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Emerging Infections and Children: Influenza and Acute Necrotizing Encephalopathy

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1. Introduction

Children can play a variety of roles in emerging infectious diseases. They can be victims, as in the vertical transmission of human immunodeficiency virus infection. They can be affected in a minor way compared with adults, as in West Nile virus infection, legionellosis, and coronavirus infection leading to severe acute respiratory syndrome (SARS). Sometimes, however, they play predominant roles—sources for other age groups—as do toddlers in out-of-the-home child care for transmission of penicillin-resistant pneumococci and cytomegalovirus to family members. Children have a uniquely central role in transmitting the influenza viruses that cause annual seasonal outbreaks and epidemic disease and could cause global epidemic (or pandemic) disease. Children themselves suffer excessive morbidity and mortality from influenza. Continuous minor changes in virus neuraminidase and haemagglutinin components (antigenic drift) or a major change in either (antigenic shift) render naïve children especially vulnerable. Anticipating that pandemic influenza could occur at any time because of a major change in a human strain of influenza virus or through acquisition of human transmissibility of reassortant avian influenza strain(s) (Nicholson et al., 2003), the international community of healthcare experts are collaborating increasingly, and countries are drafting influenza pandemic preparedness plans. A draft by the U.S. Department of Health and Human Services of "Pandemic Influenza Preparedness and Response Plan" was released for comment in August 2004 (http://www.hhs.gov/nvpo/pandemicplan). All plans highlight the critical importance of international surveillance, openness, and rapid response to investigate and contain emergent avian or human strains. In the midst of concern for novel influenza viruses, an apparently novel clinical manifestation of extant influenza virus has emerged recently. Acute necrotizing encephalopathy (ANE) is a new and severe manifestation of influenza in children.

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2. Epidemiology of Influenza

In prospective studies in the United States (Glezen and Couch, 1978; Neuzil et al., 2002) annual attack rates of influenza illness are between 15% and 42% in preschool- and school-aged children. Globally, it is estimated that 20% of children and 5% of adults have symptomatic influenza illness annually. Influenza is responsible for approximately one-third of excess outpatient visits to healthcare providers for children less than 3 years of age and for approximately one-third of excess prescriptions for antibiotics in the winter season for individuals less than 15 years of age (Neuzil et al., 2000; O'Brien et al., 2004). Antecedent influenza infection is associated with the development of invasive pneumococcal infection and staphylococcal pneumonia in children (O'Brien et al., 2000) as well as in adults.

Children have undue risk for complications of influenza and for hospitalization (Izurieta et al., 2000). Influenza-associated illnesses in children are not restricted to acute respiratory syndromes with systemic complaints or complications, and can involve a variety of organ systems (Table 1.1). Children under the age of 2 years have substantially higher risk of hospitalization than do older children. There are more than 10,000 children younger than 2 years of age hospitalized for influenza annually in the United States; rates of hospitalization range from approximately 200 to 500 per 100,000 population. The risk of hospitalization among children less than 4 years of age in one study was approximately 100 per 100,000 in healthy children and 500 per 100,000 in children with underlying conditions (Neuzil et al., 2000). The overall health impact of influenza in children, and the risk of hospitalization among children younger than 2 years of age, is similar to or greater than that among high-risk children and healthy 50- to 64-year-old adults (both groups for whom annual influenza immunization has been recommended in the United States for years). Recognizing this, universal influenza vaccine was recommended by the American Academy of Pediatrics (AAP) and the Centers for Disease Control and Prevention (CDC) in 2004 for healthy children 6 months to 24 months of age and for household contacts and out-of-home caregivers of all children younger than 24 months of age (Committee on Infectious Diseases, AAP, 2004; Table 1.2). Because of an unexpected shortage of vaccine doses in October 2004, recommendations

Table 1.1 Clinical Manifestations of Influenza Beyond Acute Respiratory Tract Illness

- Febrile illness with vomiting and diarrhea in the absence of respiratory tract symptoms
- Sepsis-like illness (especially in young infants) in the absence of respiratory tract or gastrointestinal symptoms
- Myocarditis
- Bilateral gastrocnemius myositis
- Rhabdomyolysis
- Invasive group A streptococcal, pneumococcal and meningococcal infection
- Toxic shock
- Post-influenza asthenia

