Journal of Clinical Virology 52 (2011) 307–313

Contents lists available at SciVerse ScienceDirect

Journal of Clinical Virology

journal homepage: www.elsevier.com/locate/jcv

Pediatric neurological complications associated with the A(H1N1)pdm09 influenza infection

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ARTICLE INFO

Article history:
Received 10 June 2011
Received in revised form 11 August 2011
Accepted 16 August 2011

Keywords:
Influenza-related neurological complications
A(H1N1)pdm09 influenza
Children
Basilar artery thrombosis
Acute necrotizing encephalopathy

ABSTRACT

Background: Influenza-related neurological complications (INC) have been reported during seasonal flu in children.
Objectives: To investigate the types, outcomes and incidence of INC occurring during the 2009 A(H1N1) pandemic, a retrospective analyze was conducted in the single French pediatric hospital of Lyon from October 2009 to February 2010.
Study design: All children presenting with fever, influenza-like illness, respiratory distress or neurological symptoms were tested for influenza A(H1N1)pdm09 infection from respiratory specimens using real time RT-PCR.
Results: INC occurred in 14 A(H1N1)pdm09 positive children (7.7% of A(H1N1)pdm09 positive children admitted to hospital) with a median age of 5.1 years. Admission to the intensive care unit (ICU) was required for nine children (64.3%). Half of the children with INC had comorbidity and three had coinfection, both characteristics mainly found in children requiring the ICU. All children received oral oseltamivir treatment. Febrile seizures were observed in eight children, half of them having a chronic comorbidity (2 epilepsy, 1 nonketotic hyperglycinemia, 1 anoxic encephalopathy). Other INC, less commonly reported, included 2 cases of encephalitis, 1 encephalopathy, 1 basilar artery thrombosis, 1 myasthenic crisis and 1 coma. Eleven of the 14 children (78.6%) recovered, one had a minor disability, one child developed a locked-in syndrome and one died from complications of an acute necrotizing encephalopathy.
Discussion: INC can be observed even in children with no underlying disorder. It may lead to dramatic issue in a significant number of cases.

1. Background

Influenza-related neurological complications (INC) are diverse and of variable severity and outcome. Febrile seizures, aseptic meningitis, acute and post-infectious encephalopathy/encephalitis, Reye syndrome, Guillain-Barré syndrome, stroke or decompensation of an underlying neurological disorder have been previously reported.[1] Febrile seizures are reported in 2–5% and 3–9% in children presenting with influenza-like illness (ILI) in North America/Europe and Taiwan, respectively.[2,3] In some cases, respiratory symptoms are mild while the central nervous system (CNS) symptoms are severe. Influenza-related encephalopathy/encephalitis is a rare complication with variable prognosis, mainly reported in Japan, affecting particularly children under 5 years of age.[2] The mortality rate is around 30%, and severe sequelae are observed in 9–40% of survivors.[4,5] During the 2009 A(H1N1) pandemic, neurological presentations were also reported in few series and in many case reports worldwide.[6–10] Severe cases with high morbidity and mortality have been described such as cerebral injuries,[11] acute necrotizing encephalopathy (ANE)[12] or intracranial hypertension.[13]

In France, a single pandemic wave was observed between week 43 and 52/2009 with a peak at week 48.[14] Overall, 1334 severe cases and 312 deaths were reported. Children under 5 years of age

Abbreviations: INC, influenza-related neurological complications; ICU, intensive care unit; ILI, influenza-like illness; CNS, central nervous system; HFME, Femme-Mère-Enfant Hospital; rRT-PCR, real time RT-PCR; MRI, magnetic resonance imaging; CSF, cerebral spinal fluid; WBC, white blood count.

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doi:10.1016/j.jcv.2011.08.018

represented 14% and 9% of the severe cases and death, respectively.[14] The proportion of neurological complications has not yet been reported.

2. Objectives

The present study describes the types and outcomes of INC observed during the first wave of 2009 A(H1N1) pandemic among children admitted to a single French pediatric hospital.

3. Study design

3.1. Case identification

The Femme-Mère-Enfant Hospital (HFME) of Lyon, France is the regional referral centre for pediatric infectious diseases and intensive care. It has 301 pediatric beds, 60,000 pediatric emergency visits each year, and serves a population of 1.6 million.

From 1 October 2009 to 1 February 2010, children (≤18 years old) admitted to HFME for fever, ILI, respiratory distress or neurological symptoms were tested for A(H1N1)pdm09 influenza infection using nasopharyngeal aspirations or swab samples. A retrospective study was performed to monitor A(H1N1)pdm09 positive children admitted to hospital with INC. INC were classified using definitions previously reported (Table 1).[1,7]

This study did not require any additional samples and was part of the classical diagnosis, in compliance with French laws and Hospices Civils de Lyon guidelines, and in accordance with the ethical standards of the Declaration of Helsinki. Patients were informed that "without any contrary opinion, the sample could be used for research or technical studies".

