Neurological Manifestations of Influenza Infection in Children and Adults: Results of a National British Surveillance Study

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Background. The emergence of influenza A(H1N1) 2009 was met with increased reports of associated neurological manifestations. We aimed to describe neurological manifestations of influenza in adults and children in the United Kingdom that presented at this time.

Methods. A 2-year surveillance study was undertaken through the British adult and pediatric neurological surveillance units from February 2011. Patients were included if they met clinical case definitions within 1 month of proven influenza infection.

Results. Twenty-five cases were identified: 21 (84%) in children and 4 (16%) in adults. Six (29%) children had preexisting neurological disorders. Polymerase chain reaction of respiratory secretions identified influenza A in 21 (81%; 20 of which [95%] were H1N1) and influenza B in 4 (15%). Twelve children had encephalopathy (1 with movement disorder), 8 had encephalitis, and 1 had meningoencephalitis. Two adults had encephalopathy with movement disorder, 1 had encephalitis, and 1 had Guillain-Barré syndrome. Seven individuals (6 children) had specific acute encephalopathy syndromes (4 acute necrotizing encephalopathy, 1 acute infantile encephalopathy predominantly affecting the frontal lobes, 1 hemorrhagic shock and encephalopathy, 1 acute hemorrhagic leukoencephalopathy). Twenty (80%) required intensive care, 17 (68%) had poor outcome, and 4 (16%) died.

Conclusions. This surveillance study described a cohort of adults and children with neurological manifestations of influenza. The majority were due to H1N1. More children than adults were identified; many children had specific encephalopathy syndromes with poor outcomes. None had been vaccinated, although 8 (32%) had indications for this. A modified classification system is proposed based on our data and the increasing spectrum of recognized acute encephalopathy syndromes.

Keywords. influenza; H1N1; encephalopathy; classification; surveillance.

Neurological manifestations are an important complication of influenza infection. A wide variety of acute neurological presentations are reported, of which febrile seizures and encephalopathy are the most common, and approximately three-quarters of cases occur in children [1, 2]. In Japan, influenza is the most commonly identified pathogen in acute encephalopathy, and it is notifiable [3, 4]. In the United States and Australia, 6%–19% of children hospitalized with influenza infection have neurological manifestations [2, 5, 6]. With the increasing availability of magnetic resonance imaging (MRI) and newer imaging modalities, the generic term "influenza-related...
encephalopathy” has been subclassified into a range of specific acute encephalopathy syndromes (AESs), for example, acute necrotizing encephalopathy (ANE) [7, 8]. Fewer specific AESs have been described in adults, but acute hemorrhagic leukoencephalopathy (AHL) appears to be important [9]. Identification and description of AESs is useful to help predict the prognosis and ultimately will improve our understanding of the pathophysiology of these disorders. For example, the delineation of ANE and the description of familial cases led to the discovery of inherited mutations in the Ran-binding protein 2 (RANBP2) gene [10].

The emergence of novel influenza A(H1N1) 2009 led to an increase in reports describing related neurological manifestations, many in non-Japanese populations [2, 5, 6, 11]. H1N1 2009 may be associated with more frequent and severe neurological manifestations [5, 12]. Most case series have been restricted to either adults or children and have not used standardized case definitions. We therefore undertook a national surveillance study to examine the neurological manifestations of influenza in adults and children across the United Kingdom. We report here the spectrum of manifestations seen and their sequelae, describe selected patients with a specific AES in more detail, and propose a modification of the current classification system [8].

**METHODS**

A multicenter surveillance study of children and adults was performed through the British Pediatric Neurology Surveillance Unit and British Neurological Surveillance Unit between February 2011 and February 2013. Cases identified in the preceding 6 months were notified in response to a monthly email to all members of the British Pediatric Neurology Association (BPNA) and the Association of British Neurologists (ABN), respectively. Four cases had been previously reported [13].

Cases with an acute neurological presentation occurring within 1 month of proven influenza infection were included and were defined as positive polymerase chain reaction (PCR) for influenza RNA from throat or nasal swab, respiratory secretions, serum, or cerebrospinal fluid (CSF). Clinical case definitions were adapted from those used previously for central nervous system (CNS) infections based on the presenting clinical features, CSF, and neuroimaging findings (Table 1) [14, 15]. Children were defined as those aged <18 years.

A standardized data collection pro forma was sent to the notifying clinician to request detailed clinical information including the presentation, investigations, and the Glasgow Outcome Scale (Table 2) [16]. This study fell within the remit of surveillance and therefore did not require formal ethical approval [17].