Table 1.2. Recommendations by the American Academy of Pediatrics, 2004, for Influenza Immunization

I.	High-risk children and adolescents with the following conditions • Asthma or other chronic pulmonary disease • Hemodynamically significant cardiac disease • Immunosuppressive disorders or therapy • Human immunodeficiency virus infection • Sickle cell anemia and other hemoglobulopathies • Disorders requiring long-term aspirin therapy (e.g., rheumatoid arthritis and Kawasaki disease) • Chronic renal dysfunction • Chronic metabolic disease (e.g., diabetes mellitus)
II.	Women who will be in second or third trimester of pregnancy during influenza season
III.	Persons who are in close contact with high-risk children. These include: • All healthcare professionals in contact with children in hospitals and outpatient settings • Household contacts and out-of-home caregivers of high-risk individuals of any age
IV.	Young, healthy children 6 through 23 months of age (because of excessive risk of hospitalization, morbidity, and mortality)
V.	Household contacts and out-of-home caregivers of children younger than 24 months of age[a]
VI.	Any person older than 6 months of age who (or whose parent) wishes to be protected against influenza[a]

[a] Because of shortages of influenza vaccines that occurred in October 2004, the CDC and AAP have altered these recommendations temporarily. Regarding healthy contacts of healthy children (Recommendation V), only those children under 6 months of age (too young to be immunized) are recommended to receive vaccine. Other healthy individuals to whom these recommendations apply (Recommendation VI) were asked to defer immunization in order to channel available vaccine to high-risk individuals and their contacts (CDC, 2004a, b).

were modified temporarily to include healthy contacts only for infants under 6 months of age (who are themselves too young to be vaccinated) (CDC, 2004a, b).

3. Mortality from Influenza

Death from influenza has not been a reportable disease in the United States. However, more than 150 influenza-associated deaths among children under 18 years of age were reported to the CDC in the 2003–2004 influenza season. This voluntary reporting probably reflects a gross underestimate. Death due to influenza has been made a reportable disease for 2004–2005. Preliminary data from the 2003–2004 fatal cases show a median age of approximately 3 years; two-thirds were less than 5 years of age. Approximately one-half of the children were previously healthy, the others having a wide variety of underlying conditions, especially involving the central nervous system. Deaths did not occur in fully immunized children. In more than one-quarter of fatalities, death was rapid, occurring either at home or in a hospital emergency department. Causes included viral and bacterial pneumonia, invasive bacterial infection, cardiorespiratory deaths, and central nervous system syndromes. An emerging disease, influenza-associated ANE was one cause of mortality and significant morbidity.

4. Influenza-Associated Acute Necrotizing Encephalopathy

4.1. An Illustrative Case

A 3-year old US-born, previously healthy male of Indian descent was brought to medical attention in February 2004 because of lethargy and abnormal tongue movements. From 3 weeks until 1 week prior to admission, he was traveling in India with his family where he lived rurally with extended family members. He was exposed to multiple dogs, cows, and birds. He drank unpasteurized milk and had many insect bites. He took no malaria prophylaxis. Three days prior to admission he had sudden onset of fever to 39.0°C, vomiting, diarrhea, and abdominal pain. On the day of admission he was sleepy, unwilling to rise from his bed, and had unusual tongue movements.

Physical examination revealed a well-grown boy who was difficult to arouse. He appeared to understand some commands but was mute. Vital signs were normal as was the general physical examination. Function of cranial nerves were normal as far as could be assessed as was fundoscopic examination. He had generalized tremulousness (also affecting his tongue) and increased tone on the left side. Full blood count, electrolyte and metabolic screening tests, and chest radiograph were normal. Electroencephalogram showed continuous epileptiform discharges. Cerebrospinal fluid was acellular with protein concentration of 0.6 g/l and normal glucose concentration. Magnetic resonance imaging of the brain (see Figure 1.1) was abnormal.

