DOI:10.1111/irv.12177
www.influenzajournal.com

Review Article

Influenza encephalopathy and related neuropsychiatric syndromes

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Influenza is occasionally complicated by CNS disorders, in particular impairment of consciousness. Severe disorders encompass multiple, distinct syndromes manifesting acute encephalopathy, whereas mild disorders represent multiple, ill-defined neuropsychiatric syndromes. Acute encephalopathy is manifested with seizures and coma, with or without multi-organ involvement. The outcome varies from death or neurologic sequelae to recovery and differs among syndromes. Transient neuropsychiatric disorders are manifested with delirium and/or abnormal behavior. There also are multiple syndromes. The outcome is usually favorable, although occasional fatal accidents warrant caution.

Keywords Acute encephalopathy, coma, delirium, influenza, oseltamivir.

Please cite this paper as: Mizuguchi (2013) Influenza encephalopathy and related neuropsychiatric syndromes. Influenza and Other Respiratory Viruses 7(Suppl. 3), 67–71.

Neurologic complication of influenza

Except for classical Reye syndrome, central nervous system (CNS) complications of influenza attracted little attention of physicians until around 1985, when Japanese pediatricians became aware of the fact that cases of acute encephalopathy cluster during an influenza epidemic.[1] In 1996–2000, influenza encephalopathy was widely recognized in Japan (population, 130 million), where its incidence was estimated to be 100–500 cases per year. The majority of patients were young children under 5 years of age, presenting with seizures and severe impairment of consciousness, namely coma. The fatality was about 30 percent.[2–4] A research committee was organized by the Japanese Government, and a society of patients' parents was established. In 2005–2007, other types of CNS complication drew attention, in both medical and social contexts in Japan. Patients with these conditions had mild impairment of consciousness, typically delirium and/or hallucination. Despite their benign and self-limited nature, these neuropsychiatric syndromes caused tragic deaths in some of the patients who either rushed onto a busy highway or jumped off from a high-rise apartment. Because many of these patients had taken oseltamivir, causal relationship between the drug use and delirious behavior was raised.[5]

Influenza-associated acute encephalopathy and other CNS syndromes have also been described in countries other than Japan. During the 2009 pandemic, there were multiple reports of such disorders.[6–9] In addition, several CNS disorders, such as autoimmune encephalitis, narcolepsy, and parkinsonism, are suspected as late complications of influenza.[10–12]

This article reviews CNS complications of influenza, characterized by impairment of consciousness, based primarily on the experience in Japan. The first half describes several syndromes of acute encephalopathy, and the second half discusses other neuropsychiatric syndromes.

Acute encephalopathy associated with influenza

Acute encephalopathy refers to syndromes of acute CNS dysfunction due to diffuse or widespread, non-inflammatory brain edema. Its onset is usually during the febrile period of an antecedent infection, which is viral in the majority of cases. The incidence is highest in infancy and early childhood. Its main symptoms include impaired consciousness, seizures, and signs of increased intracranial pressure.[13] In acute encephalopathy, impairment of consciousness is severe and sustained, with the level of consciousness equal to or below 13 on the Glasgow Coma Scale, and duration of impairment longer than 24 hours, according to the diagnostic criteria of the Japanese research committee on influenza encephalopathy.[14,15]

Acute encephalopathy is commonly classified in two ways: one based on the pathogen of infection and the other on the clinicopathological features of encephalopathy. Diagnoses by the virologic classification include influenza, human herpesvirus-6 (HHV-6), and rotavirus encephalopathies, whereas those by the syndrome classification include Reye syndrome, acute necrotizing encephalopathy (ANE), acute encephalopathy with biphasic seizures and late reduced diffusion (AESD), and clinically mild encephalitis/encephalopathy with a reversible splenial lesion (MERS). Any virus can cause any syndrome, but there is clear tendency that one virus is more likely to cause certain syndromes than other viruses.[13] For example, influenza is strongly associated with ANE and MERS, and HHV-6 with AESD. Among the encephalopathy syndromes following influenza, MERS is the most common, followed by AESD (10%) and ANE (6%).[16,17]

Epidemiology of influenza encephalopathy

Recent epidemiologic studies in Japan have shown that encephalopathy and conditions that often accompany ANE, such as multiple organ failure (MOF) and disseminated intravascular coagulation (DIC), are the leading cause of death from influenza in children <15 years of age.[18] Influenza is the commonest pathogen of acute encephalopathy, accounting for 27% of the cases. The incidence of influenza encephalopathy is estimated to be 200–300 cases per annum. Influenza encephalopathy affects all age groups, but is most common in children <10 years of age. In the pediatric cases, the median and mean age is 6 and 6·3 ± 3·4 years, respectively. Boys and girls are equally affected. The outcome is variable; 7% of the patients die, 17% survive with neurologic sequelae, and 76% show a full recovery. Notably, fatality has markedly declined from 30% to 7% during the last two decades. Although pediatric mortality was very low in Japan during the 2009 pandemic, acute encephalopathy was still a leading cause of influenza-associated childhood deaths.[18]