**RESULTS**

The overall response rate over 2 years was 36% from BPNA (n = 311) and 49% from ABN members (n = 1022). All 25 notified patients met the inclusion criteria; 21 (84%) were children. Twelve children had encephalopathy (1 with movement disorder), 8 had encephalitis, and 1 had meningoencephalitis. Two adults had encephalopathy with movement disorder, 1 had encephalitis, and 1 had Guillain-Barré syndrome. For 7 patients, 6 children and 1 adult, a specific AES was documented: 4 ANE, 1 AIEF (acute infantile encephalopathy predominantly affecting the frontal lobes), 1 HSES (hemorrhagic shock and encephalopathy syndrome), and 1 AHL.

The median age of the children was 4 years (range 9 months to 14 years) and of the adults was 42 years (range, 26 years to 48 years). The overall male-to-female ratio was 1:1.5. Twenty-two (88%) were white and 3 (12%) were of South Asian ethnicity. Preexisting neurological diagnoses were present in 6 (28%) children: 1 each with Sanfilippo syndrome, trisomy 21, Wolf-Hirschhorn syndrome, and idiopathic generalized epilepsy, and 2 with developmental delay and epilepsy of unknown etiology. None of these 6 children had received influenza vaccination, nor had 2 of the adults with preexisting asthma. No patients were immunosuppressed. Details of clinical presentation, investigations, diagnosis, treatment, and outcome are summarized in Table 2.

At presentation, fever and/or respiratory symptoms were present in all patients, 12 (48%) had seizures, and 3 (12%) had circulatory shock. An acute movement disorder was seen in 3 patients: 2 adults had acute parkinsonism and the child with Sanfilippo syndrome had acute nonepileptic myoclonus and dystonia.

Influenza A was detected by PCR in the respiratory secretions of 21 (84%) patients, of whom 20 (95%) had the H1N1 (2009) subtype; influenza B was detected in the respiratory secretions of 4 (16%) patients. Two patients had coinfection with Streptococcus pneumoniae: a child with pneumococcal meningitis and 1 adult with meningitis only.

**Table 1. Case Definitions for Influenza-Related Acute Neurological Illnesses**

<table>
<thead>
<tr>
<th>Definition</th>
<th>Description</th>
<th>CSF White Cell Count</th>
<th>MRI Consistent with Inflammation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Encephalopathy only</td>
<td>Alteration in consciousness including behavioral changes with no evidence of inflammation in the CNS.</td>
<td>&gt;4 cells/mm³</td>
<td></td>
</tr>
<tr>
<td>Encephalitis—encephalopathy (as above) with evidence of CNS inflammation</td>
<td>(CSF white cell count &gt;4 cells/mm³, or MRI consistent with inflammation).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meningitis—meningitis (as detailed above) in a conscious patient, with</td>
<td>A CSF white cell count of 5–20 cells/mm³, or 20–1000 cells/mm³ with a lymphocyte predominance.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meningoencephalitis—meningitis and encephalopathy (as detailed above)</td>
<td>With evidence of CNS inflammation (as detailed above).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guillain-Barré/Fisher syndrome—ascending sensory-motor flaccid,</td>
<td>Areflexic paralysis, or the triad of ophthalmoplegia, ataxia, and areflexia.</td>
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<td></td>
</tr>
</tbody>
</table>

**Table 2. Patients With Influenza-Related Acute Neurological Illnesses**

<table>
<thead>
<tr>
<th>AES Subtype</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Preexisting Diagnosis</th>
<th>Presenting Symptom(s)</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANE</td>
<td>4</td>
<td>M</td>
<td>None</td>
<td>Fever, headache</td>
<td>Antiviral</td>
<td>Death</td>
</tr>
<tr>
<td>AIEF</td>
<td>1</td>
<td>F</td>
<td>Sanfilippo Syndrome</td>
<td>Acute parkinsonism</td>
<td>Antiviral</td>
<td>Partial</td>
</tr>
<tr>
<td>HSES</td>
<td>12</td>
<td>M</td>
<td>None</td>
<td>Status asthmaticus</td>
<td>None</td>
<td>Death</td>
</tr>
<tr>
<td>AHL</td>
<td>42</td>
<td>M</td>
<td>None</td>
<td>Seizures</td>
<td>Antiviral</td>
<td>Recover</td>
</tr>
</tbody>
</table>