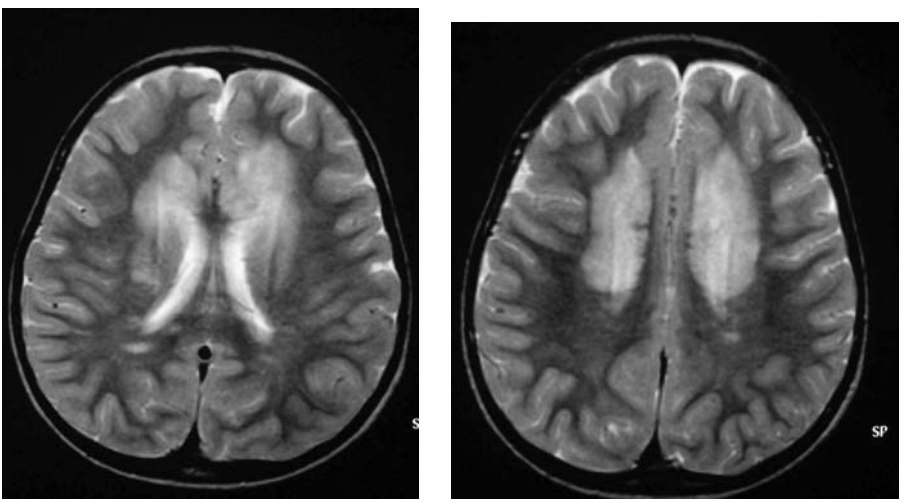

Figure 1.1. Appearance of T2-weighted images of the brain show increased signal intensity bilaterally and symmetrically in the periventricular and deep white matter (on the left) and the corona radiata (on the right). T1-weighted images were not remarkable. There was no enhancement after administration of gadolinium. Images are courtesy of Eric Faerber, M.D., Department of Radiology, St. Christopher's Hospital for Children, Philadelphia, USA

The differential diagnosis was lengthy, especially considering exposures. Multiple tests for possible aetiological infectious agents including bacterial cultures, antigen-detection tests, antibody tests, blood smears, and polymerase chain reaction assays were negative. Influenza B was isolated from the respiratory tract. The virus was subsequently identified by the CDC to be Sichuan group/Shanghai-like. Polymerase chain reaction testing for influenza was performed on the patient's cerebrospinal fluid at the CDC and was negative.

Despite all of this patient's exposures in India to what would be rather exotic infectious agents in the United States, he turned out to have an unusual manifestation of the most common infection (influenza) in the United States and Europe at that time. Incubation period would be compatible with acquisition during transcontinental travel or immediately upon return to the United States. More than 90% of influenza viruses isolated in the United States in the 2003–2004 season were type A. Type B accounted for the remainder; Sichuan group/Shanghai-like was the most common type B virus isolated.

Diagnosis was highly compatible with acute necrotizing encephalitis. Hospital course was protracted and complicated, with major problems of seizures, stupor, mutism, and left hemiparesis. Therapeutic manoeuvers included administration of oseltamivir, intravenous immunoglobulin, and solumedrol. None had immediate temporal benefit, but at the time of transfer to a rehabilitation hospital after 21 days of hospitalization under intensive care, he had increasing periods of alertness, appeared to recognize parents, demonstrated visual tracking, and made guttural sounds. Eight months after the illness, he has recovered remarkably, with mild residual hemiparesis and difficulty in speech and language.

4.2. History of Emergence of Acute Necrotizing Encephalopathy

In pandemics of influenza, as in 1918 and 1930, *Encephalitis lethargica* was a frequent cause of death. As gleaned from descriptions, the disease probably was in some cases influenza virus encephalitis and in others post-infectious encephalitis. We recognize both syndromes as occurring currently, sporadically during annual influenza seasons. In addition, rarely, hemorrhagic shock and encephalopathy, as well as Reye's syndrome can be associated with influenza, the latter especially but not always in conjunction with use of aspirin. The CNS disease represented by our case, ANE, was first described in Japanese children in 1995. By 1998, 148 cases of ANE were reported in Japan (Morishima et al., 2002) and it was estimated subsequently that more than 100 deaths were occurring annually in Japanese children from influenza-associated ANE (Kasai et al., 2000). Emergence of ANE in Japan occurred the year after cessation in 1994 of routine annual influenza immunization in children, a policy that had been in place since 1960s. Influenza A and B viruses were associated with direct proportion to causation of uncomplicated respiratory tract infection. In the United States, physicians were alerted to ANE in late 2003 and were encouraged to report cases to the CDC. More than 103 possible cases were reported. At this time, the reports of only a minority of cases meeting the screening case definition of having proven influenza plus more than 24 hr of altered mental status have been

