be attributed to the presence of macrophages.

On T2W and FLAIR sequence, lesions appear hyperintense to the cortex, and it is clearly seen the lesion margin from the adjacent gray matter (Fig 2 and Fig 5). With progression central area becomes necrotic. In some cases there are microcysts at the center of an active lesion.
Another typical imaging finding is the absence of atrophy in the active stage\(^3\).

The appearance on diffusion imaging varies according to the disease stage. In new active lesions, there is an incomplete rim of diffusion restriction (Fig 1 and Fig 3), which histopathologically correlates with swollen oligodendrocytes, bizarre astrocytes and foamy macrophages. In old lesions after therapy or at the center of a large lesion, there is facilitated diffusion due to disorganized cellular architecture, increased extracellular space secondary to dead oligodendrocytes, macrophage action and astrocytic reparative responses\(^17\).

In progressive multifocal leukoencephalopathy magnetic resonance spectra there is a substantial decrease of the NAA peak due to neuronal loss. The choline peak is elevated, perhaps reflecting myelin destruction. In early and active stage, the level of mlins increases that means local glial proliferation secondary to inflammation, and it has been described as a prognostic marker\(^18\).

**Inflammatory progressive multifocal leukoencephalopathy (iPML)**

The imaging manifestation of iPML is exactly like cPML with an additional peripheral enhancement of the lesion in contrast imaging (Fig 4) and/or mass effect due to inflammation\(^3\).

**JC virus cerebellar granule cell neuronopathy (JCVGCN)**

In the early stage of the disease, there is no specific MR finding. In later stages, there is isolated cerebellar atrophy followed by increased T2 signal intensity\(^3\).

**JC virus meningitis (JCM)**

There is no specific MR imaging finding\(^3\).

**JC virus encephalopathy (JCE)**

JCE are initially restricted to hemispheric gray matter with extension to the subcortical white matter with progression of the disease. Lesions do not enhance on contrast\(^3\).

**Treatment**

There is not specific treatment for JC virus, numerous drugs have been tried empirically (cytarabine, cidofovir and tapotecan) but none has proven effective and they have a high toxicity.
In patients with HIV infection the best therapeutic option is the optimization or initiation of highly active antiretroviral therapy, which may stabilize the clinical and imaging manifestations. In HIV-negative patients the treatment of choice is removal the drugs that cause the immunosuppresion, as much as clinically possible\textsuperscript{10}.

**Prognosis**

Progressive multifocal leukoencephalopathy is usually fatal, and the median survival of patients without HIV infection is 2.6 months. In patients HIV-positive the median survival has increased from 0.4 years to 1.8 years due to HAART\textsuperscript{19}.

**Images for this section:**

**Fig. 1:** Fig 1. Patient with immnosuppressive therapy that has supratentorial frontoparietal bilateral asymmetric lesions without mass effect. A, On Diffusion the lesions show restricted. B, On T1W the lesions are hypointense there is an incomplete rim. C, On T2W they are hyperintense. D, On the FLAIR the lesions are hyperintense and
there is a demarcation between the lesions and the adjacent grey matter. E, There is no enhancement on T1W with contrast.

**Fig. 2**: Fig 2. Lesions at the subcortical U-fibers on FLAIR sequences. We can see the separation between the lesion margin and the grey matter.
**Fig. 3:** Fig 3. Patient with rheumatic disease and corticoid therapy that has an infratentorial lesion. A, The lesion is restricted on diffusion sequences. B, On T1W it is hypointense. C, On T2W it is hyperintense. D, On FLAIR we can see supra and infratentorial hyperintense lesions in the white matter.
**Fig. 4:** VIH-positive patient receiving HAART with images features of iPML. On T1W sequences (A and C) the lesions are hypointense, on T1W after contrast (B and D) the lesions have a peripheral enhancement, and on FLAIR sequences (C and E) the lesions are hyperintense.
Fig. 5: Follow up in a patient with immunosuppressive therapy. On FLAIR sequences it could see increasing in the intensity that indicates a progressive disease.
Conclusion

There are different clinical and imaging manifestations of JCV infection of the brain, so the diagnosis should be based on histopathology and imaging appearances.

Personal Information

References