Abbreviations: CNS, central nervous system; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging.
<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Sex</th>
<th>Acute Clinical Presentation (and Any Neurological Comorbidity)</th>
<th>Influenza Subtype</th>
<th>Respiratory Secretions</th>
<th>Laboratory Values&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Head CT</th>
<th>Brain MRI</th>
<th>Clinical Case Definition</th>
<th>Diagnosis</th>
<th>Oseltamivir Treatment</th>
<th>Adjunctive Treatment</th>
<th>Days in ICU</th>
<th>GOS&lt;sup&gt;b&lt;/sup&gt; (Pre-) and Post-Illness</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9 mo</td>
<td>F</td>
<td>Fever, vomiting, hypotonia, seizures (known microcephaly, epilepsy, &amp; developmental delay)</td>
<td>A(H1N1)</td>
<td>Not performed</td>
<td>Low attenuation periventricular white matter</td>
<td>T2 hyperintensity of bilateral thalamus, dorsal midbrain, &amp; pons with associated diffusion restriction. Mild swelling of thalami.</td>
<td>Encephalitis</td>
<td>ANE</td>
<td>Given</td>
<td>Nil relevant</td>
<td>2</td>
<td>(5) 3</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>10 mo</td>
<td>M</td>
<td>Coryza, croup, and encephalopathy (known trisomy 21)</td>
<td>A(H1N1)</td>
<td>Not performed</td>
<td>Normal</td>
<td>Not performed</td>
<td>Encephalopathy</td>
<td>Acute benign encephalopathy</td>
<td>Given</td>
<td>Nil relevant</td>
<td>3</td>
<td>(5) 5</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>12 mo</td>
<td>F</td>
<td>Coryza and status epilepticus (known Wolf-Hirschhorn syndrome)</td>
<td>A(H1N1)</td>
<td>Not performed</td>
<td>Not performed</td>
<td>Not performed</td>
<td>Encephalopathy</td>
<td>Acute benign encephalopathy</td>
<td>Given</td>
<td>Nil relevant</td>
<td>1</td>
<td>(4) 4</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>12 mo</td>
<td>M</td>
<td>Coryza, dyspnea, encephalopathy, circulatory shock</td>
<td>A(H1N1)</td>
<td>Normal</td>
<td>Normal</td>
<td>Bilateral signal abnormality &amp; restricted diffusion in frontal &amp; medial parietal cortex</td>
<td>Encephalitis</td>
<td>AIEF</td>
<td>Given</td>
<td>Nil relevant</td>
<td>25</td>
<td>(5) 3</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>13 mo</td>
<td>M</td>
<td>Fever and status epilepticus</td>
<td>A(H1N1)</td>
<td>Normal</td>
<td>Normal</td>
<td>Not performed</td>
<td>Encephalopathy</td>
<td>Acute benign encephalopathy</td>
<td>Given</td>
<td>Nil relevant</td>
<td>0</td>
<td>(5) 5</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>15 mo</td>
<td>M</td>
<td>Fever &amp; status epilepticus (known developmental delay &amp; epilepsy)</td>
<td>A(H1N1)</td>
<td>Not performed</td>
<td>Not performed</td>
<td>Evidence of subtle cortical dysplasia on preillness MRI</td>
<td>Encephalopathy</td>
<td>Acute benign encephalopathy</td>
<td>Given</td>
<td>Dex</td>
<td>12</td>
<td>(4) 4</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>18 mo</td>
<td>F</td>
<td>Fever, encephalopathy, &amp; right-sided focal seizures</td>
<td>B</td>
<td>Clotted specimen, culture: no growth</td>
<td>Normal</td>
<td>Left cerebral generalized subcortical &amp; thalamic restricted diffusion secondary to seizures</td>
<td>Encephalopathy</td>
<td>Acute benign encephalopathy</td>
<td>Given</td>
<td>Nil relevant</td>
<td>13</td>
<td>(5) 4</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>19 mo</td>
<td>F</td>
<td>Fever and status epilepticus</td>
<td>B</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Encephalopathy</td>
<td>Acute benign encephalopathy</td>
<td>Given</td>
<td>Nil relevant</td>
<td>1</td>
<td>(4) 4</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>2 y</td>
<td>M</td>
<td>Fever, vomiting, encephalopathy, coagulopathy</td>
<td>A(H1N1)</td>
<td>Not performed</td>
<td>Thalami, basal ganglia, and brain stem swelling</td>
<td>Bilateral symmetrical lesions in thalam, putamina, cerebral, &amp; cerebellar white matter &amp; brain stem with marked cerebral edema</td>
<td>Encephalitis</td>
<td>ANE</td>
<td>Given</td>
<td>Man, MP, IVIG</td>
<td>3</td>
<td>(5) 1</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>3 y</td>
<td>F</td>
<td>Coryza, fever, seizures, coagulopathy, &amp; circulatory shock</td>
<td>A(H1N1)</td>
<td>Not performed</td>
<td>Diffuse cerebral edema</td>
<td>Not performed</td>
<td>Encephalitis</td>
<td>HSES</td>
<td>Given</td>
<td>Man</td>
<td>1</td>
<td>(5) 1</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>4 y</td>
<td>F</td>
<td>Coryza &amp; prolonged generalized seizure</td>
<td>A(H1N1)</td>
<td>Normal</td>
<td>Normal</td>
<td>Bilateral T2 hyperintensity of dentate nuclei, pons, midbrain, thalami, &amp; subcortical white matter of both cerebral hemispheres.</td>
<td>Encephalitis</td>
<td>ANE</td>
<td>Given</td>
<td>Nil relevant</td>
<td>4</td>
<td>(5) 5</td>
<td></td>
</tr>
<tr>
<td>Case</td>
<td>Age</td>
<td>Sex</td>
<td>Acute Clinical Presentation (and Any Neurological Comorbidity)</td>
