Updates on PML in MS Patients

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University of Washington
Multiple Sclerosis Center
Dr. von Geldern has nothing to disclose.
Progressive Multifocal Leukoencephalopathy (PML)

Rare but severe and life-threatening brain infection

Demyelination of the brain due to lytic infection of oligodendrocytes with (reactivated) JC virus

Typically occurs in patients with impaired cellular immunity

Photo courtesy E.O. Major
- PML and MS
- Risk Assessment
- Diagnosis of PML
- Treatment of PML
- PML and MS
- Risk Assessment
- Diagnosis of PML
- Treatment of PML
Conditions associated with PML

- HIV
  - AIDS-defining
  - 1/100 without HART
  - 6/10,000 with HAART

- Organ Transplant:
  - heart, lung, kidney
  - 1/1000

- Hematologic Malignancies
  - 8.3/100,000 per year in lymphoma

- The many faces of PML today

- Rheumatologic conditions
  - 1/100,000 per year

- Bone marrow transplant
  - 3.5/10,000 per year

- Immunomodulatory treatments
  - (e.g. in MS)

Mateen et al. 2011; Amend et al. 2010
PML and MS Disease Modifying Medications

Least concern for PML:
- Interferon beta, glatiramer acetate

Some concern:
- Alemtuzumab (Lemtrada®)
- Teriflunamide (Aubagio®)
- Fingolimod (Gilenya®)
- Dimethyl fumarate (Tecfidera®)

High concern:
- Natalizumab (Tysabri®)

Off-label meds: Rituximab (Rituxan®), Cyclophosphamide (Cytoxan®)

Carson et al. 2009; Berger et al. 2013
PML and Alemtuzumab

No cases of PML in MS patients
Approval for MS in 11/14

Several cases of PML in patients with chronic lymphatic lymphoma but not more than expected in that population
PML and Teriflunomide

No cases of PML in MS patients

5 cases of PML in leflunomide treatment of rheumatoid / psoriatic arthritis also on other immunosuppressants 2.5 million patient years
Several PML cases on fingolimod in patients recently switched from natalizumab

1 PML case in NMO patient in 08/13: On Rebif and azathioprine before, frequent IV steroids

1 PML case in MS in 02/15: MRI lesions but no clinical symptoms

114,000 patients on Gilenya; 195,000 patient years
PML and Dimethyl Fumarate

- 4 PML cases in psoriasis patients (1/4 also on efalizumab)
- 1 PML case in MS patient with prolonged lymphocytopenia (<500)

135,000 patients on Tecfidera; 112,000 patient years

New Prescribing Information:
- CBC before, after 6 months, then every 6-12 month
- Consider holding if lymphocyte counts <500 for > 6 months

Open Questions:
- PML risk linked to lymphopenia?
- Dose reduction?
- Re-challenge after interruption?

Rosenkranz, 2015
PML and Natalizumab

11/04 - approved by FDA
02/05 - withdrawn from market due to 3 cases of PML
06/06 - back on market, restricted to TOUCH program

<table>
<thead>
<tr>
<th></th>
<th>Worldwide</th>
<th>USA</th>
</tr>
</thead>
<tbody>
<tr>
<td># Patients exposed</td>
<td>134,600</td>
<td></td>
</tr>
<tr>
<td># PML cases</td>
<td>541</td>
<td>165</td>
</tr>
</tbody>
</table>

(1 in 250)

Biogen, March 2015
PML and Natalizumab

Natalizumab inhibits leukocyte adhesion to endothelium → prevents extravasation of T cells and monocytes into CNS → decreased CNS immunosurveillance

mobilizes lymphoid precursors (CD34+) from bone marrow

Stüve et al. 2006

Major, unpublished
- PML and MS
- Risk Assessment
- Diagnosis of PML
- Treatment of PML
Risk Factors

1. JCV antibody positivity
2. Prior immunosuppressive therapy
3. Natalizumab treatment duration
PML and Natalizumab Treatment Duration

Duration of natalizumab 8 to 92 doses (mean 44) 86% had >24 doses at the time of PML diagnosis
Risk Stratification

Adapted from Soelberg et al. 2012 per Biogen data 11/2013
JCV Antibody Test

Stratify Test (Focus Lab) 2 step assay

- ELISA with capsid protein VP1
- Confirmatory test (cross-reactivity to other polyoma viruses)

