Etiology of Many Encephalitis Cases Unknown

BY MICHELE G. SULLIVAN

BANGKOK, THAILAND — Many cases of encephalitis lack pathologic evidence for a specific etiology even though methods for detecting infectious agents have improved, suggesting that new infectious agents could be the source of some cases, according to the results of two studies.

Julia Granerod reviewed the etiology of encephalitis in 45 studies and concluded that the cause of up to 65% of cases remains a mystery. Because methodologic differences among the studies did not account for the unknown cases, other causes must be considered.

"It's important to consider the incidence in a global context, because with the threat of newly emerging infectious agents, increasing international travel, and global warming, there may be shifts in incidence over time," Ms. Granerod said at the World Congress of Neurology.

Her colleague, Dr. Nicholas Davies, a fellow in neurology at St. Vincent's Hospital, Sydney, came to a similar conclusion in his prospective study of encephalitis etiology. In the largest proportion of cases (38%), no infectious or inflammatory cause for the disease could be determined.

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In her review, Ms. Granerod, the national scientific coordinator of the U.K. Health Protection Agency Centre for Infections, included studies from Asia, Africa, Europe, and North America. Encephalitis incidence ranged from 0.07 to 12.6/100,000 per year. She also found that the incidence significantly decreased over time, due to the introduction of vaccines for some encephalitis vectors, such as Japanese encephalitis, yellow fever, and tick-borne encephalitis.

Etiology varied by geography. The most common etiology in Asia was Japanese encephalitis, whereas in Europe most cases were caused by herpes simplex viruses (HSV) and varicella zoster virus (VZV). *Mycoplasma pneumoniae* also caused a significant amount of encephalitis in Europe. In North America, insect vectors (ticks and mosquitoes) contributed the greatest number of identifiable cases.

The etiology was unknown in 65% of the North American cases, 43% of the European cases, and 59% of the Asian cases. "The most striking thing was that in 63% of the studies, more than 50% of the cases had an unknown etiology," Ms. Granerod said. "That is a very significant finding."

To determine the effect of methodologic differences between the studies, she conducted a multivariate regression analysis. "We considered year—the more sensitive diagnostic methods, such as polymerase chain reaction, were started in the mid-90s, so studies conducted after that should have had a lower proportion of unknown etiology. We also considered age, continent, subsyndrome, the number of agents tested for, whether the study was retrospective or prospective, and the case definition."

Only year, continent, and subsyndrome remained significantly associated with etiology. "These findings support an emerging unknown etiology of encephalitis," she said.

The review's findings may be more fully explained by a soon-to-be-published U.K. trial. The Etiology of Encephalitis in England study, sponsored by the country's Health Protection Agency, included patients recruited over a 4-year period from 18 hospitals and neurology centers in the U.K. Preliminary observations suggest that many of the cases with unknown etiology may be immune-mediated, most notably by antibodies associated with the *N*-methyl D-aspartate receptors, Ms. Granerod said.

While he was a research fellow at Guy's & St. Thomas' Hospital, London, Dr. Davies and his colleagues prospectively studied 61 adult patients with en-

cephalitis treated at any of three London hospitals. In addition to describing the disease etiology, the researchers obtained clinical outcomes and quality of life data on the patients after discharge.

Of the 61 patients, 46% were female; the mean age was 40 years. The researchers analyzed 91 cerebrospinal fluid samples, including 52 that were obtained in the first 14 days and 39 that were obtained after 2 weeks.

An identifiable infectious etiology was found in 21 (34%) patients. Those were HSV (15), VZV (2), a combination of HSV and VZV (1), and *Toxoplasma gondii* (1) and bacterial infections (2). A noninfectious, inflammatory etiology was noted in 14 patients (23%). These included acute disseminated encephalomyelitis (6), fulminant multiple sclerosis (3), antiphospholipid syndrome (2), antineutrophil cytoplasmic autoantibodies (ANCA)-associated vasculitis (2) and a paraneoplastic encephalitis (1). Three (5%) patients had other identifiable etiologies.

The etiology was unknown in 23 (38%) patients. Three of these patients had Epstein-Barr virus in their blood, but the viral load was less than 50 copies/million leukocytes, which was too low to cause symptoms. Two patients had herpesvirus 7, but there was no evidence of a primary infection.

The subgroups were similar in terms of clinical findings, with the exception of fever. Patients with an infectious etiology had higher temperatures at admission than did those with inflammatory, unknown, or other causes.

Overall mortality was 21%, and was highest among those with inflammatory causes (43%). Mortality rates were 14% in those with infections and 9% in those with an unknown etiology.

After a mean follow-up of 20 months, morbidity was significantly better in the unknown etiology group than in the infectious and inflammatory groups. The Glasgow Outcomes Score was less than 4 in 67% of patients in the infectious group, 57% of the inflammatory group, and 24% of the unknown group. ■

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