<td>Influenza Subtype Respiratory Secretions</td>
<td>Laboratory Values*</td>
<td>Head CT</td>
<td>Brain MRI</td>
<td>Clinical Case Definition</td>
<td>Diagnosis</td>
<td>Oseltamivir Treatment</td>
<td>Adjunctive Treatment</td>
<td>Days in ICU</td>
<td>GOS (Pre- and Post-illness)</td>
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<tr>
<td>12</td>
<td>4 y</td>
<td>F</td>
<td>Fever, lethargy, rash, and vomiting</td>
<td>B Normal</td>
<td>Not performed</td>
<td>Not performed</td>
<td>Encephalopathy</td>
<td>Acute benign encephalopathy</td>
<td>Given</td>
<td>Nil relevant</td>
<td></td>
<td>0 (5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>5 y</td>
<td>F</td>
<td>Coryza &amp; status epileptic</td>
<td>A(H1N1) Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Encephalopathy</td>
<td>Acute benign encephalopathy</td>
<td>Given</td>
<td>Nil relevant</td>
<td></td>
<td>3 (5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>6 y</td>
<td>M</td>
<td>Coryza, fever, &amp; seizures (known previous febrile seizures)</td>
<td>A(H1N1) Normal</td>
<td>Occipital lobe calcification</td>
<td>Bilateral T2 hyperintensity &amp; mild occipital focal atrophy related to previous ischemic insult</td>
<td>Encephalopathy</td>
<td>Acute benign encephalopathy</td>
<td>Given</td>
<td>Nil relevant</td>
<td></td>
<td>2 (5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>8 y</td>
<td>F</td>
<td>Coryza, fever, encephalopathy, &amp; cranial nerve VI palsy</td>
<td>A(H1N1) Normal</td>
<td>Not performed</td>
<td>T2 hyperintensity in pons, posteromedial thalami, &amp; the right external capsule</td>
<td>Encephalitis</td>
<td>ANE</td>
<td>Given</td>
<td>MP, IVIG</td>
<td></td>
<td>0 (5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>10 y</td>
<td>M</td>
<td>Encephalopathy, &amp; status epileptic</td>
<td>A(H1N1) wcc 16, rcc 1, protein 2.09, glucose 3.8, no growth</td>
<td>Normal</td>
<td>Normal</td>
<td>Encephalitis</td>
<td>Acute benign encephalitis</td>
<td>Given</td>
<td>IVIG</td>
<td></td>
<td>14 (5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>11 y</td>
<td>M</td>
<td>Coryza, fever, vomiting, encephalopathy, &amp; seizures</td>
<td>B wcc 184, rcc 140, protein 1.02, glucose 4.2, no growth</td>
<td>Normal</td>
<td>Normal</td>
<td>Encephalitis</td>
<td>Acute benign encephalitis</td>
<td>Given</td>
<td>Nil relevant</td>
<td></td>
<td>3 (5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>12 y</td>
<td>F</td>
<td>Fever, headache, encephalopathy, and photophobia</td>
<td>A(H1N1) wcc 900, rcc 1200, protein 4.8, glucose &lt;0.1, culture: S. pneumoniae</td>
<td>Normal</td>
<td>Cerebellar tonsilar herniation with ischemia at the craniocervical junction</td>
<td>Meningoencephalitis</td>
<td>Meningoencephalitis</td>
<td>Given</td>
<td>Dex</td>
<td></td>
<td>5 (5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>13 y</td>
<td>F</td>
<td>Fever, headache, irritability, &amp; encephalopathy</td>
<td>A(non-H1N1) Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Encephalopathy</td>
<td>Acute benign encephalopathy</td>
<td>Given</td>
<td>MP, IVIG</td>
<td></td>
<td>0 (5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>13 y</td>
<td>F</td>
<td>Fever, headache, &amp; acute facial and upper limb dyskinesia (known Sanfilippo syndrome)</td>
<td>A(H1N1) wcc 0, protein &amp; glucose normal, low CSF pyridoxal 5-phosphate, normal CSF neurotransmitters</td>
<td>Not performed</td>
<td>Changes consistent with Sanfilippo syndrome, no acute lesions</td>
<td>Encephalopathy &amp; movement disorder</td>
<td>Acute dyskinesia with low CSF pyridoxal 5-phosphate</td>
<td>Not given</td>
<td>Pyridoxal phosphate (resolution)</td>
<td></td>
<td>0 (3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>14 y</td>
<td>F</td>
<td>Coryza &amp; status epileptic (known idiopathic generalized epilepsy)</td>
<td>A(H1N1) Not performed</td>
<td>Normal</td>
<td>Not performed</td>
<td>Encephalopathy</td>
<td>Acute benign encephalopathy</td>
<td>Given</td>
<td>Nil relevant</td>
<td></td>
<td>1 (4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>26 y</td>
<td>F</td>
<td>Fever, headache, irritability, &amp; intermittent resting tremor right hand, upper limb rigidity</td>
<td>A(H1N1) Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Encephalopathy &amp; movement disorder</td>
<td>Acute benign encephalopathy with movement disorder</td>
<td>Given</td>
<td>Nil relevant</td>
<td></td>
<td>67 (5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>42 y</td>
<td>M</td>
<td>Fever, encephalopathy, circulatory shock, &amp; cranial diabetes insipidus</td>
<td>A(H1N1) Not performed</td>
<td>Significant cerebral edema</td>
<td>Not performed</td>
<td>Encephalitis</td>
<td>AHL</td>
<td>Given</td>
<td>HC</td>
<td></td>
<td>9 (5)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
meningitis (case 18) and an adult with pneumococcal sepsis (case 23), both of whom died.