Table 1.3. Clinical Characteristics of Influenza-Associated Necrotizing Encephalopathy

- Clinical
  - Age <5 years, rarely >10 years
  - Onset *during* the peak of the febrile illness (fever ± cough, vomiting)
  - Presentation with seizures
  - Presentation with altered mental status
  - Propensity for finding of akinetic mutism
  - Multiorgan failure that *follows* CNS symptoms
  - Disseminated intravascular coagulopathy that *follows* CNS symptoms
  - Unremarkable severity of influenza symptoms
  - Unremarkable complete blood count, serum chemical and hepatic enzyme tests
  - Normal cerebrospinal fluid (may have increased pressure, or protein elevation <100 mg/dl)
  - Negative polymerase chain reaction test for influenza on CSF
  - Autopsy → edema, apoptosis/necrosis but no inflammatory cells
- Cranial magnetic resonance imaging
  - Diffuse, bilateral, symmetric, high-intensity signal on T2-weighted images
  - Propensity for involvement of periventricular and deep white matter (thalamus, brain-stem tegmentum, cerebellum, or medulla)
  - No enhancement with gadolinium

investigated. The median age of cases is 4.5 years (1 month–17 years). States of children's residences have been broad. One-half have had seizures. One-half have made a full recovery while approximately one-quarter died and one-quarter have significant neurological sequelae.

4.3. Clinical Manifestations of ANE

As currently recognized, the course of ANE is characteristic (Table 1.3). Within 12–48 hr of onset of the febrile illness in an unimmunized child, the child has abrupt onset of seizures or mental status change or both. Findings range from obtundation to coma. Specific neurological abnormalities are not universal, but speech abnormalities and akinetic mutism occur frequently (Newland et al., 2003). Cerebrospinal fluid is acellular with normal glucose and protein concentration, or mildly elevated protein concentration. Multiorgan system failure can occur in some cases and *follows* rather than precedes onset of CNS symptoms and signs. Thrombocytopenia and severely elevated serum aspartate aminotransferase levels (AST > 1,000 IU/l) were associated with poor prognosis in Japanese children (Morishima et al., 2002). This disease is distinct from Reye's syndrome, which is encephalopathy with fatty degeneration of the liver and is associated with specific clinical and pathological abnormalities of the liver, hypoglycemia, and hyperammonemia.

Magnetic resonance imaging of the brain on T2-weighted images in ANE shows high-intensity signal diffusely in the periventricular and deep white matter bilaterally—characteristically affecting the thalamus, the brainstem, and the cerebellum. Autopsy of fatal cases has been remarkable, showing apoptosis of neurones with edema but no inflammatory infiltrate or vasculitis.

4.4. Pathogenesis of ANE

The pathogenesis of influenza-associated acute encephalopathy is unknown, but investigations in Japan have led to credible speculation. Influenza virus infection is necessary, but ANE is an uncommon event among infected individuals. While virus is present in the respiratory tract in ANE cases, viral RNA can be detected in cerebrospinal fluid of $<10\%$ of affected children, and the presence of virus in brain tissue in autopsied cases has not been proven despite testing by culture and gene amplification. This with the absence of inflammatory cells in the CSF or in samples of brain tissue suggests that direct viral invasion leading to tissue damage is unlikely to be the cause of CNS disease. On the other hand, in influenza-associated encephalopathy, elevated concentrations in the serum or CSF or both of several pro-inflammatory cytokines and cytokine receptors—interleukin (IL)-6, IL-1β, tumor necrosis factor (TNF) alpha, soluble TNF receptor-1 (sTNF-R1)—have been documented, with elevations in proportion to the clinical severity of disease (Ichiyama et al., 1998; Togashi et al., 1999; Aiba et al., 2001). In 2003, Kawada et al. further demonstrated up-regulation of IL-6, IL-10, and TNF-alpha genes in patients with influenza-associated ANE, strengthening the postulation that glial cells in the CNS are cytokine releasing cells (similar to blood macrophages) that can overproduce pro-inflammatory cytokines in response to respiratory tract influenza virus, causing a "cytokine storm" in the CNS.

