

# Central Nervous System and Renal Vasculitis Associated With Primary Varicella Infection in a Child

June M. Caruso, DO\*; Glenn A. Tung, MD‡; and William D. Brown, MDS§

**ABSTRACT.** A 7-year-old girl with primary varicella presented with encephalopathy and focal neurologic deficits 10 days after her first skin lesions appeared. She was discovered to have bilateral wedge-shaped renal infarctions, and ischemic lesions in the conus medullaris, cerebral cortex, and deep gray matter consistent with a medium and large vessel arteritis on magnetic resonance imaging. This complication has never before been reported in an immunocompetent child with primary varicella infection, and it represents a rare but serious complication of childhood chickenpox. *Pediatrics* 2001;107(1). URL: <http://www.pediatrics.org/cgi/content/full/107/1/e9>; varicella, child, vasculitis, cerebral arteritis, renal arteritis.

ABBREVIATIONS. VZV, varicella-zoster virus; MRI, magnetic resonance imaging; CSF, cerebrospinal fluid; IgG, immunoglobulin G; IgM, immunoglobulin M; PCR, polymerase chain reaction.

Varicella-zoster virus (VZV) may produce a wide spectrum of neurologic diseases in children, including postinfectious encephalitis,<sup>1</sup> Reye's syndrome,<sup>2</sup> acute cerebellar ataxia,<sup>3</sup> and herpes zoster ophthalmicus with delayed contralateral hemiparesis.<sup>4,5</sup> VZV recurrence in the trigeminal or cervical distribution may be associated with a vasculopathy affecting both large and small arteries, typically producing stroke or stroke-like symptoms weeks to months after eruption of the vesicles.<sup>6</sup> This vasculopathy is more common in immunocompromised patients.<sup>7</sup> We describe a VZV arteritis in an immunocompetent child occurring 10 days after the onset of the initial rash of primary varicella, producing ischemic vascular lesions in the brain, spinal cord, and kidneys.

## CASE REPORT

A 7-year-old girl in good health presented with confusion, lethargy, and right-sided weakness for ~2 hours on the day of admission. She had healing skin lesions consistent with a recent

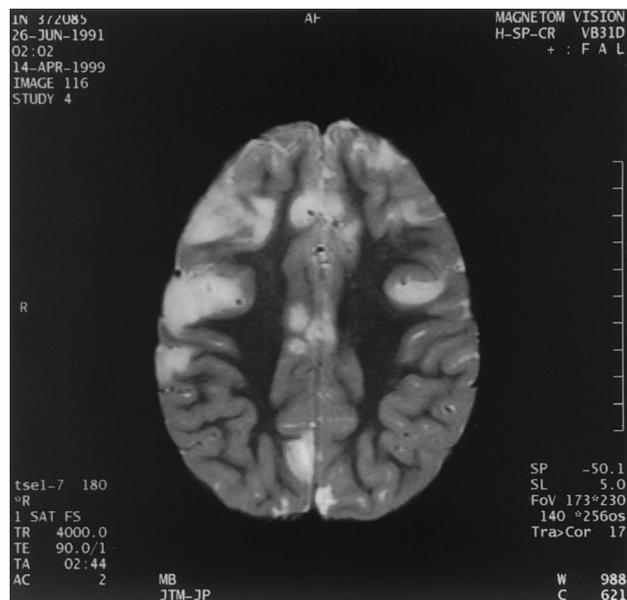
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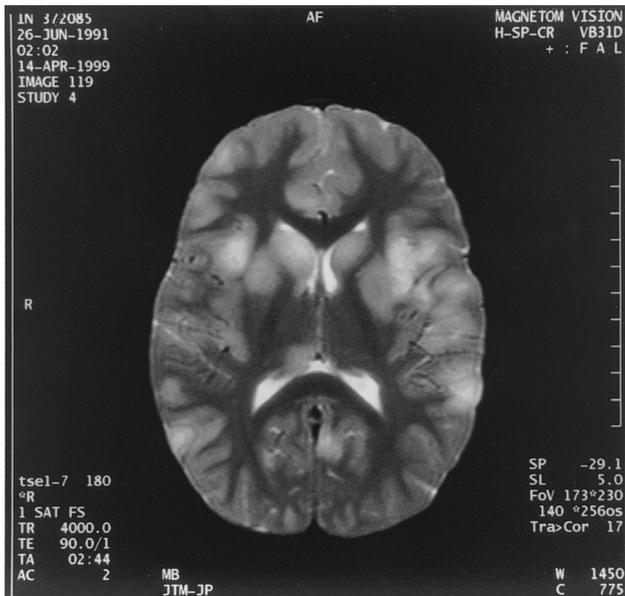
history of primary varicella 10 days before presentation. Her initial rash resolved after a few days with no new lesions, and 7 days before admission she had returned to school. Four days before admission, she complained of headache and eye pain on exposure to light and developed a low-grade fever with occasional vomiting. Over the next 48 hours, she became difficult to awaken. She could not stand without support and was unsure of what to do with a popsicle offered to her. The act of swallowing would induce projectile vomiting. She began to repeat the words "I am" in response to all questions. On the day of admission, she could not be aroused and was brought to the hospital.

