Influenza A(H1N1)–Associated Ischemic Stroke in a 9-Month-Old Child

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Aim: This study aimed to report a rare clinical course of pandemic influenza A(H1N1) infection, ischemic stroke, in a 9 month-old child.

Case: A 9-month-old girl with no previous medical problem presented to our pediatric emergency department with high fever (39°C/102°F) lasting for 48 hours. Soon after admission, she started generalized tonicclonic seizures that ceased after 2 injections of diazepam. Six hours later, she presented 2 short episodes of partial clonic seizures of the right arm followed by monoplegia. Lumbar puncture was normal. Noncontrast computed tomographic imaging of the brain was performed and revealed an acute infarct in the left middle cerebral artery territory with no mass effect. Electroencephalogram revealed important slowing in the left hemisphere. A magnetic resonance imaging was performed the next day and confirmed an ischemic stroke in the left posterior middle cerebral artery region. Nasal swab polymerase chain reaction was positive for influenza A(H1N1) and polymerase chain reaction detection negative in cerebrospinal fluid. She fully recovered her right-arm function on day 3 and was discharged on day 10 without sequelae.

Comments: Seasonal influenza is known to cause neurological complications in children. Influenza increases the stroke risk especially in adults at high risk. This is a rare event in childhood, and we believe this is the first report associated with H1N1 new variant.

Conclusions: Acute viral infection, notably influenza, is associated with increased susceptibility to stroke, and vaccination against influenza may reduce the risk of stroke.

Key Words: influenza A, H1N1, stroke

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CASE

A 9-month-old girl with no previous medical problems presented in our pediatric emergency department with high fever (39°C/102°F) lasting for 48 hours and associated with shivering and episodes of lips cyanosis. On arrival, her vital signs were as follows: temperature, 38°C (100°F); heart rate, 155 beats per minute; respiratory rate, 32 breaths per minute; blood pressure, 107/80 mm Hg; and 100% finger probe pulse oximetry. As she was installed in the waiting area, she started generalized tonicclonic seizures that ceased after 2 rectal injections of diazepam (0.5 mg/kg). Examination during the postictal period revealed a Glasgow Coma Scale score of 9, normal reactive pupils, absence of peripheral motor impairment, normal peripheral reflexes, and stertorous respiration. Laboratory investigations including a complete blood cell count and basic metabolic panel were significant for hyponatremia (125 mmol/L). Lumbar puncture was normal. She was treated with isotonic saline infusion. Her postictal neu-

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of 15. Six hours later, she had 2 short episodes of partial clonic seizures of the right arm followed by monoplegia. Intravenous antiviral therapy (acyclovir 500 mg/m² per 8 hours) was started. Initial hyponatremia was corrected after intravenous treatment. Noncontrast computed tomographic (CT) imaging of the brain was performed and revealed an acute infarct in the left middle cerebral artery territory with no mass effect. Electroencephalogram revealed important slowing in the left hemisphere. A magnetic resonance imaging (MRI) was performed the next day and confirmed an ischemic stroke of the left posterior middle cerebral artery region (Figs. 1-3) without any sign of stenosis or parietal irregularities of the artery on the magnetic resonance angiography. Nasal swab polymerase chain reaction was positive for influenza A(H1N1) and negative for respiratory syncytial virus. Polymerase chain reaction detection for H1N1 and herpes simplex virus was negative in the cerebrospinal fluid (CSF). She has not been vaccinated for seasonal or H1N1 influenza. Evaluation for potential stroke factors revealed no family history, normal level of antithrombin III activity, homocysteine, absence of antiphospholipid antibodies, antinuclear antibodies, and factor V Leiden mutation. Protein C and S activities were equal to 52% and 62%, respectively. Serology panel (cytomegalovirus, parvovirus B19, herpes simplex virus, varicella zoster virus, Epstein-Barr virus, and Borrelia burgdorferi) showed previous immunization. Electrocardiogram, echocardiography, and Doppler ultrasound of the neck vessels were also normal. Her treatment was completed by a 5-day course of oseltamivir and aspirin (5 mg/kg per day); clonazepam was progressively replaced by carbamazepine (15 mg/kg per day). Under this regimen, she fully recovered her right-arm function on day 3. She was discharged on day 10 with carbamazepine and aspirin treatment. Follow-up appointment for cerebral MRI scheduled within the next 3 months showed a discrete cortical residual atrophy.

