Influenza Virus and Febrile Convulsions

To the Editor—Recently, Kawada et al. [1] described systemic cytokine responses in infants and children with influenza-associated encephalopathy and febrile convulsions (FCs). The authors suggested that the pathogenesis of FCs is similar to that of encephalopathy and that the differentiation of encephalopathy and complex FCs may be difficult. The mechanism of FCs is a controversial topic, and the perspective of a pediatric neurologist with a long-time interest in FCs (J.G.M.) may be appropriate.

Influenza A virus is a frequent cause of FCs in Japan [1] and in other Asian countries. In Hong Kong, influenza A virus infection accounted for up to 35%–44% of hospital admissions for FC during peak influenza months in 1997 and 1998, a much higher incidence than for FCs associated with parainfluenza and adenovirus infection [2]. In contrast, except for 1 epidemic in the United Kingdom in 1972 [3], influenza A virus is an uncommon cause of FCs in western Europe and the United States. Among 6790 patients worldwide with FCs reported in 33 publications between 1929 and 1964 (none from Japan), the causes of fever were noted for a total of 7036 febrile episodes, and the prevalence of the various infections was tabulated [4]. Apart from roseola infantum in 1.4% of cases, viral infections as a cause of FCs were rarely reported in the first half of the twentieth century, and influenza virus infection was not recorded.

In the United States, infection with human herpesvirus (HHV)–6 is a more frequent cause of FCs than is infection with influenza A virus and accounts for one-third of all first-time febrile seizures in children ≤2 years old [5]. The risk of FCs due to HHV-6 infection is 29% (for HHV-6 associated with roseola, the risk of FCs is 17%), compared with a risk of only 9% due to non–HHV-6 infection. The risk of FCs due to HHV-6 infection is correlated with a high fever and with low levels of immunoglobulin. FCs due to HHV-6 may be complex, and, like those due to influenza infection, a possible encephalitis/encephalopathy is suspected in some cases [4, 6].

Infections play a role in the etiology of FCs by ≥1 mechanism: (1) the degree of fever per se, (2) an abnormal immune state and allergic response to infection, (3) the presence of a neurotropic bacterial toxin (e.g., Shigella dysenteriae), or neurotropic virus (e.g., HHV-6 or influenza A virus), or (4) an unrecognized mild viral encephalitis or toxic encephalopathy [4]. An elevated cytokine response independent of the severity of infection, with either influenza A virus [1] or other pathogens [7], is now added as a probable factor in the mechanism of FCs. On the basis of the study by Kawada et al. [1] and as suggested by earlier references to immune reactions in young children with FCs [4], it is proposed that the pathogenesis of FCs, especially complex FCs, is similar to that of encephalopathy and is a consequence of systemic immune responses [1]. In children with proven viral infections and for whom virus was isolated from cerebrospinal fluid, complex FCs (i.e., those that are >15 min long, focal, or repeated in 24 h) are no more prevalent than simple FCs (i.e., those that are <15 min long and generalized) [8], which suggests that simple and complex FCs have similar mechanisms.

Further studies of the role of viral infections in the cause of FCs, a relatively neglected field of research in pediatric neurology, should help elucidate the mechanism of the seizure and the differentiation of simple and complex FCs. Do complex FCs, with their associated poor prognosis, have a different mechanism from the simple and relatively benign FCs, or do they both result from fever and infection, which, in complex FCs, are neurotropic and encephalopathic to a greater degree?

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References

Reply
To the Editor—We appreciate the comments of Millichap and Millichap [1] concerning our recently published article [2].