In the emergency department, her temperature was 98.6°F with pulse, 74 beats per minute; respiratory rate, 16 breaths per minute; and blood pressure, 112/70 mm Hg. Numerous healing cutaneous lesions consistent with recent varicella infection were present. No open vesicles were noted on her skin, ears, or mouth; hepatosplenomegaly or lymphadenopathy was not present. She was awake but minimally responsive to forceful pinching. Pupils were equal, round, and reactive with a right gaze preference. A left facial droop was noted with tongue deviation to the right. She had no spontaneous vocalizations and no purposeful or spontaneous motor movements. She could not be induced to follow commands but did answer occasional questions correctly with 1-word answers. She was diffusely hyperreflexic on the left with bilateral plantar extensors and bilateral sustained ankle clonus.

Computed tomography of the brain within 30 minutes of presentation disclosed multiple hypodensities in the cerebral cortex. Magnetic resonance imaging (MRI) was obtained within 10 hours of admission and showed diffuse asymmetric hyperintensities both in superficial and deep gray matter bilaterally (Figs 1 and 2). Magnetic resonance angiography demonstrated beading of the vessels of the Circle of Willis, including M1 and A1 segments (Fig 3). Initial cerebrospinal fluid (CSF) evaluation showed a normal



**Fig 1.** Transaxial turbo-spin echo T2-weighted (TR/effTE = 4000/90) image shows bilateral asymmetric hyperintense lesions involving the frontal and parietal gray matter.



**Fig 2.** At a more caudal level, hyperintense lesions are seen in the basal ganglia, insula, parietal, and temporal lobe cortex. There is also swelling of the corpus striatum. The brainstem and cerebellum were spared.



**Fig 3.** Three-dimensional time of flight (TR/effTE = 32/6) magnetic resonance angiogram shows beaded appearance of the A1 and M1 segments (arrows) of the anterior and middle cerebral arteries, consistent with medium vessel arteritis.

opening pressure with white cell count of 21 leukocytes/mm<sup>3</sup> (3% neutrophils, 79% lymphocytes, and 18% monocytes), 0 erythrocytes, glucose (68 mg/dL), protein (23 mg/dL), and CSF immunoglobulin G (IgG; 1.54 mg/dL). Serum VZV IgG was elevated at 1:512 and VZV immunoglobulin M (IgM) also elevated at 1:8192; CSF VZV IgG and IgM were both <1:8. CSF VZV polymerase chain reaction (PCR) was positive (Specialty Laboratories, Santa Monica, CA). Additional studies to evaluate for possible secondary causes, including hypercoagulopathy panel (antinuclear antibody, Lupus anticoagulant, protein C and protein S, resistance to activated protein C, anti-thrombin III, anticardiolipin antibodies, and antiphospholipid antibodies), toxin screen, blood and CSF bacterial and viral cultures, serum Epstein-Barr virus and cytomegalovirus titers, myelin basic protein, oligoclonal bands, and PCR for herpes simplex virus I and II and Epstein-Barr virus were all negative. An electroencephalogram on the morning of admis-

sion revealed bilateral slowing in the frontotemporal regions with periodic polyspike and wave reversals in the right temporal area.

Immediate treatment with acyclovir (500 mg/m<sup>2</sup>, every 8 hours) and intravenous methylprednisolone (2 mg/kg/day) was begun. Sixteen hours after initiating treatment, she was more awake and responsive with a profound expressive aphasia, although she was inconsistent in her responses to extend 2 fingers, close her eyes, and extend her tongue on command. She demonstrated no response to visual threat on the right. She had a moderate right upper extremity paresis and a marked left hemiparesis but could wiggle her left great toe with encouragement. Reflexes were hyperactive on the left with crossed adductors and triple flexion withdrawal, as well as bilateral plantar extensors. Ankle clonus was present bilaterally. No seizures occurred.

Two days after admission she was awake more consistently, although with abulia and a flat affect. No emotional facial expression was present. She was able to follow simple, but not multiple, motor commands and the left-sided weakness persisted. Urinary incontinence was noted without hematuria or proteinuria. A spinal cord MRI performed 2 days after admission showed abnormal signal in her distal conus medullaris, as well as bilateral wedge-shaped lesions in her kidneys consistent with renal artery infarction (Fig 4).

Eleven days after admission her neurologic examination had nearly normalized with only minimal Broca's aphasia and a mild residual right upper and left lower extremity weakness. She was able to stand and walk, but fatigued easily. Intermittent bladder incontinence persisted. Fourteen days of intravenous acyclovir were completed, and steroids were tapered with oral prednisone over 2 weeks on an outpatient basis.