Major syndromes of influenza encephalopathy

Acute necrotizing encephalopathy (ANE)

Acute encephalopathy is the most common cause of death from childhood influenza in Japan. Among encephalopathy syndromes, ANE is characterized by the highest rate of fatal outcome.[16] First described in the 1990s, ANE is a fulminant type of encephalopathy characterized by the multiple and symmetric brain lesions, affecting the bilateral thalami, and by the involvement of systemic organs leading to DIC or MOF in the severest cases.[19] The main pathogenesis of ANE is cytokine-driven, systemic inflammatory responses.[13] Viral infections, such as influenza[20] and exanthem subitum (HHV-6), when combined with certain genetic predisposition, such as mutation of a nuclear membrane protein, Ran-binding protein 2 (RANBP2), and polymorphism of a mitochondrial enzyme, carnitine palmytoyltransferase II (CPT2), cause encephalopathy.[21–26] Excessive production and action of proinflammatory cytokines, such as tumor necrosis factor-α and interleukin-6, cause vascular endothelial injury and apoptosis of parenchymal cells in the brain and other organs, resulting in brain edema and systemic organ damage.[13] Due to the breakdown of blood–brain barrier, cerebrospinal fluid (CSF) often contains an increased amount of protein, despite the absence of inflammatory cells and influenza viruses.[16] The use of non-steroidal anti-inflammatory drugs (NSAIDs), such as diclofenac sodium and mefenamic acid, increases the fatality of influenza-associated encephalopathy, including ANE.[13]

Acute necrotizing encephalopathy is most prevalent in young children between 1 and 5 years of age. The outcome of ANE is poor; many patients die (28%) or are left with sequelae (61%). In Japan, the incidence of influenza-associated ANE is estimated to be about 10 cases per annum.[16,17]

Acute encephalopathy with biphasic seizures and late reduced diffusion (AESD)

The term AESD has several eponyms, including acute encephalopathy with febrile convulsive status epilepticus (AEFCSE).[13] First described as AEFCSE in a Japanese journal (2000),[27] and as AESD in 2006 in an international journal (2006),[28] this syndrome is characterized by the biphasic clinical course and by a typical magnetic resonance imaging (MRI) finding of subcortical white matter lesions in the cerebral cortex. The main pathogenesis of AESD is considered to be excitotoxicity; febrile infections, when coupled with genetic predisposition such as polymorphism of CPT2 and adenosine receptor A2A (ADORA2A),[24,29] cause status epilepticus. Excessive release of glutamate, an excitotoxin, may provoke selective and delayed death of the cerebral cortical neurons.[13] AESD is most prevalent in infants <2 years of age. Its outcome is characterized by the low fatality (1%) and high probability of neurologic sequelae (66%), including intellectual and motor deficits and epilepsy. In Japan, the incidence of influenza-associated AESD is about 20 cases per annum.[16,17]

Clinically mild encephalitis/encephalopathy with a reversible splenial lesion (MERS)

In contrast to ANE and AESD, MERS is a mild and benign disorder. First described in 2004, this syndrome is characterized by neurologic symptoms, such as delirium, stupor, and seizures, and by the typical MRI finding of a lesion in the splenium of the corpus callosum.[30] Pathogenesis remains unclear. MERS is most prevalent in children between 3 and 8 years of age and is the commonest type of encephalopathy

among schoolchildren. The outcome is good; most patients show full recovery within 10 days. The rate of death and sequelae was 0 and 7%, respectively. The incidence of influenza-associated MERS is about 40 cases per annum.[16,17]

Other syndromes

Although less common compared with the above disorders, other encephalopathy syndromes occasionally occur in association with influenza. Congenital disorders of metabolism of organic and fatty acids may be rapidly exacerbated by influenza, mimicking acute encephalopathy.[31] There also are case reports of acute encephalitis with refractory, repetitive partial seizures (AERRPS), and posterior reversible encephalopathy syndrome (PRES).[16,17,32,33]

Guideline for influenza encephalopathy

A research committee on influenza encephalopathy, supported by the Ministry of Health, Labour, and Welfare of Japan, compiled a guideline for influenza encephalopathy. The first edition was published in 2005,[14] and the second edition in 2009.[15] This guideline has been widely read and used by pediatricians in Japan, and translation into English is now under way.

Neuropsychiatric syndromes associated with influenza

Influenza is associated with a wide spectrum of neuropsychiatric complications. This review focuses on delirium and abnormal behavior that are commonly seen in children and adolescents. Essentially, they are mild, transient, and reversible impairment of consciousness. Many patients have delirium with varying degrees of mental confusion with excitement and/or anxiety. Some also have hallucination, which is visual in most cases.