3.2. Virological analysis

Detection of A(H1N1)pdm09 was carried out by real time RT-PCR (rRT-PCR) on all respiratory specimens as previously described.[15] Other respiratory pathogens were also investigated, including rhinovirus (in house rRT-PCR as described in[16]), RSV (rRT-PCR, RSVA/B r-gene, Argene SA, Verniolle, France), *Mycoplasma pneumoniae* (in house rPCR as described in[17]) and parainfluenzae (in house ELISA as described in,[18] antibodies anti-parainfluenzae 1, 2 and 3 kindly provided by Dr. O. Ferraris).

All cerebrospinal fluids (CSF), when available, were tested using rPCR or rRT-PCR, at least for herpes simplex virus (SmartCycler®HerpesSimplex, Cepheid, Sunnyvale, CA, USA), enteroviruses (SmartCycler®Enterovirus, Cepheid) and influenza A viruses.[5] For some patients, the panel of viruses tested for in the CSF included varicella zoster virus (SmartCycler®Varicella, Cepheid), cytomegalovirus (CMV r-gene, Argene SA), Epstein Barr virus (EBV r-gene, Argene SA), HHV6 (HHV6 r-gene, Argene SA), *M. pneumoniae* and adenovirus (ADV r-gene, Argene), as part of the routine tests for detection of viral infections in patients with meningitis/encephalitis.

4. Results

During the first pandemic wave, 2353 children were tested for A(H1N1)pdm09 infection. Of the 654 positive children, 181 required admission to hospital and 24 of them (13.3%) were admitted to the ICU (Fig. 1). INC were observed in 14 children (7.7% of the A(H1N1)pdm09 positive children admitted). Seven children presented with classical ILI associating fever, cough and sore throat as respiratory signs, whereas the seven others had only fever as prodromal symptoms. Patients 1, 2 and 11 developed pneumonia. Neurological signs were absent at the onset of the fever or ILI

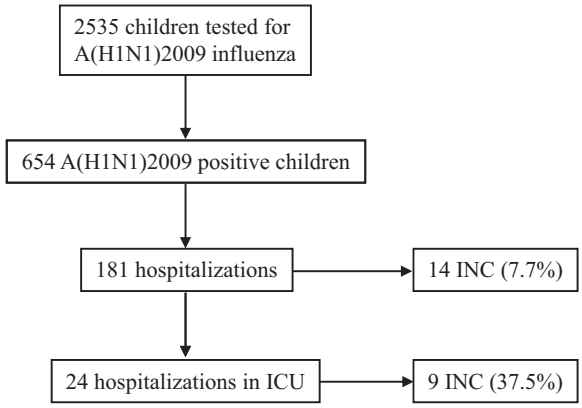

Fig. 1. Overview of INC in A(H1N1)pdm09 positive children admitted to hospital. ICU, intensive care unit; INC, influenza-related neurological complications.

symptoms in 10 of the 14 children. The median age of the A(H1N1)pdm09 positive children who developed INC was 5.1 years (interquartile range: 2.8–8.0 years). Clinical data are summarized in Table 2. Half of the children with INC had a previous and significant CNS history, and six of these seven children were admitted to the ICU. Three children, all admitted to the ICU, presented a coinfection with either *M. pneumoniae*, HHV6 or rhinovirus. All received oral oseltamivir treatment when admitted to hospital, leading to an onset of treatment varying from 0 to 7 days after onset of symptoms (Table 2). Of the 24 children in the ICU, nine (37.5%) presented severe INC, five of them requiring ventilation. The most frequent neurological presentation was febrile seizure (eight children, 57.1%). Two of them presented with simple febrile seizures, two with complex febrile seizures and four with other seizures related to an underlying chronic disease: 2 with epilepsy, 1 with nonketotic hyperglycinemia and 1 with anoxic encephalopathy. Other INC included 2 cases of encephalitis, 1 encephalopathy, 1 vertebro-basilar artery thrombosis, 1 myasthenic crisis and 1 coma complicating a maple syrup urine disease. Eleven of the 14 children (78.6%) rapidly recovered, one was left with a minor disability, one child developed a locked-in syndrome secondary to vertebro-basilar artery thrombosis (patient 1) and one died of a complicated encephalopathy (patient 2). With regard to the uncommon and severe neurological outcomes, clinical details, medical care and cerebral MRI of these two patients are described in Figs. 2 and 3.

5. Discussion

Although rare, INC can result in severe sequelae and even death. The real incidence of A(H1N1)pdm2009 CNS complications in France is unknown, but reports were described worldwide.[7,6] In our study, INC were observed in 7.7% of the children admitted to hospital with a proven A(H1N1)pdm2009 infection. This percentage is in accordance with previous studies, reporting 4–7.5% of neurological manifestations in children during the A(H1N1)pdm09 flu season, with frequent relatively severe complications (6 patients out of 14), which seems less consistent with the literature.[9,6,19–21] Before the A(H1N1)pdm09 pandemic, INC have been reported in 2.8% and 8.6% of Taiwanese and American children admitted to hospital, respectively,[1,3] and a 9-year Canadian and a 10-year Japanese studies reported 22 and 89 cases of acute encephalopathy/encephalitis, respectively.[4,5] It is extremely difficult to know whether A(H1N1)pdm09 INC are more common, similar, or less common than with seasonal influenza. Discrepancies may result from difference in INC clinical survey, some being restricted to acute encephalopathy/encephalitis,[5,6] from genetic susceptibility as in Japanese population,[6] from awareness of possible complications in