Mouse inoculation studies of human and avian recombinant influenza virus (human influenza not being pathogenic in mice) performed two decades ago may be pertinent (Reinacher et al., 1983). Intranasal inoculation causes viral spread to the olfactory bulbs, then to the trigeminal ganglion, and later to the brainstem, pons, cerebellum, reticular formation, and posterior colliculi. Virus subsequently spreads to the respiratory tract and bloodstream. Following intraperitoneal inoculation, virus spreads predominantly to the visceral organs, lungs, and bloodstream with no involvement of the midbrain or brainstem and only occasional evidence of virus presence in the CNS, in the lining of the ventricles. In a further experimental step, passively transferred antibody in high levels protected against both routes of inoculation.

The postulated route of influenza virus spread in children with ANE is the olfactory tract, which then could lead to access and stimulation of a CNS glial cytokine response. Occurrence of ANE in unimmunized children; the timing of encephalopathy early in the course of the influenza illness; the site, symmetry, and pattern of magnetic resonance imaging abnormalities; and inability to detect virus in serum or CSF of most affected patients, all support this pathogenetic sequence. It is further speculated that cytokine-induced disruption of the blood–brain barrier could lead additionally to "backward flow" of accumulated cytokines into the circulation to cause the systemic inflammatory response syndrome (SIRS) that appears to follow CNS malfunction in some patients (Morishima et al., 2002). At neuronal level, these aberrant responses lead to mitochondrial respiratory failure, edema, and apoptotic and necrotic cell death (Yokota et al., 2000).

If validated, what new virus-associated, host-associated, or environmental factor might be postulated to explain the emergence of influenza-associated cytokine deregulation that leads to ANE? No single influenza strain or unusual epidemic was

identified in association with ANE in Japan. Emergence of ANE after cessation of routine immunization may indicate importance of rapid spread or primary infections in children. First recognition in Japanese children suggested a possible genetic predisposition, which has not been discounted. However, description of cases in the United States and anecdotally in many European countries, notably in children of non-Asian ancestry, makes a racial genetic predisposition unlikely. It is likely that a changing environmental factor may be responsible. In Japan, use of non-steroidal anti-inflammatory drugs (NSAIDs) (especially diclofenate sodium and mephenamate) in febrile children was common by the mid-1990s, and NSAID use has recently become common in the United States. The NSAIDs belong to the class of medications known as cyclooxygenase (COX) inhibitors. They have antipyretic, analgesic, and anti-inflammatory effects. Antipyretic effect is attributable predominantly to inhibition of COX-derived prostaglandin E2. Direct anti-inflammatory effect of suppressing leukocyte–endothelial cells interactions, as well as causing fever-dependent and—independent dysregulation of inflammatory mediators could cause aberrant host–virus interactions. Does NSAID use in the context of early uninhibited virus replication in the nose precipitate or facilitate the CNS "cytokine storm"? Currently, a case–control study is ongoing in Japan to clarify the relationships between these drugs and the occurrence and severity of ANE. Meanwhile, pediatricians in Japan, highly attuned to influenza-associated ANE, now advise against the usage of NSAIDs in children with suspected influenza.

4.5. Suggestions

Collection of more clinical, epidemiological, and laboratory data, as well as performance of case–control studies of environmental exposures are urgently needed to attempt to understand this highly morbid, emerging disorder. If an environmental exposure such as NSAID use is identified, a remarkable opportunity for prevention exists. With the early imperfect evidence of possible associations of aspirin with Reye's syndrome, this clinician advised against aspirin use in children. Not fearful that failure to provide aspirin then or NSAIDs now would negatively impact upon children, it seems prudent to advise parents of children with possible influenza to (1) provide comfort, (2) avoid use of NSAIDs, and (3) give acetaminophen or paracetamol judiciously and carefully. There are decades of history of non-deleterious effect of these agents on the course of influenza in children. However, there are also reports of severe hepatic toxicity and fatality from inadvertent overdose of acetaminophen, especially in infants and during viral illnesses (Committee on Drugs, AAP, 2001). The most effective means of preventing influenza-associated morbidities is the widespread use of influenza vaccine as recommended in children and their caretakers in the healthcare system, at home, and in the community.

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