Syndromes of influenza-associated neuropsychiatric disorders

There are at least four syndromes that vary in their association with age, sex, and oseltamivir use.

1. *MERS:* This is the mildest form of acute encephalopathy described in the previous section. In some patients with MERS, impairment of consciousness is too mild and transient to strictly meet the diagnostic criteria of acute encephalopathy. Thus, MERS constitutes a part of the spectrum of mild neuropsychiatric disorders and accounts for a sizable subpopulation of children with delirious behavior associated with influenza.[34–36] There is no evidence for the association of this condition with oseltamivir.
2. *Febrile delirium:* Febrile delirium is a common but ill-defined syndrome prevalent among young children with acute febrile diseases.[35–38] Clinically, this condition is a mild impairment of consciousness, manifested with fear, anxiety, disorientation, and hallucination, lasting for several minutes or hours. Hundreds of Japanese children with influenza reportedly have this condition every year. Although some Japanese investigators suspected a decrease in the risk of febrile delirium by oseltamivir use, there are no published data to support this notion.
3. *Delirium with rushing/jumping behavior:* According to the national surveillance in Japan, about 100 cases of rushing onto a busy street and jumping off from a high-rise apartment occur every year. Children between 5 and 15 years of age are most frequently affected, with a marked male preponderance (male: female = 2–4:1).[39] There is no clear temporal relationship between oseltamivir use and delirious behavior. The same kind of abnormal behavior is observed also in some patients with influenza but without oseltamivir.[40,41] Thus, it is evident that oseltamivir is not the main cause for this condition. Whether oseltamivir increases its risk attracted much attention, but still remains obscure.[42]
4. *Reproducible neuropsychiatric adverse effects of oseltamivir:* This condition is extremely rare. To the author's knowledge, only four cases have ever been reported to the Japanese government. All the patients were children under 10 years of age and had multiple episodes of delirium, each consisting of oseltamivir intake, latency for 1–2 hours, abnormal behavior and/or hallucination up to 2 hours, sleep for several hours, and full recovery. Multiple episodes with a clear temporal relationship suggest causality. Although this condition may represent "true" adverse effects of oseltamivir, the number of cases is tiny, and the information is only anecdotal.

Controversy over oseltamivir's relationship to neuropsychiatric symptoms

Influenza-associated delirium and hallucination are transient and benign, but occasionally cause abnormal behavior leading to accidental trauma and sometimes death, particularly in Japanese teenagers. In the 2005–2006 season, controversy arose over alleged adverse effects of oseltamivir, which had been taken by many of these patients.[43] Warning was issued in 2007 against prescription of oseltamivir for teenagers.

The Japanese government organized multiple research committees to conduct epidemiologic and pharmacologic studies, which led to the following conclusions:

1. Regardless of oseltamivir use, influenza was occasionally complicated by mild neuropsychiatric symptoms.
2. Children under 10 years of age were most commonly affected, followed by teenagers. With regard to the rushing/jumping behavior, teenagers were the most common.
3. Some of the patients had family history or history of parasomnia, a sleep disorder.

In the 2006–2007 season, a nation-wide epidemiologic study was conducted in Japan to reveal the relationship between drugs and neuropsychiatric symptoms. About 10 000 patients with influenza under 18 years of age were recruited. Based on the data obtained, one study group concluded that they found no positive association between oseltamivir and abnormal behavior.[44] Using the same data, however, another group suggested that oseltamivir may slightly increase the risk of this condition, with a hazard ratio of 1·51 (95% confidence interval, 0·95–2·40; $P = 0·061$) adjusted for risk factors, including body temperature, sex, age, and history of impaired consciousness or abnormal behavior, by multivariate analysis of the proportional hazard model. This study also reported an increase in the incidence of unconsciousness with oseltamivir use, with a hazard ratio of 1·79 ($P = 0·0389$).[45] This discrepancy may have resulted partly from the different hypothesis and methodology and partly from the heterogeneity of the conditions studied, as described above. As a consequence, controversy remained unsettled over the adverse effects of oseltamivir in Japan.[5] It was impossible to exclude the possibility that oseltamivir slightly increased the risk of impairment of consciousness in Japanese children and adolescents infected with influenza.

Conclusions

Recent studies of acute encephalopathy clearly defined multiple syndromes, such as ANE, AESD, and MERS, and enabled classification of many of the influenza-associated cases into either of these conditions. Improved options for diagnosis and treatment were described in the Japanese guideline for influenza encephalopathy, contributing to the decline of fatality in Japan. Genetic predispositions and pathogenetic mechanisms have also been elucidated. By contrast, much remains obscure with regard to other neuropsychiatric syndromes, many of which are poorly defined. Their etiology and pathogenesis, as well as association with antiviral drugs, require further investigation.

Conflict of interests

The author has no competing interests to declare.

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