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Original Article

Post-Varicella Angiopathy: A Series of 4 Patients With Focus on Virologic and Neuroimaging Findings

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ABSTRACT

BACKGROUND: Post-varicella angiopathy is an important cause of childhood stroke and follows a particular pattern. Specific treatment guidelines have not been developed because of a lack of epidemiological, laboratory, and neuroimaging data. Prospective randomized controlled trials evaluating different treatment strategies have not been performed, and expert opinions on diagnostic criteria, prognosis, and treatment are diverging. **METHODS:** This case series describes the clinical course, laboratory, and neuroimaging findings of four children with post-varicella angiopathy, who all underwent cerebrospinal fluid assessment and received antiviral, immunosuppressive, and antiplatelet treatment. **RESULTS:** Cerebrospinal fluid analysis was positive for varicella-zoster virus markers in three children. At follow-up, three children had a mild hemiparesis and one child had no neurological symptoms. Neuroimaging showed complete vascular remission in three patients and improvement in one. **CONCLUSIONS:** Systematic search for virologic markers in cerebrospinal fluid will contribute to the understanding of the pathogenesis of idiopathic childhood stroke and can be considered as a prerequisite for the development of clear diagnostic criteria and relevant treatment strategies for post-varicella angiopathy. The role of antiviral and immunosuppressive medication needs to be clarified.

Keywords: angiopathy, children, outcome, stroke, treatment, varicella zoster

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Introduction

Arterial ischemic stroke (AIS) during childhood is relatively rare, but can cause significant morbidity.[1,2] The etiologies are multifactorial and related to an arteriopathy in many cases. Post-varicella angiopathy (PVA) has been recognized since 1985 and seems to be one of the most important causes of childhood stroke, accounting for up to 30% to 40% of cases with AIS.[1,3,4]

PVA is usually categorized as a transient cerebral arteriopathy, and preceded by varicella zoster virus (VZV) infection within the past 12 months before AIS.[5] PVA has been proposed as a diagnostic entity, characterized by infarction in the lateral lenticulostriate territory resulting from unilateral intracranial arterial wall disease that affects the distal internal carotid artery (ICA) and/or the proximal middle and/or anterior cerebral artery (MCA, ACA). With time, the arteriopathy stabilizes, improves, or resolves in most cases, sometimes after initial worsening during the first few months.[6,7]

The knowledge concerning epidemiology, presentation, and outcome of PVA is still limited and consistent treatment regimens have not been established.

The objectives of the present case series study were to describe the clinical and neuroimaging findings in four children with PVA, to contribute to a better understanding

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of the disease and to discuss treatment on the background of pathogenesis and outcome.

Patients and Methods

Four children with AIS secondary to PVA are reported. They were admitted to a primary pediatric referral center in southern Denmark between December 1, 2003 and December 31, 2012.

PVA was defined as an AIS that (1) followed a verified varicella infection within 12 months; (2) had an accompanying evidence of a vascular disease affecting the supraclinoid internal carotid artery, A1 or A2 segments of the anterior cerebral artery, or M1 or M2 segments of the middle cerebral artery; and (3) did not have any other possible etiologies. Coagulation defects, metabolic and hematological diseases, and cardiac disorders were excluded by the diagnostic evaluation.

Cerebrospinal fluid (CSF) samples were analyzed for cells, protein, glucose, and virologic markers. The virologic investigations included analysis of (VZV DNA) by polymerase chain reaction and analysis of intrathecal VZV immunoglobulin G (IgG) antibody synthesis by capture enzyme-linked immunosorbent essay.

Magnetic resonance imaging (MRI) included axial T1- and T2-weighted images, axial diffusion-weighted imaging, and coronal fluid-attenuated inversion recovery. Magnetic resonance angiography (MRA) was based on time-of-flight angiography. The severity of arterial abnormality was categorized based on the classification proposed by Miravet[8]: grade 1: turbulence without evidence of reduced distal flow; grade 2: stenosis with reduced distal flow; grade 3a: occlusion with distal flow via collaterals; and grade 3b: occlusion without distal flow. MRI and MRA were repeated following 3 to 6 months.

All children were treated with both intravenous acyclovir 30 mg/kg per day for 14 days and with oral prednisone. Three children received oral prednisone 2 mg/kg per day for 2 weeks with tapering over 2 to 4 weeks; one child received oral prednisone 1 mg/kg per day for 5 days. Three children started treatment at the onset of symptoms, and one child 3 months later, when the arteriopathy became evident on MRA. All children received salicylic acid (aspirin) 3-5 mg/kg for a minimum of 1 year.

Results

Clinical symptoms/signs

The children were 13 to 22 months old at onset of symptoms. Interval from varicella rash to AIS ranged from 4 weeks to 6 months. Neurological symptoms evolved gradually over 24 hours and are summarized in Table 1. Consciousness was unimpaired in all children. One patient (patient 1) had two MRI-confirmed episodes of AIS with an interval of 4 days. The remaining three children had a single clinical episode of AIS, but one patient had neuroimaging evidence of a previous clinically silent infarction (patient 2).

At clinical follow-up (range 6 months to 8 years), three children showed mild motor and cognitive deterioration, whereas one child was unimpaired (Table 1).

CSF findings

CSF findings are summarized in Table 2. CSF was obtained at onset of symptoms in three patients and with a delay of 3 months in one patient (patient 1). This child had a spinal tap when the arteriopathy became evident on MRA 3 months after the debut of symptoms.

Neuroimaging

Neuroimaging findings are summarized in Table 3. All children had neuroimaging evidence of infarction in the MCA territory. Infarction of putamen and globus pallidus was seen in all children. The nucleus caudatus was involved in two patients, and the surrounding subcortical white matter in three children. Two patients had neuroimaging evidence of recurrent infarctions; in one child, the infarction had been clinically silent (patient 2). MRA showed stenosis of the M1 segment of the MCA, classified as grade 1 arteriopathy in three children. One child had a stenosis of the supraclinoid ICA and the M1 segment of the MCA, classified as grade 2 arteriopathy. At follow-up after 6 months, the arteriopathy had resolved in three patients. In one child (patient 4), an improvement was seen, but the severity of the arteriopathy was still classified as grade 2. MRI and MRA of patients 2 and 4 are shown in the Figure.

Discussion

This series underlines the important role of PVA in childhood stroke and illustrates the typical clinical presentation in the pediatric population. PVA should be suspected in a young child with acute hemiparesis and basal

TABLE 1.
Clinical Findings at Onset and Follow-Up

Patient	Gender	Age at AIS (Months)	Interval From Varicella to AIS	Symptoms	Clinical Outcome at Follow-up	Follow-up Period
1	Female	22	4 wk	Nearly complete left hemiparesis Vomiting	Left hemiparesis Mild dystonia GMFCS I, MACS I	8 yr
2	Male	15	6 mo	moderate left hemiparesis	Healthy	3 yr
3	Male	18	5 mo	Moderate right hemiparesis	Right hemiparesis Minor attention deficit GMFCS I, MACS I	2 yr
4	Female	13	6 wk	Nearly complete right hemiparesis Vomiting	Right hemiparesis Minor attention deficit GMFCS I, MACS I	6 mo

Abbreviations:
AIS = Arterial ischemic stroke
GMFCS = Gross motor function classification system[19]
GMFCS I = Child walks without limitations, running and jumping speed and balance and coordination are limited
MACS = Manual ability classification system[20]
MACS I = Child handles objects easily and successfully, limitations in speed and accuracy without restrictions in daily activities