At least 2.5% false negative

5-10% seroconversion per year

→ Need to monitor serostatus during natalizumab treatment

Gorelik et al. 2010; Rossi et al. 2014
High Prevalance of Asymptomatic JCV

400 adult blood donors in Switzerland:

- Anti-JCV IgG 58%
  - 50% in 20-29 year old
  - 68% in 50-59 year old

- Urine JCV PCR positive 19%
- Plasma JCV PCR positive in none

Kean et al. Plos Pathogen, 2009

Egli et al. JID 2009
# JCV Antibody Index

## TABLE 2. PML Risk Estimates by Index Threshold in Anti-JCV Antibody–Positive Patients with No Prior IS Use

<table>
<thead>
<tr>
<th>Anti-JCV Antibody Index</th>
<th>1–24 Months (99% CI)</th>
<th>25–48 Months (99% CI)</th>
<th>49–72 Months (99% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤0.9</td>
<td>0.1 (0–0.15)</td>
<td>0.5 (0–1.28)</td>
<td>0.6 (0–1.25)</td>
</tr>
<tr>
<td>≤1.1</td>
<td>0.1 (0–0.23)</td>
<td>0.7 (0–1.85)</td>
<td>0.7 (0–1.98)</td>
</tr>
<tr>
<td>≤1.3</td>
<td>0.1 (0–0.28)</td>
<td>1.0 (0–2.38)</td>
<td>1.2 (0–2.56)</td>
</tr>
<tr>
<td>≤1.5</td>
<td>0.2 (0–0.30)</td>
<td>1.1 (0.20–2.61)</td>
<td>1.4 (0.24–2.78)</td>
</tr>
<tr>
<td>&gt;1.5</td>
<td>1.2 (0.84–1.07)</td>
<td>8.8 (7.06–8.98)</td>
<td>10.1 (7.41–9.46)</td>
</tr>
<tr>
<td>No index³</td>
<td>0.6 (0.42–0.88)</td>
<td>5.2 (4.28–6.19)</td>
<td>5.4 (4.03–7.14)</td>
</tr>
</tbody>
</table>

Adapted from Plavina et al. 2014
Kuesters et al. 2015
PML Risk in JCV Antibody Negative Patients

- 241/481 natalizumab-associated PML patients with known JCV Ab test prior to PML diagnosis
- 2/241 were JCV Ab negative (8 and 9 months before PML diagnosis)

PML case at UW with negative JCV Ab only 2 weeks prior to PML symptoms

Gagne-Brosseau et al. 2015
Risk Perception: Patients and Physicians

80% of patients accept high risk
50% of physicians accept high risk

Heesen et al. 2010
Risk Perception: Patients and Physicians

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Patients</th>
<th>Physicians</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>MS as malignant disease (VAS)*</td>
<td>8.5 (6.5–9.5)</td>
<td>6.5 (5.7–8.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1-year risk of walking distance &lt; 100 m°</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>without natalizumab</td>
<td>40% (20–50)</td>
<td>10% (0–30)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>with natalizumab</td>
<td>10% (&lt;10–30)</td>
<td>&lt;10% (&lt;10–20)</td>
<td>0.062</td>
</tr>
<tr>
<td>10-year risk of becoming wheelchair-bound°</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>without natalizumab</td>
<td>40% (20–60)</td>
<td>30% (20–40)</td>
<td>0.081</td>
</tr>
<tr>
<td>with natalizumab</td>
<td>10% (&lt;10–30)</td>
<td>10% (&lt;10–20)</td>
<td>0.956</td>
</tr>
<tr>
<td>Patients without progression after 2 years treatment with natalizumab°</td>
<td>50% (30–70)</td>
<td>50% (30–70)</td>
<td>0.931</td>
</tr>
<tr>
<td>General natalizumab-associated PML risk (VAS)*</td>
<td>4.5 (1.7–6.0)</td>
<td>3.1 (1.8–5.0)</td>
<td>0.195</td>
</tr>
<tr>
<td>Continue natalizumab treatment (VAS)*</td>
<td>9.0 (5.1–9.5)</td>
<td>6.1 (3.7–7.5)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Heesen et al. 2010
Does Risk Stratification Decrease the Risk of Natalizumab-Associated PML?