All patients with AES had normal renal function, serum electrolytes, glucose level, and ammonia level. Alanine transaminase (ALT) was raised in the 3 children with AES (described in further detail below). Two children with ANE were tested for the RANBP2 mutation and 1 had positive results (case 15).

Eighteen (72%) patients had CSF examination and 7 had clinical contraindications to a lumbar puncture. The CSF was abnormal in 4 (22%) patients: 3 had pleocytosis (median, 184 [range, 16–900] × 10⁶ cells/L), and the child with Sanfilippo syndrome had an unexplained low-pyridoxal 5-phosphate. All CSF samples underwent Gram staining and bacterial culture; 1 sample (from case 18) grew *S. pneumoniae* and all others were negative. CSF was tested for influenza RNA by PCR in 10 (53%) patients, and oligoclonal bands were tested in 3 patients; all results were negative.

Electroencephalography (EEG) was undertaken in 12 patients: 8 had abnormal results, 6 showed diffuse slowing of the background activity in keeping with an encephalopathy, and 2 had low-amplitude, impoverished recordings in keeping with severe bichemispheric dysfunction. None showed epileptiform activity.

Cerebral imaging was performed in 23 patients; 3 had MRI, 6 had computed tomography (CT), and 14 had both. Abnormalities included specific AES in 5, and nonspecific changes including cerebral edema or diffusion restriction in 5 patients.

Twenty patients (80%) required admission to an intensive care unit; the median length of stay was 3 days (range, 1–67 days). Oseltamivir was commenced in 23 (92%) patients. Presumptive antibiotic therapy with a third-generation cephalosporin for suspected meningitis was started for 18 (72%) patients, 9 of whom also received clarithromycin. Twelve (48%) were also treated empirically with acyclovir. Using the Glasgow Outcome Scale (GOS), 8 patients (32%) had a good outcome, 13 (52%) had a poor outcome, and 4 (16%) had a very poor outcome, all of whom died. Median deterioration in GOS from preillness baseline was 0 (range, 0–4) for those who did not have a specific AES, and 1.5 (range, 0–4) for ANE. Deterioration from baseline GOS was 2 for AIEF, and 4 for HSES and AHL.

**CASE REPORTS**

Below are further descriptions illustrating the particular clinical and radiological features of 4 patients, to help clinicians recognize these rare manifestations of influenza.

**Case 4—Acute Infantile Encephalopathy Predominantly Affecting the Frontal Lobes**

A 1-year-old white boy presented with a 2-day coryzal illness. On examination, he was floppy, with respiratory distress, circulatory shock, and decorticate posturing. A plain chest

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**Table 2 continued.**

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Sex</th>
<th>Clinical Case Definition</th>
<th>Diagnosis</th>
<th>Laboratory Valuesa</th>
<th>Head CT</th>
<th>Brain MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>42 y M</td>
<td>Fever, headache, neck stiffness</td>
<td>Acute encephalopathy &amp; movement disorder</td>
<td>Guillain-Barré syndrome</td>
<td>CSF, white and red cell count/mm³: 75, protein, 0.9 g/L; glucose, 2.5 mmol/L</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>25</td>
<td>48 y F</td>
<td>Ascending flaccid paralysis</td>
<td>Acute benign encephalopathy with movement disorder</td>
<td>Guillain-Barré syndrome</td>
<td>CSF, white and red cell count/mm³: 75, protein, 0.9 g/L; glucose, 2.5 mmol/L</td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>

Abbreviations: AIEF, acute infantile encephalopathy predominantly affecting the frontal lobes; AES, acute encephalopathy with movement disorder; ANE, acute necrotizing encephalopathy; CSF, cerebrospinal fluid; CT, computed tomography; Dex, dexamethasone; GOS, Glasgow Outcome Scale; HC, hydrocortisone; HSES, hemorrhagic shock and encephalopathy syndrome; ICU, intensive care unit; IVIG, intravenous immunoglobulin; Man, mannitol; MRI, magnetic resonance imaging; Nil, none; rcc, red cell count; wcc, white cell count.

