STROKE AFTER VARICELLA VACCINATION

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Two children presented with acute hemiparesis 5 days and 3 weeks following varicella vaccination. Both showed unilateral infarction of the basal ganglia and internal capsule, a distribution consistent with varicella angiopathy. Both children had small patent foramen ovale (PFO), and one child also had severe iron-deficiency anemia, which may have predisposed the patient to this adverse effect. (*J Pediatr 2004*;145:845-7)

lthough complications of varicella have been reported,¹ the association of varicella with pediatric stroke was only recognized in 1983.² Numerous reports of lacunar infarction around the internal capsule associated with varicella now have been reported with onset of symptoms 24 hours before to months after eruption of the exanthem.³

Live attenuated varicella vaccine was licensed in the United States in March 1995 and is recommended in both the United States and Canada for all healthy children 12 months of age or older who have not had varicella.^{1,4} No case of cerebral vasculopathy leading to stroke has been described following varicella vaccination.

We report 2 children who presented with hemiparesis 5 days and 3 weeks following varicella immunization. Both were found to have unilateral infarction of the basal ganglia, typical of varicella angiopathy following chickenpox. We postulate that immunization with the varicella vaccine may, in rare cases, predispose to stroke.

CASE I

An 18-month-old girl developed acute left hemiparesis 1 week after varicella vaccine. The weakness resolved overnight, and her family did not seek medical attention. Two weeks later, hemiparesis recurred, and she was brought to our center. She had been well previously, with no intercurrent infections or trauma. Past medical history was unremarkable, and there was no family history of hypercoaguability or vascular disease.

Her examination was remarkable for left lower facial droop and grade 4, predominantly distal weakness of the left upper and lower extremity. Reflexes were pathologically brisk in both the left upper and lower extremity, and the left plantar response was extensor. Sensory exam was normal.

Her brain computed tomography (CT) scan showed a hypodensity in the right posterior limb of the internal capsule and putamen. Magnetic resonance imaging (MRI) confirmed infarction of the right external capsule, the posterior aspect of the lentiform nucleus, and the posterior limb of the internal capsule (Figure 1). A magnetic resonance angiogram (MRA) showed possible narrowing of the M1 segment of the right middle cerebral artery (Figure 1). Her complete blood count was unremarkable. Coagulation workup was normal, including anticardiolipin antibody, plasma homocysteine, prothrombin time, international normalized ratio 3 (INR), partial thromboplastin time, lupus type inhibitor, prothrombin G20210A, antithrombin, proteins C and S, activated protein C resistance, factor V Leiden, and thrombin time. Evaluation for vasculitis also was unremarkable, with an erythrocyte sedimentation rate of 5 mm/hour and normal serum antinuclear antibody, C3, C4, and rheumatoid factor. Serum and cerebrospinal fluid (CSF) lactate concentration and CSF cell count, protein, and glucose were normal. CSF varicella zoster virus polymerase chain reaction was negative. Both serum IgM and IgG (enzyme immunoassay) for varicella

CSF	Cerebrospinal fluid	MRI	Magnetic resonance imaging
CT	Computed tomography	PFO	Patent foramen ovale
MRA	Magnetic resonance angiogram		

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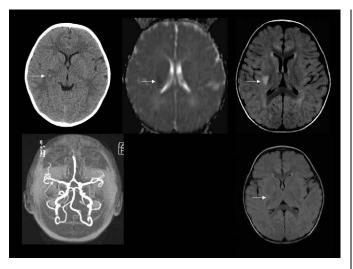


Figure 1. Patient 1. From left to right, top to bottom: Axial CT scan showing a right putaminal hypodensity, axial apparant diffusion coefficient (ADC) map showing restricted diffusion in the right putamen and axial FLAIR sequence showing T2 hyperintense right putamen. MRA showing possible narrowing in the mid-M1 segment of the middle cerebral artery. Follow-up axial fluid attenuated inversion recovery (FLAIR) image 3 months poststroke showing substantial resolution of the right putamenal lesion.

were positive. Echocardiography showed a small patent foramen ovale (PFO) with left to right shunting. The patient was treated with acetylsalicylic acid (40 mg/day) for 1 year. Repeat MRI after 3 months showed resolution of the middle cerebral artery narrowing but persisting change from the infarction. Twelve months later, weakness had completely resolved, and neurologic examination was normal.

CASE 2

A 14-month-old girl developed anorexia and left-sided weakness 5 days after varicella vaccine. She was diagnosed with severe iron-deficiency anemia (Hgb 4.1 g/dL, mean corpuscular volume 51.9 fL, platelets 654,000 /mm³); she was transfused and begun on iron. She was seen in our center 6 weeks later because of persisting left-sided weakness. Past medical history was remarkable for mild asthma. Family history was negative for vascular disease or coagulopathies.

On examination, she had loss of the left nasolabial fold, mild left hemiparesis, and a left upgoing Babinski reflex.

Her CT scan showed a hypodensity in the right caudate nucleus and internal capsule. An MRI confirmed subacute infarction involving the right caudate, anterior limb of the internal capsule, globus pallidus, and putamen with normal cerebral MRA (Figure 2). Serum lactate and erythrocyte sedimentation rate were normal, and hemoglobin was 10.7 g/ dL. CSF was not assessed. Evaluation for abnormality of coagulation (as for case 1) was normal. Echocardiography showed a small 2- to 3-mm PFO with left to right shunting. At follow-up 6 months later, hemiparesis had improved; however, she had poor fine motor function in her left hand and dragged her left leg when fatigued.

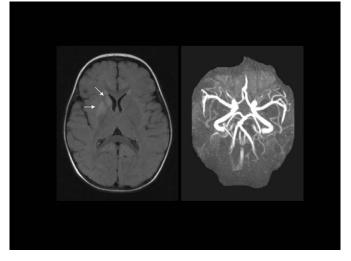


Figure 2. Patient 2. From left to right. Right putamenal and caudate head stroke seen on axial FLAIR image as a T2 hyperintense signal. MRA of the circle of Willis showing a normal right middle cerebral artery.

DISCUSSION

The lifetime risk of developing varicella is high,⁴ and universal immunization is now recommended for all children 12 months of age and older.^{1,4} The vaccine appears efficacious and safe in controlled clinical trials.^{5,6}

Ischemic stroke affects approximately 1.2 per 100,000 children per year.⁷ Cerebral angiopathy with lacunar infarction in the basal ganglia and internal capsule has been well-documented after primary varicella infection^{2,3} but never following vaccination. Narrowing and beading affecting predominantly the middle cerebral arteries may be seen.

The pathogenesis of varicella-associated stroke is poorly understood. Angiopathy may result from direct infection of the vessels with varicella, presdisposing to inflammatory changes and thrombosis, or may result from a postviral, immune-mediated reaction.⁸

Both of our case patients had small PFOs, which are present in about 10% of the healthy population. The etiologic contribution of PFOs to childhood stroke has not been studied, but observational studies in adults have suggested a possible association.^{9,10} Our second case patient had severe iron-deficiency anemia, a known risk factor for stroke.¹¹ In the United States, 9% of 1- to 2-year-old children, precisely the age group receiving varicella vaccine, are iron deficient.¹²

These two cases of stroke in temporal association with varicella vaccination may represent chance occurrence. However, the characteristic location of infarcts raises the possibility of varicella vasculopathy. Although both patients had small PFOs and the second patient also had severe iron deficiency, contribution of varicella vaccination may be significant, as many children with stroke harbor multiple risk factors.

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