rological status improved shortly with a Glasgow Coma Scale score

COMMENTS

The role of infectious and inflammatory causes of stroke is much more significant in children than in adults. Viruses may produce transient ischemic attacks and stroke. The most wellstudied viruses are varicella zoster virus, cytomegalovirus, and human immunodeficiency virus.¹ The etiology of neurological complications in influenza infection is unclear. Different pathophysiological mechanisms have been implicated in the resulting vasculitis: a direct infection of cerebral arteries, the product of transient autoantibodies to phospholipids and coagulation proteins (indirect autoimmune reactivity).¹ Influenza virus proteins influence hemostasis; influenza infection has a prothrombotic effect by activating procoagulant pathway and inhibiting anticoagulant pathways. Proinflammatory cytokines are particularly involved; they reduce the expression of thrombomodulin and, in association with C-reactive protein, induce tissue factor expression by monocytes and macrophages.² Only rarely is influenza virus detected in CSF, suggesting that neurological manifestations might be an indirect effect of influenza respiratory

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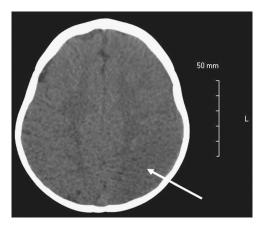


FIGURE 1. CT scan and axial diffusion-weighted MRI (with apparent diffusion coefficient map) showing hypodensity and diffusion restriction (arrows) in the left middle cerebral artery territory.

tract infection. Seasonal influenza is known to cause neurological complications in children, including seizures, encephalopathy, acute encephalitis, myositis, transverse myelitis, Guillain-Barre syndrome, Reve syndrome, and acute necrotizing encephalitis. Influenza A-associated stroke was reported in 2003 in a 4-year-old boy. His MRI showed a subacute infarct of the left middle cerebral artery, and he fully recovered without sequelae.⁴ As in the present case, the child did not have any evidence of direct central nervous system invasion of the virus as shown by normal CSF analysis. As with other reports of virus-related stroke in a pediatric population, neurological involvement was limited to the middle cerebral artery.¹ At that time, it was the first description of a pediatric clinical presentation. Since 2003, similar pediatric case reports have not been published. For H1N1 influenza in 2009, the description of neurological complications is emerging.⁵ The most common neurological manifestations were seizures (60%–70%) and encephalopathy (25%–50%).^{6–8} Seasonal influenza A or B reported rate for neurological complications is 8.5%. Reported rates for pH1N1 hospitalized children were between 6% and 19%, and most of the patients with neurological complica-

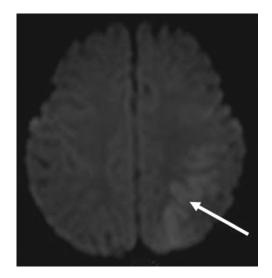


FIGURE 2. CT scan and axial diffusion-weighted MRI (with apparent diffusion coefficient map) showing hypodensity and diffusion restriction (arrows) in the left middle cerebral artery territory.

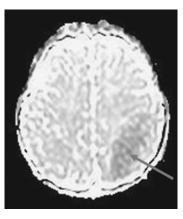


FIGURE 3. CT scan and axial diffusion-weighted MRI (with apparent diffusion coefficient map) showing hypodensity and diffusion restriction (arrows) in the left middle cerebral artery territory.

tions had underlying neurological conditions. The delay from onset of respiratory tract symptoms to neurological symptoms was short and was within the first 48 hours for seizures, meningitis, encephalitis, myelitis, or acute encephalopathy. The potential effects of antiviral medications on the development of neurological symptoms has not been proven in pediatric H1N1 cohorts mainly because neurological complications occurred shortly after respiratory symptoms and before any antiviral treatment was started. In adults, oseltamivir seems to reduce the stroke risk especially those with cardiovascular risk factors.^{1,2}

CONCLUSIONS

Acute viral infection, notably influenza, is associated with increased susceptibility to stroke, and vaccination against influenza may reduce the risk of stroke, particularly in children already at high risk. Clinicians should remain aware of the potential for severe neurological sequelae associated with seasonal or novel influenza A(H1N1) virus infection.

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