- JCV antibody test available since 2010
- Incidence of PML in natalizumab treated MS patients 2010-2014 unchanged

Possible reasons:
- Difficult to stop Tysabri
- Patients willing to take risk
- Sero-conversions/false negative test
- Too soon to see effect?

Cutter and Stüve, 2014
Other Potential Markers to Help in Risk Assessment

- JCV DNA in urine
- JCV DNA in blood (pathogenic genotype)
- JCV DNA in CD34 cells or B cells
Other Potential Markers to Help in Risk Assessment

- Increase in JCV antibody index
- JCV antibody in CSF
- T cell responses
- CD62L positive CD4

JCV antibody index in serum ↑

- PML and MS
- Risk Assessment
- Diagnosis of PML
- Treatment of PML
Diagnosis of PML

PML diagnostic criteria
Consensus statement from the AAN Neuroinfectious Disease Section

<table>
<thead>
<tr>
<th>Certainty of PML diagnosis</th>
<th>Compatible clinical features</th>
<th>Compatible imaging findings</th>
<th>CSF PCR for JC virus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definite</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Probable</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Possible</td>
<td>+</td>
<td>+</td>
<td>-/ND</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Not PML</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 2: Establishing the diagnosis with clinical, radiographic, and laboratory data

Berger et al. 2013
Clinical Features

Cognitive changes (aphasia, apraxia)
Personality changes
Visual changes (hemianopia)
Seizures

Not: optic neuritis, spinal, fever

<table>
<thead>
<tr>
<th></th>
<th>PML (n=45)</th>
<th>RRMS (n=100)</th>
<th>P Value</th>
<th>Adjusted P Valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monosymptomatic presentation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemiparesis</td>
<td>24</td>
<td>5</td>
<td>.001</td>
<td>.005</td>
</tr>
<tr>
<td>Altered mental status</td>
<td>19</td>
<td>0</td>
<td>&lt;.0001</td>
<td>.006</td>
</tr>
<tr>
<td>Brainstem</td>
<td>2</td>
<td>18</td>
<td>.007</td>
<td>.015</td>
</tr>
<tr>
<td>Cerebellar</td>
<td>2</td>
<td>11</td>
<td>.076</td>
<td>.076</td>
</tr>
<tr>
<td>Optic neuritis</td>
<td>0</td>
<td>33</td>
<td>&lt;.0001</td>
<td>.001</td>
</tr>
<tr>
<td>Acute spinal cord presentation</td>
<td>0</td>
<td>18</td>
<td>&lt;.0001</td>
<td>.006</td>
</tr>
</tbody>
</table>

Boster et al, 2009
MRI sensitive but not specific

- hyperintense on T2/FLAIR, hypointense on T1
- ill-defined borders; diffuse, multifocal
- no Gd enhancement (except in IRIS)
- no mass effect (except in IRIS)
JC virus PCR in CSF:

- specificity 92-100%
- sensitivity 72-93%

PCR at NIH (Major lab) more sensitive
detection threshold 10 copies/µl (Focus labs 500)

Clifford et al, 2010
Warnke et al, 2010
How to Assess a Patient with Concern for PML

- Clinical assessment of new neurological symptoms if suggestive of non-MS-related disease

  - Suspend dosing

    - MRI assessment
      - Cannot exclude PML
        - PML unlikely
          - Dosing may be resumed
        - JCV not detected and low clinical suspicion
        - JCV detected
          - Treat as PML
        - JCV not detected and high clinical suspicion
          - Repeat assessment

Kappos et al. 2007
Prognosis of Natalizumab Associated PML

23% mortality

HIV before antiretrovirals 90% mortality
with antiretrovirals 25% mortality

Survivors have worsened disability

Dong-Si et al. 2014
- PML and MS
- Risk Assessment
- Diagnosis of PML
- Treatment of PML
PML Treatment

- No specific treatment
- Restoring the immune system:
  antiretrovirals in HIV
  plasma exchange to remove natalizumab
- No proven benefit:
  Ara C, IFN gamma, IL-2,
  cidofovir, mefloquine, mirtazapine
- Case report: 2 patients with CD4 lymphopenia
  IL-7 and vaccination with JCV VP1 protein

Sospedra et al. 2014
Plasma exchange x3 (over 5-8 days)

Accelerates clearance of free natalizumab (but still alpha-4 integrin receptor binding)

Side effects: clearance of other medications, hypotension, pulmonary edema (volume shift)
Immune Reconstitution Syndrome (IRIS)

