Clinical Features of Vascular Thrombosis Following Varicella

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Objective. — To define the clinical characteristics, neuroimaging features, and outcome of five patients with post—primary varicella zoster virus infection hemiparesis and to offer a hypothesis to explain the predilection for the involvement of the cerebral vasculature in this condition. Design. — Patient series.

Setting. — Five patients were treated during a 14-month period in a private pediatric neurology practice in a medium-size southwestern city.

Interventions.—Steroids (two patients) and antiplatelet drugs (two patients). No observed effects of therapy.

Results.—The onset of the hemiparesis occurred several weeks (mean, 5.4 weeks) following an episode of the chickenpox. Magnetic resonance imaging was more sensitive than computed tomography or angiography in demonstrating the area of involvement deep in the cerebral hemispheres. The prognosis was good regardless of the therapy administered, as all patients recovered completely or nearly completely.

Conclusions. — Primary varicella zoster virus infection with delayed-onset hemiparesis typically occurs approximately 6 weeks after primary varicella zoster virus infection. Magnetic resonance imaging is the most sensitive neuroimaging tool in these children. The prognosis is good, with recovery of function and no recurrences in our patients. The innervation of the carotid artery and the characteristics of the varicella zoster virus itself together provide the local and systemic factors that may trigger the vasculopathy responsible for this syndrome.

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A variety of nervous system manifestations of primary varicella zoster virus (VZV) infections (chickenpox) have been reported. These include encephalitis, meningoencephalitis, aseptic meningitis, myelitis, postinflammatory leukoencephalopathy (acute cerebellar ataxia), Guillain-Barré syndrome, facial nerve palsy, and Reye's

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syndrome.¹ Neurologic complications of chronic VZV involving the trigeminal nerve (varicella zoster ophthalmicus) are also seen. Among the complications of chronic VZV infection is the occurrence of a delayed contralateral hemiparesis, presumably the result of direct viral spread to contiguous structures from the ophthalmic nerve, causing a cerebral angiopathy.² During the last decade, six patients with delayed-onset cerebrovascular thrombosis following primary VZV infections have been described in the English-language literature.³⁵ Although primary VZV infection is a systemic disease, evidence suggests that cerebral angiopathy also underlies the cerebrovascular event in these patients.⁴ To our knowledge, no explanation of the predilection for involvement of the cerebral vasculature in these patients has been provided.

Herein, we describe five children with delayed onset of hemiplegia 3 to 8 weeks following primary VZV infection and define the clinical characteristics, course, and neuroimaging features. The propensity of the VZV to produce a retrograde infection of the peripheral nerve, the intense sensory stimulus provided by the chickenpox lesions, the dense sympathetic innervation of the carotid artery, and the systemic reaction to the primary VZV infection provide a combination of local and systemic factors that may account for the unusual clinical features of this condition.

PATIENTS AND CLINICAL DATA

All five patients were treated by one of us (M.R.H.) during the 14-month period between May 1989 and July 1990. The presence of the preexisting chickenpox was ascertained by history from the parents. In each child, the diagnosis had been established on clinical grounds alone. Only one patient (patient 4) was not seen during the acute stage of the illness (Table). The patient ages ranged from 3 to 7 years (mean, 5.4 years). Patient 1 had right-sided weakness, and the remaining patients had left-sided involvement. The neurologic deficit had a stuttering onset (neurologic deficit developing in a stepwise fashion during a 6- to 36-hour period) in three patients (patients 1, 3, and 4). Two patients (patients 3 and 5) had seizures at onset, although patient 3 had a preexisting seizure disorder.

Laboratory studies, including neuroimaging studies, were performed in all patients. Electroencephalography in three patients (patients 1, 2, and 5) revealed unilateral findings in patients 1 and 2. Computed tomographic scans were abnormal in two of four patients, although the area of ischemia was seen on magnetic resonance imaging (MRI) scans in all patients. Only patient 5 had identifiable cortical involvement; the remainder had predominant involvement of the deep structures of the ce-

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Variables	Patients				
	1	2	3	4	5
Clinical Features			,		
Age, y/Sex (mean age, 5.4 y)	6/F	6/M	5/M	7/M	3/F
Interval from varicella to onset (mean, 5.4 wk)	3 wk	2 mo	6 wk	6 wk	1 m
Hemiparesis	R	L	L	L	L
Arm	+	+	+	+	+
Leg	+	+	+	+	+
Face	+	+	+	+	+
Neurologic deficit at onset, complete (C)/stuttering (S)	S	С	S	С	С
Headache at onset	+	-	-	-	_
Lethargy/somnolence	+	_	+	_	+
Seizures at onset	-	-	+	_	+
Laboratory features					
Unilateral electroencephalographic findings	+	+	ND	ND	-
Computed tomographic evidence of stroke	+	ND	_	+	-
Magnetic resonance imaging evidence of stroke					
Deep	+	+	+	+	-
Cortex	-	_	+	_	+
Angiography (vasculopathy)	+	_	-	ND	ND
Echocardiography	-	-	-	ND	_
Hematologic evaluation	-	-	-	ND	-
Lumbar puncture	-	ND	ND	ND	-
Results					
Therapy: prednisone (S), dipyridamole (D), or aspirin (A)	S			D	S, A
Interval to follow-up examination, wk	8	8	6	8	5
Nearly complete recovery	+	+	+	+	+

*Plus sign indicates present; minus sign, absent; and ND, not done.

rebral hemisphere, including the basal ganglia and internal capsule (Figure). Of the three patients who underwent arteriographic examination, in patient 1 only the study showed evidence of vasculopathy with beading and segmental narrowing of the middle cerebral artery. Hematologic evaluation in four patients included determinations of protein C level, protein S level, antithrombin III antibody level, platelet count, antinuclear antibody titer, rheumatoid factor level, and erythrocyte sedimentation rate, as well as lipoprotein electrophoresis. Results were normal in all patients. Echocardiography yielded normal findings in the four patients in whom this procedure was performed. Lumbar puncture yielded normal findings in patients 1 and 5.

