Influenza-associated encephalopathy and neurologic features of novel influenza A (pH1N1) virus infection*

Seasonal influenza infection is extremely common and, very occasionally, strains are associated with encephalitis or encephalopathy, particularly among young children (1). So-called “influenza-associated encephalopathy” (IAE) has been more frequently reported with influenza A, especially H3N2 virus infection (2). Also, IAE has mostly been reported in Japan and Taiwan, but cases have been reported from Europe and North America and in Caucasian children (3–7).

The pathophysiology of IAE is not well understood. A number of authors (8) have written about typical neurologic complications, including febrile convulsion, decreased sensorium, delirium, and coma. In 2007, Mizuguchi and colleagues (9) presented a new construct for considering the diverse forms of IAE that brings together thinking about pathophysiology with one of three patterns of presentation or syndromes: 1) Encephalopathy caused by metabolic derangement and associated with various inherited metabolic disorders inducing the classic Reye syndrome; 2) encephalopathy associated with inflammation, hypercytokinemia, and vasogenic cerebral edema, including Reye-like syndrome, hemorrhagic shock, and encephalopathy syndrome, and acute necrotizing encephalopathy (ANE); in this group, severe cases are complicated by a sepsis-like state with multiple organ failure and disseminated intravascular coagulation; and 3) an excitotoxic encephalopathy syndrome, cerebral involvement is due to transient edema or inflammation. A case series of 11 Japanese children with varying emotional lability, visual hallucinations, delirium, and incoherent speech has been described (12), but the specificity of the splenial lesion as a sign of IAE has been questioned (13). IAE causing fluctuating level of consciousness and reversible splenial lesion has been reported in a 2.5-yr-old Caucasian Belgian girl who, in addition, had cerebellar involvement and transient mutism during recovery (14).

When it comes to considering treatment of IAE that goes beyond providing support of vital functions and use of antiepileptic medications, most reports have come from Japan and are based on an inflammatory hypothesis. For example, in 2005, Nunoi and colleagues (15) reported laboratory findings in 53 children (average age, 2.5 yrs) with influenza A infection, 11 of whom had IAE. Serum levels of cytochrome c, tumor necrosis factor-α, and interleukin-8 were elevated in those with IAE; the elevation of cytochrome c also reflected the severity and time course of disease and clinical outcome. Because cytochrome c is an intramitochondrial protein that can initiate apoptosis, its presence in serum suggests tissue (most likely hepatic and possibly brain parenchyma) apoptosis under the influence of hypercytokinemia. Another report (16) in a series of ten children with IAE showed that, in addition to the acute changes in serum tumor necrosis factor-α and cytochrome c, those who developed cerebral atrophy had markedly increased cytochrome c in the cerebrospinal fluid. Finally, a report (17) in 27 children with influenza-related mild neurologic complications (ten patients with delirium and 17 with febrile seizures) showed abnormal serum interleukin-6 levels, particularly those with generalized slow waves on electroencephalography (EEG). Taken together, these reports of a hypercytokinemia and apoptosis have undoubtedly led some to the use of plasma exchange, pulsed doses of methylprednisolone, and mild hypothermia for their cases of IAE (18–20).

In this issue of Pediatric Critical Care Medicine, the publication (21) from Pittsburgh, PA confirms previous observations from Texas (22), Florida (23), and Australia (24), that novel influenza A pH1N1 is also encephalopathic. In contrast with the other reports, the report by Dr. Baltagi and colleagues (21) provides us with unique clinical, EEG, cerebral imaging, and biochemical characterization of the condition. Their four cases includes the already known spectrum of IAE: the typical form with altered sensorium and diffuse EEG slowing; the state with fever, unusual behaviors like mild encephalopathy with reversible splenial lesion, and diffuse EEG slowing; and the severely debilitating neuroinflammatory pattern with ANE (group 3). In addition, the authors identified something new associated with IAE. They cared for a child with abnormal movements, truncal ataxia, hallucinations, and diffuse EEG slowing whose cerebrospinal fluid contained N-methyl-D-aspartate receptor (NMDAr) antibodies. The finding of two rare conditions—ANE and anti-NMDAr encephalitis—in such a small series, over a period of 9 months, raises some interesting possibilities concerning IAE.

*See also p. xxx.

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Consider three recent findings about ANE. In a clinical review of 22 children with ANE (11 cases of IAE and 11 noninfluenzal cases), the pathogenesis of the condition did not seem to depend on infectious agents (25). Second, the identification of an autosomal dominant form of infection-triggered or recurrent ANE (ANE1) caused by mutations in a component of the nuclear pore, mitochondria, and microtubules—Ran Binding Protein 2 (26). Third, a 9-yr-old Caucasian child with recurrent ANE aged 9 months and 9 yrs has been reported as having ANE1 (27). Brain imaging during both episodes was typical and the later episode was associated with influenza A infection. Importantly, before genetic testing, the child was considered a case of sporadic ANE. The main implication of these observations is that host genotype accounts for the phenotype of the severe form of IAE, rather than infection per se. The other implication is that we need to think about this genetic susceptibility. The clinical phenotypes of ANE and ANE1 overlap significantly and family history of ANE or postviral “encephalitis/polynuertis,” although supportive of ANE1, is not necessary before undertaking diagnostic investigation, as de novo mutation in Ran Binding Protein 2 can also occur (26).

Consider, also, what is now known about anti-NMDAR encephalitis. The original description was of young women with ovarian teratoma and antibodies against the NR1-NR2 heterodimers of the NMDAR, who presented with psychosis or memory problems, rapidly progressing to multiple neurologic deficits, requiring prolonged intensive care support (28). A more expanded phenotype for this immune-mediated disorder has now been described in a series of 100 patients, which includes low-grade fever or a non-specific viral-like illness within 2 wks of admission, seizures, fall in consciousness, hypoventilation, autonomic imbalance, or abnormal movements (29). Forty-one percent of patients did not have a clinically detectable tumor, and men and children were also affected. The finding by Dr. Baltagi and colleagues (21) of anti-NMDAR antibodies in one of their cases of IAE is intriguing, especially because the clinical picture—periods of increased confusion followed by somnolence, fever, bizarre speech, truncal ataxia, and rhythmic movements of her extremities—and investigations are consistent with anti-NMDAR encephalitis (30). Perhaps this excito-toxic pattern of IAE (group 3) has gone unrecognized because of incomplete cerebrospinal fluid testing; it may be that this condition is the same as acute encephalopathy with biphasic seizures and late reduced diffusion. If this child’s immunologic condition was due to novel influenza A (pH1N1) virus infection, then it suggests that more work is needed on immune activation and immune-mediated mechanisms in IAE. (For example, what was the role of the prodomal febrile seizures occurring 10 days before presentation in the authors’ case?)

Dr. Baltagi and colleagues (21) have provided a careful and detailed description of neurologic sequelae of pH1N1 influenza in children. As a consequence, they have not only added to the classic description of IAE but also contributed to the current conceptual framework of the condition (9).

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REFERENCES
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