Letters

RESEARCH LETTER

ABO Blood Groups and Risk for Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML), caused by JC virus (JCV), has remained one of the deadliest opportunistic infections in HIV-infected patients despite combined antiretroviral therapy, with only a 50% 1-year survival rate. Progressive multifocal leukoencephalopathy has also been diagnosed in patients with autoimmune diseases treated with immunomodulators such as natalizumab. A consistent feature of PML is the predominant location of lesions in the subcortical white matter on magnetic resonance imaging, with corresponding demyelinating areas at the gray-white junction (GWJ) on histology. Interestingly, 64% of brain metastases are also found at the GWJ. This is likely owing to hemodynamic factors, where emboli of cancerous cells bind to endothelial receptors and remain in areas of sudden reduction of vascular caliber. Ultrastructural studies of the cortical microvasculature showed abrupt narrowing of perforating endarterioles coming from the brain surface into the cortical gray matter, with a dense bed of deep cortical capillaries at the GWJ.

JC virions can circulate either cell free or in association with B lymphocytes. The virions can attach to the surface of a number of cell types and have the capability to aggregate type O erythrocytes, which is the basis of the hemagglutination inhibition assay, for detection of JCV antibody in patients’ serum. The presence of JCV on the surface of B lymphocytes in individuals with type O blood may promote the aggregation of lymphocytes and erythrocytes, causing cell clumping that becomes impacted in narrow cortical capillaries with low blood flow at the GWJ. We sought to determine whether type O blood was a risk factor for PML.

Methods | We characterized ABO blood group antigen on blood samples of 76 patients with PML (62 were white and 14 were African American) followed up in our neurology clinic. Owing to their low number and different distribution of ABO blood group, African American individuals were excluded from statistical analyses. Of the 62 white patients with PML, 36 (58%) were HIV positive, 14 (23%) had underlying hematologic or oncologic diseases, and 12 (19%) included patients with autoimmune diseases, transplant recipients, idiopathic lymphocytopenia, or other forms of minimal immunosuppression. One patient had natalizumab-treated multiple sclerosis (MS).

Results | Of 62 patients with PML, 31 (50%) were type O, 20 (32%) type A, 8 (13%) type B, and 3 (5%) type AB (Table). In comparison with the blood type frequency of white individuals in the United States, the odds ratio of PML in type O patients compared with all other blood types was 1.22 (95% CI, 0.72-2.07; \( P = .45 \)), while it was 0.71 (95% CI, 0.39-1.24; \( P = .24 \)) in type A patients compared with patients with all other blood types. Based on this pilot data, to reject the null hypothesis that blood type has no influence on PML risk would require 794 patients with PML with type O blood and 295 patients with PML with type A blood.

Discussion | As of August 2013, approximately 118,200 patients have received natalizumab, mainly for treatment of MS, and 395 have developed PML. Patients with anti-JCV antibodies, prior use of immunosuppressants, and treatment with natalizumab for 24 months or longer have an approximate 1 in 90 risk for developing PML. If our data are reproduced in other studies, the implication is that among these high-risk individuals, extrapolation of our pilot data would predict 1 extra case of PML per 409 type O patients and 1 fewer case of PML per 310 type A patients. Larger PML cohort studies, including patients with MS treated with natalizumab or other immunosuppressants and a more diverse ethnic population, will be necessary to determine the role of O and A blood types in PML risk stratification. Future algorithms might include type O blood testing in addition to the currently accepted risk factors mentioned here when deciding whether patients with MS are suitable candidates for natalizumab. If verified, our hypothesis could also pave the way for new avenues of research on PML pathogenesis.

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Author Contributions: All the authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Khoury, Koralnik.

Acquisition of data: Khoury, Koralnik.

Analysis and interpretation of data: All authors.

Table. Distribution of ABO Blood Types Among White Patients With Progressive Multifocal Leukoencephalopathy and the General Population

<table>
<thead>
<tr>
<th>Population</th>
<th>Blood Type</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>O  A  B  AB</td>
</tr>
<tr>
<td>With Progressive Multifocal Leukoencephalopathy, No. (%)</td>
<td>31 (50) 20 (32) 8 (13) 3 (5)</td>
</tr>
<tr>
<td>United States, %</td>
<td>45 40 11 4</td>
</tr>
</tbody>
</table>
Drafting of the manuscript: Khoury, Koralnik.

Critical revision of the manuscript for important intellectual content: Mittleman.

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Administrative, technical, or material support: Koralnik.

Study supervision: Koralnik.

Conflict of Interest Disclosures: Dr Koralnik has received a research grant from Biogen Idec and the National Multiple Sclerosis Society; served on scientific advisory boards for Hoffmann-LaRoche, GlaxoSmithKline, and Merck Serono; and received consulting fees from Bristol-Myers Squibb, Ono Pharmaceuticals, Merck Serono, Hoffmann-LaRoche, Perseid Therapeutics, Vertex Pharmaceutical, and Johnson & Johnson. No other disclosures were reported.

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Disclaimer: The content is solely the responsibility of the authors and does not necessarily represent the official views of Harvard Catalyst, Harvard University and its affiliated academic health care centers, or the National Institutes of Health.


CORRECTION

Incorrect Information in Table and Affiliations: In the Original Investigation entitled “Nocturnal Rapid Eye Movement Sleep Latency for Identifying Patients With Narcolepsy/Hypocretin Deficiency” published in the July 2013 issue of JAMA Neurology (2013;70[7]:891-902. doi:10.1001/jamaneurol.2013.1589), incorrect information appeared in Table 2 and the Author Affiliations section. In Table 2, in the row “NPSG REML/H11349 15 min, No. (%),” the results for Comparison 4 should be 55 (46.6)% in the “Patients With Low CSF Hcrt Levels” column and 21 (17.8)% in the “Patients With Normal CSF Hcrt Levels” column. In the row “NPSG TST, mean (SD), min,” the results for Comparison 4 should be 423.3 (69.0) [55] in the “Patients With Low CSF Hcrt Levels” column and 420.1 (69.4) [49] in the “Patients With Normal CSF Hcrt Levels” column. In the Author Affiliations section, the affiliations for Drs Poli and Plazzi should have been “Sleep Disorders Center, Department of Biomedical and Neuromotor Sciences, University of Bologna and IRCCS Istituto delle Scienze Neurologiche, Bologna, Italy.” This article was corrected online.