Non-herpetic Acute Limbic Encephalitis: a New Subgroup of Limbic Encephalitis?

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To the Editor: In the previous issue, we reported 6 new patients with non-herpetic acute limbic encephalitis (non-herpetic ALE), together with clinical data, including cerebrospinal fluid (CSF) cytokine and magnetic resonance imaging findings (1). The level of CSF interleukin (IL)-6 in this type of ALE was elevated, but the level of CSF interferon-γ was not. These cytokine findings may be helpful for diagnosing this type of ALE. More recently, special issues around this type of ALE were published in a Japanese neurological journal; Yuasa et al (2) proposed a wider spectrum of limbic encephalitis/encephalopathy, along with the demonstration of glutamate receptor ε2 in reversible acute limbic encephalitis. Ide et al (3) reviewed ALE cases associated with collagen diseases such as systemic lupus erythematosus or Sjögren’s syndrome. Also, Takahashi et al (4) described the increase of CSF IL-6 in 2 patients with non-herpetic ALE and reported the efficacy of steroid pulse therapy.

Reports of non-herpetic ALE have rapidly increased in Japan in recent years; approximately 50 patients with this subgroup were reported through the end of 2002, mainly in the Kyushu and Kanto districts, as well as Chugoku, Tokai, Hokuriku, and Tohoku. The patients’ mean age was 38.5 years (n=39, range 18–73 years) with a 17:22 male : female ratio. As far as we know, no case of non-herpetic ALE has been reported outside of Japan.

What exactly does “non-herpetic” indicate in the term “non-herpetic ALE”? “Non-herpetic” forms initially exhibited lack of evidence of herpes simplex virus (HSV)-1 or -2 infections by sensitive polymerase chain reaction (PCR) and enzyme immunoassay (EIA) testing. Presently, the tests include those for varicella-zoster virus, Epstein-Barr virus, cytomegalovirus, human herpesvirus-6, and a few neurotropic RNA viruses. However, various tests for so many herpesvirus groups and other viruses are not available within the limits of medical insurance. In addition, negative results are not always conclusive, because pseudonegative phenomena can occur. For example, HSV DNA negative sampling can result from testing at a very early stage, while late-stage negative sampling can occur for only a limited amount of HSV DNA.

The non-herpetic ALE proposed in Japan is probably a new subgroup of limbic encephalitis/encephalopathy. However, the cause and pathogenesis of this type of ALE remain to be clarified, and how to form the spectrum of non-herpetic ALE and related diseases is still controversial (1–4). Evidence of further cases and critical opinions from other Asian and Western countries are highly welcomed.

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