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radiograph demonstrated patchy changes bilaterally. A CT brain scan was normal. Intensive care was required and antimicrobial treatment included cefotaxime, clarithromycin, acyclovir, and oseltamivir.

The ALT level was elevated (1319 IU/L). An MRI brain scan (day 10) demonstrated cerebral atrophy and bilateral symmetrical restricted diffusion involving the frontal cortex (Figure 1). He had severe sequelae: a tracheostomy was necessary, and at 6 months he was unable to sit unaided or use his hands for purposeful activities and was mute. Bulbar function was abnormal, and he required a percutaneous gastrostomy.

Case 9—Acute Necrotizing Encephalopathy
A previously well 2-year-old white boy presented with a 2-day history of pyrexia, diarrhea, and vomiting. Over several hours, his Glasgow Coma Score dropped to 4/15, and he developed signs of raised intracranial pressure. He was mechanically ventilated and received intravenous mannitol, ceftriaxone, acyclovir, and oseltamivir. An initial CT of the brain demonstrated edema of the thalami, basal ganglia, and brainstem.

He developed acute renal and liver failure (ALT, 13 713 IU/L) with coagulopathy. The brain MRI (day 5) demonstrated multiple symmetrical lesions in the thalami (Figure 2). He died despite treatment with intravenous methylprednisolone and immunoglobulin. Investigations to look for underlying metabolic, genetic, and autoimmune causes were negative.

Case 10—Hemorrhagic Shock and Encephalopathy Syndrome
A 3-year-old girl of South Asian ethnicity presented with a 2-day coryzal illness and a brief generalized tonic-clonic seizure. She was drowsy with refractory circulatory shock. Initial antimicrobial treatment included ceftriaxone and acyclovir. During intubation, she became bradycardic and required cardiopulmonary resuscitation.

She developed acute renal and hepatic failure, coagulopathy, hypernatremia, and lactic acidosis. ALT was markedly raised (3192 IU/L). The CT brain scan demonstrated diffuse cerebral edema. Antimicrobial cover was broadened to include cefotaxime, clarithromycin, oseltamivir, and acyclovir. Twelve hours after presentation, she had signs of brainstem death and bilateral retinal hemorrhages; treatment was withdrawn.

Case 23—Acute Hemorrhagic Leukoencephalopathy
A 42-year-old white woman with well-controlled asthma presented with a 1-day history of left-sided pleuritic chest pain, dyspnea, and pyrexia. She was started on co-amoxiclav and clarithromycin; subsequently, piperacillin/tazobactam and oseltamivir were added. She deteriorated, requiring vaspressors and invasive ventilation.

Blood cultures grew S. pneumoniae, and antibiotic cover was narrowed to intravenous benzylpenicillin according to sensitivities. Initial CT scanning of the brain demonstrated significant cerebral edema, and EEG reflected severe encephalopathy. The patient was treated with mannitol and mechanical hyperventilation. Three days later, a further brain CT demonstrated worsening cerebral edema (Figure 3). She lost brain stem reflexes, and care was withdrawn. Postmortem examination demonstrated AHL.

DISCUSSION
Influenza-related neurological manifestations were first reported in 1918 [18]. There were then few reports until the 1990s, when increasing descriptions of influenza-related acute encephalopathy emerged predominantly from Japan [3]. Since the emergence of
The other pediatric AES cases we identified (HSES and AIEF) had typical presentations. HSES was first described by Levin et al in 1983, as a high-mortality condition presenting with hyperpyrexia, encephalopathy, diarrhea, circulatory shock, multisystem dysfunction, and coagulopathy [26]. Neuroimaging typically demonstrates cerebral edema [27]. Various pathogens have been linked to the condition, including rotavirus and adenovirus [27]. As the shock in HSES is not precipitated by hemorrhage, we propose revised nomenclature: acute shock with encephalopathy and multiorgan failure, or ASEM. First described by Yamanouchi and Mizuguchi in 2006, AIEF is characterized of these conditions. Despite the relatively similar clinical presentation of severe acute febrile encephalopathy in our patients with a specific AES, there were marked differences in neuroimaging findings. Of the 4 case examples described above, 2 had differing patterns of focal cerebral involvement (ANE and AIEF) and 2 had diffuse cerebral edema (HSES and AHL). Mild encephalitis/encephalopathy with reversible splenial lesion was not reported in our study. We classified encephalopathic cases in our cohort that did not fulfill criteria for a specific AES as “acute benign encephalopathy/encephalitis”; all patients had either normal neuroimaging or minor abnormalities, and all but 1 (case 13) had minimal residual effects. Using data from our study, and additional reports in the published literature, we propose an expanded version of the categorization of neurological manifestations of influenza developed by Akins et al (Table 3) [8, 9, 22–24]. This expanded categorical table contains the most up-to-date list of AESs reported, incorporating prognostic information from our cohort.