Clinical worsening due to improvement of immune function
rapid worsening neurological symptoms, fever, seizure

In most patients with natalizumab (up to 90%)
3-6 weeks after antiretrovirals or plasma exchange

- MRI:
- enlarged lesions
- contrast enhancement
- mass effect

von Geldern et al. 2013; Harrison et al. 2011
## IRIS Treatment: Glucocorticosteroids

### Corticosteroids associated with better outcome

<table>
<thead>
<tr>
<th></th>
<th>Good outcome (n = 7)</th>
<th>Poor outcome (n = 5)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Steroid dose</strong></td>
<td>Prednisone 1-2 mg/kg/day (n = 3); dexamethasone 32 mg/day (n = 1)</td>
<td>Prednisone 1-2 mg/kg/day (n = 2); methylprednisolone 500 mg/day (n = 1); dexamethasone 10 mg/day (n = 1)</td>
<td></td>
</tr>
<tr>
<td><strong>Time to steroid treatment, wk, mean (SD)</strong></td>
<td>3 (1.4), n = 2</td>
<td>12.3 (17), n = 3</td>
<td>0.80</td>
</tr>
<tr>
<td><strong>Duration of steroid treatment, wk, mean (SD)</strong></td>
<td>13.3 (7.5), n = 4</td>
<td>3 (1.7), n = 3</td>
<td>0.06</td>
</tr>
<tr>
<td><strong>Lesion load on PML-IRIS MRI, no. of regions, mean (SD)</strong></td>
<td>2.71 (1.89), n = 7</td>
<td>2.80 (0.45), n = 5</td>
<td>0.76</td>
</tr>
<tr>
<td><strong>No. (%) of patients with contrast enhanced PML-IRIS MRI</strong></td>
<td>6/7 (85.7)</td>
<td>1/5 (20)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

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**Lack of effect of dexamethasone on JCV replication in astrocytes**

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*Johnson unpublished*
Natural History Study of Progressive Multifocal Leukoencephalopathy (PML)

This study is currently recruiting participants.

Summary

Background:
- Progressive multifocal leukoencephalopathy (PML) is a severe viral infection of the brain. It is caused by JC virus. Many people have this virus in their bodies all their life, but it is usually kept in check by their immune system. If the immune system does not work right because of a disease or medication, the virus becomes active and can damage cells in the brain. Not much is known about PML or how it affects the immune system. Researchers want to study people with PML to better understand the natural history of the disease.

Objectives:
- To study the natural history of PML.

Eligibility:
- Individuals at least 2 years of age who have PML.

Design:
- Participants will be screened with a physical exam, medical history, and imaging studies.
- Participants will have several visits to the National Institutes of Health Clinical Center. There will be an initial visit, monthly visits for the next 6 months, a 12-month visit, and possible visits afterward.
- At the initial visit, participants will give blood, urine, and spinal fluid samples. They will also have neurological tests and imaging studies of the brain.
- For the next five visits, participants will give blood and urine samples.

<table>
<thead>
<tr>
<th>Number</th>
<th>13-N-0017</th>
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</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>National Institute of Neurological Disorders and Stroke (NINDS)</td>
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<tr>
<td>Recruitment Detail</td>
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</tr>
<tr>
<td>Type</td>
<td>Participants currently recruited/enrolled</td>
</tr>
<tr>
<td>Gender</td>
<td>Male &amp; Female</td>
</tr>
<tr>
<td>Min Age</td>
<td>2</td>
</tr>
<tr>
<td>Max Age</td>
<td>999</td>
</tr>
<tr>
<td>Referral Letter Required</td>
<td>No</td>
</tr>
<tr>
<td>Population Exclusion(s)</td>
<td>None</td>
</tr>
<tr>
<td>Special Instructions</td>
<td>Currently Not Provided</td>
</tr>
<tr>
<td>Keywords</td>
<td>Immune Reconstitution Syndrome; Human Immunodeficiency Virus; Multiple Sclerosis</td>
</tr>
</tbody>
</table>
PML Registry

- Collect clinical data on PML patients entered by healthcare providers
- Source of information for physicians and patients/family

https://pmlregistry.ninds.nih.gov
PML Registry

Easy to use online form for data entry

- secure website
- anonymized data

https://pmlregistry.ninds.nih.gov
Thank you

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