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References


Cerebellitis Associated with Influenza A(H1N1)pdm09, United States, 2013

To the Editor: Central nervous system (CNS) manifestations of influenza are uncommon, especially in adults (1,2), and influenza-associated cerebellitis is exceedingly rare: 8 cases have been reported (3–7; online Technical Appendix). We describe a case of cerebellitis caused by influenza A(H1N1)pdm09 in an adult woman.

The 37-year-old female patient who sought medical care in Florida, United States, on January 5, 2013, described a 4-day history of intermittent fever of 38.5°C, generalized fatigue, diffuse headache, mild nonproductive cough, 3 episodes of vomiting, and decreased oral intake. On January 4, she experienced acute onset of ataxia and dysarthric speech with slurred pronunciation. She reported no contact with sick persons, recent travel, or exposure to pets or birds. She had a medical history of asthma since childhood, controlled by using montelukast tablets and inhaled steroids. The patient denied having ever received an influenza vaccination.

The patient appeared ill; her oral temperature was elevated at 38.3°C, but other vital signs were within normal limits (blood pressure 109/70 mm Hg; pulse rate 88 beats/minute; respiratory rate 15 breaths per minute; and oxygen saturation 98% at room air). Muscular membranes appeared normal. No neck stiffness or palpable lymph nodes were noted. Results of heart examination were normal. Lungs were clear to auscultation, and the abdomen was soft, indicating no hepatosplenomegaly or palpable masses. No rash was seen. The neurologic examination revealed normal mental status but moderate ataxic dysarthria. Her cranial nerves were intact, and motor strength was 5/5 throughout. Results of a sensory
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Purpose: Cerebellitis, or acute cerebellar ataxia, is an inflammatory process of the cerebellar white matter that occasionally is manifested after systemic viral or bacterial infections (8). The pathogenic mechanism of influenza virus infection on the CNS can be either a direct invasion of the virus that causes acute illness or, more typically, a delayed autoimmune demyelinating postviral encephalopathy (9,10). Amplification of viral DNA in CSF is rare in most influenza-related CNS infections (10). In this case, the positive RT-PCR results for influenza A and the pertinent brain MRI findings, as well as the concurrent influenza prodromal symptoms, suggest that acute influenza cerebellitis, rather than a postinfluenza encephalopathy, caused the associated neurologic findings.

The limitation of this report includes the lack of sequence data comparing the patient’s viral RNA from the CSF and the nasopharynx and the absence of sequential sampling during the course of her illness. In conclusion, influenza virus, though rare, should remain a consideration in patients who have acute cerebellitis during influenza season.
Acknowledgments

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4. Titi-Graiss K, Mhiri Souei M, Mlaiki B, Apok V, Alamri A, Qureshi A, Donaldson-Edwards J, Maroun M. Sfeir and Hiep T, Hart IJ, Absoud M, Chang G, et al. Imaging of acute cerebellitis in different numberings). Besides A/Alberta/01/2014 (clade 2.3.2.1c), the mutation G225R has been found in 3 other H5N1 sequences: A/duck/Hunan/15/2004 (clade 2.3.3), A/chicken/Xinjiang/53/2005, and A/chicken/Xinjiang/27/2006 (both clade 7, all lineage assignments made with LABEL, http://label.phiresearchlab.org/). Although few G225R mutations were found, they were all found in avian hosts, indicating that the mutation can occur sporadically and avian-like receptor-binding properties may not be fully abolished by G225R.

Potential Human Adaptation Mutation of Influenza A(H5N1) Virus, Canada

To the Editor: In December 2013, influenza associated with pandemic influenza A H5N1 was reported in Canada in a patient who had traveled to China; the patient died in January 2014. This case leaves unanswered questions.

In the absence of direct poultry contact by the patient, the possible route of transmission and infection, often influenced by receptor-binding properties of the virus, requires special attention. The full genome and phylogenetic analysis by Pabbaraju et al. (1) provides a summary of what can typically be deduced from the sequence. The authors also mention 2 novel mutations, R189K and G221R, in the hemagglutinin (HA) protein (R193K and G225R in H3 numbering, used hereafter). When mapped to the H5 HA protein structure by using fluSurver in GISAID (http://www.gisaid.org, http://flusurver.bii.a-star.edu.sg), both mutations are found in the immediate receptor-binding pocket, and G225R has been known to change specificity of an H3N2 virus toward human erythrocytes (2). The same position is also known for receptor recognition changes in the 2009 pandemic H1N1 virus (mutations D222G, D225G, or D239G in different numberings). Besides A/Alberta/01/2014 (clade 2.3.2.1c), the mutation G225R has been found in 3 other H5N1 sequences: A/duck/Hunan/15/2004 (clade 2.3.3), A/chicken/Xinjiang/53/2005, and A/chicken/Xinjiang/27/2006 (both clade 7, all lineage assignments made with LABEL, http://label.phiresearchlab.org/). Although few G225R mutations were found, they were all found in avian hosts, indicating that the mutation can occur sporadically and avian-like receptor-binding properties may not be fully abolished by G225R.