Acute encephalopathy syndromes such as ANE are characterized by their neuroimaging, and to a lesser extent their clinical presentation. ANE, first described by Mizuguchi et al in 1995, is characterized by bilateral, symmetrical necrotic lesions affecting the thalami [7]. Whereas influenza is the most common associated pathogen, human herpesvirus 6 has also been frequently described [4, 7]. Supportive investigations for ANE include elevated serum aminotransferases, raised CSF protein, and characteristic neuroimaging. Of our 4 patients with ANE, 3 had typical neuroimaging (cases 1, 9, and 11), and 1 child (case 15) atypically had more prominent brainstem lesions. She had suffered a previous episode of influenza-related encephalopathy, which prompted testing for RANBP2 mutations: this was positive for the previously described p. Ile656Val mutation, which was subsequently also found in her mother and maternal grandmother [10]. Mutations of RANBP2 (a nuclear pore protein) are associated with familial and recurrent ANE characterized by autosomal dominant inheritance and incomplete penetrance [10]. Particular markers of a poor prognosis in ANE include hemorrhagic lesions or cavitation on neuroimaging, although these were not found in those with poor outcomes in our study [25].

Figure 3. Axial unenhanced computed tomography of the brain of case 23, who had acute hemorrhagic leukoencephalopathy, on admission, demonstrating diffuse cerebral edema, loss of gray-white matter differentiation, and effacement of the basal cisterns.

neurological manifestations of influenza through British adult and pediatric neurological surveillance units. In contrast to the majority of previous series, our cohort represents a more severe spectrum of neurological manifestations: 4 died, 13 had poor outcomes, and 20 required intensive care unit management [5, 6, 11]. Many of those with poor outcomes had a specific AES. More children than adults were identified, and neurological manifestations were commonly observed in children with preexisting neurological diagnoses, an unexplained but well-reported phenomenon [2, 19, 20].

In our cohort we describe the clinical and radiological features of a variety of specific AESs, in contrast to the existing literature, which consists predominantly of isolated case reports

of novel influenza A(H1N1) 2009, there has been considerable global interest. The first report described 4 children from the United States with seizures and/or encephalopathy, all of whom recovered [11]. Subsequently, pediatric case series have described a variety of neurological manifestations, ranging in severity from febrile seizures to specific AESs associated with poor outcomes [2, 6, 19, 20]. The corresponding adult literature is predominantly confined to single case reports [9]. There is limited evidence that H1N1 2009 is associated with more severe forms of acute encephalopathy compared with pre-2009 influenza subtypes [5]. The incidence of neurological manifestations has been estimated at 1.2 per 100 000 symptomatic H1N1 2009 infections [1]. However, good epidemiological data are limited, due in part to a lack of standardized case definitions, such as the generic term “influenza-associated encephalopathy/encephalitis” [1, 21].

We prospectively applied clinical case definitions to undertake the first study of neurological manifestations of influenza through British adult and pediatric neurological surveillance units. In contrast to the majority of previous series, our cohort represents a more severe spectrum of neurological manifestations: 4 died, 13 had poor outcomes, and 20 required intensive care unit management [5, 6, 11]. Many of those with poor outcomes had a specific AES. More children than adults were identified, and neurological manifestations were commonly observed in children with preexisting neurological diagnoses, an unexplained but well-reported phenomenon [2, 19, 20].
by fever, encephalopathy, seizures, and radiological changes in
the frontal lobes [23]. Frontal lobe dysfunction, such as speech
regression, typifies the sequelae, as in our patient (case 4). It
has been regarded as a subtype of acute encephalopathy with biphase
seizures and late reduced diffusion, and has been reported in
association with human herpesvirus 6, measles, and pre-2009
influenza subtypes [23, 28]. We are not aware of any other cases
reported in association with influenza A(H1N1) 2009.

AESs are rare in adults; we identified 2 patients with AHL.
AHL is characterized by acute encephalopathy with diffuse
hemorrhagic necrosis and perivenular demyelination of the
brain and spinal cord, with characteristic EEG and MRI find-
ings [29]. It has been associated with several infections, includ-
ing *Mycoplasma pneumoniae* and Epstein-Barr virus [30, 31]. A
previous reported case with H1N1 2009 was associated with
poor outcome, similar to that in our patient (case 23) [9].