At 8 months of follow-up, she had complete resolution of all deficits. Repeat neuroimaging showed nearly complete resolution of the cerebral and vascular lesions. One year after presentation, she had a focal seizure at home during sleep. Neurological examination and neuroimaging were unchanged, and carbamazepine was begun. She is now a fourth-grade student and her academic performance is excellent.

## DISCUSSION

Complications of primary varicella infection in immunocompetent children may be difficult to distinguish from unusual direct effects of the infection itself.<sup>8</sup> Because the treatment of postinfectious complications may differ from the treatment of the underlying disease, attention to temporal relationships



**Fig 4.** Transaxial turbo-spin echo T2-weighted (TR/TE = 5084/90) image through the upper abdomen shows wedge-shaped hyperintense lesions in both kidneys, consistent with renal infarctions.

between disease onset and the unexpected complications or unusual signs of primary disease extension is important. The incubation is 14 to 16 days but may be as early as 10 or as late as 21 days after contact. Patients are contagious from 1 to 2 days before the appearance of the rash to shortly after the last vesicle appears ~5 days later.

The presenting clinical features of our patient most closely resemble those previously described by Bodensteiner et al<sup>9</sup> with delayed (onset 6.3 weeks) hemiparesis after primary varicella infection. However, the duration of symptoms in our patient was much shorter, beginning only 10 days after the appearance of the varicella lesions, making the acute hemiplegia more directly related to the primary infection. Additional unusual features of her presentation included bilateral hemiparesis, expressive aphasia, and encephalopathy.

Pathogenesis of herpes zoster ophthalmicus or acute hemiplegia of childhood secondary to VZV is unknown. An early study by Rose et al<sup>10</sup> in 1964 reviewed 40 patients with diffuse meningoencephalitis secondary to VZV. Cases autopsied demonstrated infiltration of the vascular intima and adventitia with giant and mononuclear cells, in both the brain and spinal cord. The route of infection for focal cerebral angiitis has been postulated by MacKenzie et al<sup>11</sup> to be direct spread of virions from the trigeminal ganglion to adjacent blood vessels and cerebral tissue. Other mechanisms for viral access to both deep and superficial cerebral vessels may include hematogenous seeding of nerves or spreading via sympathetic nervous system pathways.<sup>12</sup> Neuropathologic evaluation may demonstrate initial involvement of the proximal anterior or middle cerebral arteries with widespread infarction and diffuse thromboses of the leptomeningeal arteries.<sup>12-14</sup>

We deferred cerebral angiography for our patient based on her critical status at time of admission. The magnetic resonance angiography demonstrated segmental narrowing of the proximal middle and anterior cerebral arteries in the M1 and A1 segments bilaterally. Hilt and colleagues<sup>15</sup> reported cerebrovascular abnormalities in 25 adult patients with VZV including stenoses of the cavernous portion of the internal carotid artery, intracranial carotid artery siphon, and intracranial carotid artery at the level of the carotid bifurcation. In the case we present, ischemic lesions of the basal and cerebral cortex are believed to be secondary to a vasculopathy resulting from damage to the vessel wall media by direct viral invasion, immune-complex reactions, or a combination of both.<sup>16</sup>

Knowledge of VZV-induced mechanisms of neurologic disease in children is limited. This may result from intrinsic biologic properties of VZV, such as the intracellular location of the virus, difficulties in growing VZV in culture, and lack of a suitable animal model.<sup>17</sup> Culture of VZV is difficult but the presence of serum or CSF VZV antibodies, IgM and IgG, and elevated VZV IgG antibody index can provide serologic evidence of an acute VZV infection. PCR has a high probability (>95%) of detecting viral DNA during early infectious stages in vesicles,

crusts, CSF, and throat swabs when VZV-specific IgM is detectable.<sup>18</sup>

Prevention of varicella infection has been recommended by universal immunization with the varicella vaccine, licensed since 1995 for use in healthy persons 12 months of age and older without previous history of the disease. Use of this live-attenuated preparation of the wild Oka strain has been based on the frequency of serious complications and death after infection with varicella and the efficacy and safety of the vaccine. Most common adverse effects include varicella-like syndrome (1%–4%), minor injection site reaction (20%), generalized varicella-like rash (3%–5%), and low-grade fever (10%).<sup>19</sup> The incidence of serious neurologic injury as a consequence of primary varicella infection can be expected to occur with widespread use of this vaccine.

This case of central nervous system and renal arteritis illustrates a rare complication of primary varicella in a child. The absence of endogenous CSF IgG and IgM production, the detection of VZV fragments in the CSF by PCR, and the exclusive involvement of cortical and subcortical gray matter identify this as an early primary manifestation of VZV infection, rather than a secondary phenomenon or postinfectious process. Johnson and colleagues<sup>20</sup> reported a 35% mortality in their patients with cerebral vasculitis associated with VZV. Prompt diagnosis and treatment to counteract the progression of cerebral vasculopathy associated with primary varicella infection is imperative to maximize the possibility of recovery of neurologic function.

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