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In the absence of glycan-binding data or crystal structures, which take longer to deduce, computational structural modeling is an efficient and safe alternative for fast preliminary assessment of these mutations in their natural structural context of H5N1 binding pockets. We have shown (3) that a method using the classical AMBER03 molecular mechanics force field (4) with an implicit solvation model in combination with short molecular dynamics simulations in YASARA (5) can reproduce relative preference for human-like α2,6-linked versus avian-like α2,3-linked sialic acid receptors. The interaction energies of all atoms in a system are described and combined with distance-dependent functions for different interaction types, including bonds, various angles, van der Waals, electrostatics, and solvent, which leads to consideration of the concerted effects of all residues in the binding pocket. By using this energy function, short molecular dynamics simulations enable all atoms to move for specified intervals within the constraints of their interactions. These simulations are used to minimize and finally predict the energies of the wild-type and mutant HA proteins for their ligand-bound and unbound states considering their respective ligands (see Methods section of [3] for details).
Cerebellitis Associated with Influenza A(H1N1)pdm09, United States, 2013

Technical Appendix Table. Characteristics of 8 reported cases of influenza cerebellitis in 5 published articles before this study. Six of the cases were described in children. Five patients had possible diagnosis of influenza cerebellitis. One patient had a complicated course.

<table>
<thead>
<tr>
<th>Published case, year of publication</th>
<th>Characteristics, signs, symptoms</th>
<th>Brain imaging</th>
<th>CSF analysis</th>
<th>Confirmed (C) or probable (P) influenza cerebellitis</th>
<th>Lower respiratory tract symptoms and chest radiography findings</th>
<th>Treatment</th>
<th>Resolution of symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hayase Y et al, Internal Medicine 1997 (English)</td>
<td>Woman, 31 y; fever and ataxia</td>
<td>Normal brain CT and MRI</td>
<td>Normal cell count, glucose and protein</td>
<td>(C) High serum hemagglutination inhibition titer to influenza B, and positive CSF RT-PCR for influenza B nucleoprotein gene</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Tili-Graiess K et al, J Neuroradiol. 2006 (French)</td>
<td>4 children, 2-7 y; headache, fever, and vomiting; ataxia was present in 2 cases</td>
<td>Initial MRI (2 cases) demonstrated increased intensity on T2W and Flair sequences of the cerebellar gray matter</td>
<td>High lymphocytes and proteins in samples from 3 children; normal values for 1 child</td>
<td>(P) Viral serologic tests were negative for 3 cases; serum sample from 1 child was positive for Epstein-Barr virus</td>
<td>No respiratory symptoms noted. No chest radiograph</td>
<td>Prednisone ×5 d for 3 cases and ×10 d for 1 case.</td>
<td>Complete resolution of symptoms in 3 cases; persistent mild right upper limb paresis in 1 child</td>
</tr>
<tr>
<td>Apok V et al, J Neurol Neurosurg Psychiatry Poster 0102,2010 (English)</td>
<td>Teenaged girl with acute fulminant cerebellitis following a course of antiviral for H1N1 virus</td>
<td>Hydrocephalus</td>
<td>NA</td>
<td>(P) Influenza RT-PCR in CSF was negative</td>
<td>Patient had cough and fever and was started on antiviral therapy; no chest radiograph</td>
<td>NA</td>
<td>Residual left-sided ataxia after 3 months.</td>
</tr>
<tr>
<td>Hackett I et al, Ir Med J. 2013 (English)</td>
<td>Child, 6 y; headache, worsening dysarthria and ataxia; coordination revealed significant bilateral dysdiadochokinesi s</td>
<td>MRI brain revealed findings consistent with a diagnosis of cerebellitis, no enhancement was noted post contrast</td>
<td>Lumbar puncture parameters were normal</td>
<td>(C) CSF samples RT-PCR–positive for influenza A and influenza B and nasopharyngeal aspirate RT-PCR–positive for influenza A(H1N1) and B.</td>
<td>2 weeks before treatment sought, patient had rhinitis, cough, and fever; chest radiography showed mild bilateral bronchial prominence</td>
<td>Oseltamivir ×5 d</td>
<td>All symptoms fully resolved after 1 week</td>
</tr>
<tr>
<td>Ishikawa T et al, Rinsho Shinkeigaku. 2006 (Japanese)</td>
<td>Woman, 25 y; fever and headache</td>
<td>T2-weighted brain MRI demonstrated a high signal lesion in the cerebellar cortex.123I-</td>
<td>Pleocytosis</td>
<td>(C) Nasal swab sample positive in the influenza assay and a &gt;4× change in the antibody titer to influenza virus A</td>
<td>Not available</td>
<td>Oseltamivir</td>
<td>Truncal ataxia normalized after 3 mo.†</td>
</tr>
<tr>
<td>Published case, year of publication, (Language of publication)</td>
<td>Characteristics, signs, symptoms</td>
<td>Lower respiratory tract symptoms and chest radiography findings</td>
<td>Resolution of symptoms</td>
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<td></td>
<td>IMP-SPECT showed hypoperfusion in the cerebellum</td>
<td>(H3N2) detected by hemagglutination inhibition</td>
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*NA: not available.
†Follow-up imaging showed cerebellar cortical lesion observed on MRI had resolved 80 days after hospitalization; laboratory data indicated that cerebrospinal fluid pleocytosis had normalized ≈3 months later.