Most patients in our study presented during the period when
influenza A(H1N1) 2009 was the predominant subtype in cir-
culation, which thus accounts for the majority of isolates in our
cohort [32]. Influenza viruses do not appear to demonstrate
neurotropism, and viral RNA is rarely identified in the CSF [8].
There is unlikely to be a single mechanism underlying the path-
ophysiology of the wide spectrum of neurological manifesta-
tions of influenza. Some have suggested that duration of
influenza-like illness preceding neurological manifestations
may afford distinction into 2 broad categories: (1) acute, in
association with an innate immune response and a “cytokine
storm,” and (2) subacute, with an adaptive, cell-mediated re-
response [8]. Increased concentrations of proinflammatory
cytokines have been found in the serum and CSF of children
with neurological manifestations of influenza [33]. Adaptive
immune-mediated pathophysiology is associated with subacute
neurological syndromes, including Guillain-Barré syndrome
[34]. Although none of those in our cohort had evidence of
inborn errors of metabolism, the thermolabile phenotype of
carnitine palmitoyltransferase II may precipitate dysfunctional
fatty acid oxidation during fever with influenza; such variations
may be more common in East Asians [35].

Coinfection with *S. pneumoniae* was observed in 2 patients
(cases 18 and 23); both developed malignant cerebral edema
and died. It is possible that the poor outcome of these patients
is solely attributable to invasive pneumococcal disease.
However, pneumococcal/influenza respiratory coinfection is a
recognized distinct clinical entity associated with poor outcome
[36, 37]. While the pathophysiology underlying the synergy
between the 2 organisms is poorly understood, proposed
factors include the role of influenza virulence factors in epithe-
lial damage and subsequent facilitated entry of pneumococcus,
as well as upregulation of the inflammatory response [38].

The management of AESs is largely supportive, and there are
no randomized trials of specific therapies. Early steroid treat-
ment in ANE is thought to be beneficial, but the efficacy of in-
travenous immunoglobulin remains uncertain [39].

Influenza vaccination programs decrease the burden of influen-
za infection [40]. Vaccination is also likely to be important in
the prevention of neurological manifestations of influenza.
None of our cohort had received influenza vaccination, despite
8 patients having clinical indications (of whom 3 died and 5

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**Table 3. Proposed Classification of Neurological Manifestations of Influenza**

<table>
<thead>
<tr>
<th>Acute Onset—Cytokine Storm</th>
<th>Subacute Onset—Adaptive Immune Responses</th>
<th>Late Onset—Unknown Pathophysiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Febrile seizures</td>
<td>Guillain-Barré syndrome</td>
<td>Post-viral parkinsonism</td>
</tr>
<tr>
<td>Acute movement disorder</td>
<td>Transverse myelitis</td>
<td>Encephalitis Lethargica</td>
</tr>
<tr>
<td>Acute benign encephalopathy/encephalitis</td>
<td>Acute disseminated encephalomyelitis (ADEM)</td>
<td></td>
</tr>
<tr>
<td>Acute encephalopathy syndromes (AESs): Mild encephalitis/encephalopathy with reversible splenial lesion (MERS)</td>
<td>Myelitis</td>
<td></td>
</tr>
<tr>
<td>Acute encephalopathy with biphasic seizures and late reduced diffusion (AESD)</td>
<td>Cerebellitis</td>
<td></td>
</tr>
<tr>
<td>Acute infantile encephalopathy predominantly affecting the frontal lobes (AIEF)</td>
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<tr>
<td>Acute shock with encephalopathy and multiorgan failure (ASEM)*</td>
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<tr>
<td>Acute hemorrhagic leukoencephalopathy (AHL)</td>
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</table>

* Proposed revised nomenclature for hemorrhagic shock and encephalopathy syndrome (HSES). Source: Adapted from Akins et al [8].
had poor outcomes). This may reflect wider systematic challenges in delivering influenza vaccination to at-risk groups in the United Kingdom [41].

A limitation of our study is that the reporting system relies on the willingness of individual clinicians to notify patients; some UK centers reported several cases whereas others reported none. The overall reporting rates were low (especially in pediatrics); therefore, we were unable to report an incidence of adults and children with neurological manifestations of influenza. The overall reporting rates were low (especially in pediatrics); UK centers reported several cases whereas others reported none. We therefore, were unable to report an incidence of adults and children with neurological manifestations of influenza. The overall reporting rates were low (especially in pediatrics); therefore, we were unable to report an incidence figure. Our methodology is likely to have led toward a bias favoring more severe cases, because the reporting was via neurologists rather than general clinicians. Effective surveillance systems and the use of standardized case definitions will be crucial to the success of similar epidemiological work in the future.

In conclusion, this UK surveillance study described a cohort of adults and children with neurological manifestations of influenza, many with poor outcomes. None of the patients had been vaccinated despite indications, and therefore their deaths or poor outcome may have been prevented. A broad spectrum of acute encephalopathy syndromes was identified, frequently associated with poor outcomes. These data are used to propose a new classification of influenza-related neurological manifestations.

Notes

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References