Therapy with steroids, aspirin, or dipyridamole was attempted in three patients (patients 1, 4, and 5). The first patient was treated with steroids, because the arteriographic picture was interpreted as suggesting arteritis. No therapeutic benefit was observed in any of these patients during the study. Follow-up examinations were performed in all patients between 5 and 8 weeks after the onset of the hemiparesis and revealed nearly complete resolution of the neurologic deficits in all but patient 1. One year after onset, no deficits could be detected. None of the patients has had a second episode of hemiparesis to date.

COMMENT

The clinical features of these five patients closely resemble those of the previously described six patients with delayed hemiparesis following primary VZV infec-

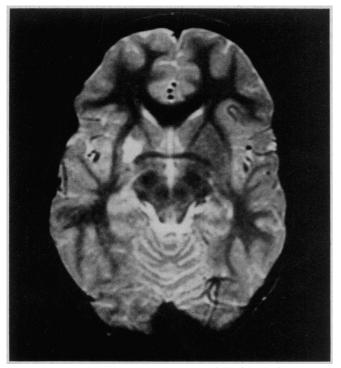
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tion. The mean age of the 11 patients was 4.2 years, and the mean interval from primary VZV infection to the onset of the hemiparesis was 6.3 weeks. Eight of the 11 patients had left-sided hemiparesis (four of six in the previous reports and four of five in our series). All but two of the 11 patients had primarily large-vessel involvement, resulting in ischemia of the deep structures of the affected hemisphere.

The computed tomographic scan was not as sensitive as the MRI scan in documenting the location and extent of the ischemic lesion. Only one arteriogram was abnormal; however, it suggested that vasculitis/ vasculopathy was the underlying pathologic mechanism for this condition, confirming the findings of previous reports.⁴ Electroencephalography, cerebrospinal fluid examination, hematologic studies, and echocardiography are useful only as a means of eliminating other pathogenic possibilities.

Although six patients have been previously described, to our knowledge, no information is available in the literature concerning outcome in this condition. The patients in this series all did well despite large lesions seen on MRI scans. All of our patients had return of function at the time of subsequent examination. It is possible that the lesions were less extensive than originally believed from MRI scan interpretation due to some edema of tissues sur-

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 T_2 -weighted magnetic resonance image of the brain of patient 4. Note the area of increased signal intensity involving the putamen and internal capsule on the right side.

rounding the ischemic area. Convalescent MRI scans to document the ultimate extent of the lesions were not obtained. The observation that all of these patients recovered premorbid function will be helpful in evaluating the effectiveness of possible therapies that might be suggested in the future. The fact that we were able to accumulate five patients during a period of 14 months suggests that there is a selection bias unknown to us or that this condition is more common than generally recognized.

A number of different pathogenic mechanisms have been proposed for the various neurologic conditions associated with varicella infections in humans. These mechanisms range from direct viral invasion of the brain in the primary infection to autoimmune responses to antigens exposed as a result of tissue injury due to virus in postinflammatory leukoencephalopathy. The mechanism of delayed contralateral hemiparesis following herpes zoster ophthalmicus, namely, vasculopathy caused by the contiguous spread of the herpes zoster virus to the cerebral vessels, has been well documented.^{2,6,7} The suggested mechanism of delayed hemiparesis following primary VZV infection is also that of a cerebral vasculopathy.⁴ Direct spread from contiguous structures via the ophthalmic nerve has been proposed, as has hematogenous spread of virus.^{4,6-8} The predilection for cerebral thrombosis and the predominance of involvement of the large vessels of the cerebral hemisphere are unexplained. This selective involvement resembles that seen in Moya Moya disease, and the mechanisms involved in the two disorders may be similar. Suzuki and Takaku⁹ and Suzuki¹⁰ demonstrated, in animal models, that stimulation of the superior cervical ganglion would predispose the carotid artery on that side to vasculopathy induced by circulating immune complexes. This phenomenon could be blocked by ganglionectomy. According to Suzuki and Takaku,9 in Moya Moya disease, stimulation of the sympathetic nerves because of intense acute, recurrent, or chronic inflammation of the head and face predisposes to arterial thrombosis on the ipsilateral side. The nature of the stimulus to the sympathetic nerves appears to be nonspecific, however, and might include toxins, such as a wasp sting.¹¹ This sympathetic stimulation combined with the production of systemic antibodies and antigen-antibody complexes might then result in an vasculopathy with thrombus formation.¹⁰ In the patient with primary VZV infection, the primary lesions (chickenpox) provide the stimulation of the superior cervical ganglion either because of intense local irritation or by providing a direct route for the VZV (with a known propensity to produce a retrograde infection of peripheral nerve) to involve the cervical sympathetic ganglion. The delay between the onset of the primary VZV infection and the onset of the hemiparesis is consistent with the time required for the development of the circulating antigen or antigen-antibody complexes that are necessary to induce vasculopathy and thrombus formation in the affected artery. Primary VZV infection thus provides the combination of local and systemic factors required for the development of cerebral thrombosis in these previously healthy children.

We conclude that primary VZV infection with delayedonset hemiparesis may be more common than has been recognized, typically affecting young children 3 to 8 weeks after primary VZV infection. Magnetic resonance imaging is the most sensitive neuroimaging tool in these children. Prognosis is good, with recovery of function and no recurrences in our patients. The innervation of the carotid artery and the characteristics of the VZV itself combine to provide the local and systemic factors that may trigger the vasculopathy responsible for this syndrome.

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