Humoral Immune Responses After Rabies Infection

Survival from rabies is rare in the absence of pre-exposure or postexposure prophylaxis. Since 1971, 4 cases of rabies survival have been reported.1-4 To determine factors that alter the outcome of individuals exposed to rabies virus, we performed database searches of the National Library of Medicine, the National Institutes of Health, and the Centers for Disease Control and Prevention Morbidity and Mortality Weekly Report using the keywords “human” and “rabies” for the period from 1971 to 2006. All cases of physician-diagnosed and laboratory-proven human rabies in nonendemic areas according to the world survey of rabies for the year 1999 by the World Health Organization were included. On initial review of reported cases from endemic areas, it was apparent that laboratory data were often incomplete. Thus, all cases of human rabies diagnosed and treated in endemic areas were excluded. Abstracted data included the following variables: age at disease onset, sex, vector, incubation time, prodrome duration, pre-exposure prophylaxis, postexposure prophylaxis, antiviral therapy, humoral immune response kinetics in the peripheral blood or cerebrospinal fluid (CSF), maximum antirabies antibody titer in serum or CSF, cause of death, seizures, therapeutic coma induction, performance and results of antemortem diagnostic tests (computed tomography scan, magnetic resonance imaging, electroencephalogram, electromyogram, nerve conduction studies, and cerebral vascular angiograms), and performance and results of postmortem diagnostic tests (polymerase chain reaction, inoculation of experimental animals with rabies virus isolated from patients, autopsy, and biopsy). Statistical analysis was performed with GraphPad Prism 4 software (GraphPad Software, Inc, San Diego, California). Normally distributed variables were compared by t tests whereas non–normally distributed samples were compared using the Mann-Whitney U test. To determine nonrandom associations between 2 categorical variables, the 2-sided Fisher exact test was used. Significance was defined as P < .05.

A total of 116 cases of human rabies were identified. Twenty cases were excluded because of insufficient clinical information. Four patients survived, and 92 died from their rabies virus infections. There were no significant differences between survivors and nonsurvivors with regard to the following variables: age at disease onset, sex, vector, incubation time, prodrome duration, postexposure prophylaxis, antiviral therapy, seizures, or the performance and results of antemortem and postmortem diagnostic tests. One survivor and 1 nonsurvivor received pre-exposure prophylaxis (antibody titer, 64 000), and 1 survivor received neither pre-exposure nor postexposure prophylaxis (antibody titer, 32 768). In the CSF, the median antirabies antibody titer was 9712 (range, 2048-160 000) in the survivor group as opposed to a median titer of 10 (range, 4-2560) in the nonsurvivor group (P < .007). Median antibody titers in the CSF of survivors devoid of pre-exposure prophylaxis were 3200 (range, 2048-160 000), remaining statistically significantly different from nonsurvivors (P < .01). The 2 survivors who only received postexposure prophylaxis had antibody titers of 3200 and 16 000. One survivor received only pre-exposure prophylaxis (antibody titer, 16 225), and 1 survivor received neither pre-exposure nor postexposure prophylaxis (antibody titer, 2048). In the vast majority of rabies cases analyzed in this study, antibody titers were only determined at 1 time point. There was no difference between survivors and nonsurvivors regarding the time point at which antibody titers were measured in serum or CSF in relation to time of exposure.

Herein we show that survivors with and without pre-exposure prophylaxis had significantly higher antira-
Biomarkers in Dementia

Fagan et al1 followed up a group of 61 normal elderly individuals (Clinical Dementia Rating [CDR] 0, >60 years old) for a mean time of 3 to 4 years to study cognitive decline. Individuals who progressed during the follow-up from a CDR of 0 to a CDR of 0.5 or higher were defined as converters toward very mild or mild dementia. All the other subjects were considered nonconverters. A cutoff value of 0.214 or greater for the ratio of cerebrospinal fluid (CSF) phosphorylated tau181/β-amyloid1–42 (ptau181/AB42) at baseline was adopted to predict converters and nonconverters at follow-up. The authors’ conclusion is that, “CSF tau/AB42 ratios show strong promise as antecedent (preclinical) bio-

markers that predict future dementia in cognitively normal older adults.”

We would like to raise 2 objections. First, on the basis of the data reported in the article, it is possible to define the 2-by-2 chart outlined in the Table. The sensitivity, specificity, and positive and negative predictive values are 38.5%, 91.7%, 55.5%, and 84.6%, respectively. The low sensitivity and low positive predictive value do not support, in our opinion, the authors’ conclusion. The same situation can be observed also for the tau/AB42 biomarker.

Second, the article does not report how many subjects, among the 13 converters (21%), had a CDR of 0.5 or a CDR of 1 and at what times. So in this group, subjects with mild cognitive impairment (MCI) are not distinguished from subjects with mild dementia. This choice is questionable because many epidemiological studies show that up to 40% of subjects with MCI reverted to a normal cognitive condition after 2 to 3 years.2

We believe that further research is necessary before suggesting the use of these biomarkers as possible predictors of progression from normal cognition/MCI to MCI/dementia in clinical practice. This issue is crucial because, taking into account the wide off-label use of cholinesterase inhibitors in MCI,1 physicians could be encouraged to prescribe these drugs for subjects classified as “positive” on the basis of CSF markers even though scientific evidence on their risk-benefit profile in MCI shows negative results.4,5

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Table. Converters and Nonconverters in Relation to CSF ptau181/AB42 Ratio

<table>
<thead>
<tr>
<th>CSF ptau181/AB42 Ratio</th>
<th>Converters, No. (n = 13)</th>
<th>Nonconverters, No. (n = 48)</th>
<th>Total, No. (N = 61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥0.214</td>
<td>5</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>&lt;0.214</td>
<td>8</td>
<td>44</td>
<td>52</td>
</tr>
</tbody>
</table>

Abbreviations: AB42, β-amyloid42; CSF, cerebrospinal fluid; ptau181, phosphorylated tau181.

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3. Two suspected cases of human rabies in sur-