RESEARCH LETTER

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 (P < .04). The nonsurvivor had an undetectable antirabies antibody titer after prophylaxis. Fifty percent of survivors received postexposure prophylaxis as opposed to 12% of nonsurvivors (P < .09). The median antibody titer in serum among survivors was 63 500 (range, 32 768–640 000) as compared with 280 (range, 1–32 768) in the nonsurvivor group (P < .002). When comparing median antibody titers in serum only between patients devoid of pre-exposure prophylaxis, the difference between survivors (63 000; range, 32 768–640 000) and nonsurvivors (280; range, 1–32 768) remained statistically significant (P < .007). Two survivors only received postexposure prophylaxis (antibody titers, 63 000 and 64 000). Antibody titers were expressed as the result of dilution series.2 None of the survivors received passive immunization with antirabies serum or immune globulin. One survivor only 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 160 000. 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 very 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-
A biomarker antibody titers than nonsurvivors. This observation is compelling and suggests that a quantitatively higher humoral immune response against the rabies virus in survivors is not exclusively directed against the vaccine.

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We agree with Drs Watson and Woo that these data are promising and that the methodology used is sound. However, 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, 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.

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