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Transient Cerebral Arteriopathy in a Child Associated With Cytomegalovirus Infection

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Abstract

Vascular wall injuries account for up to 80% of childhood strokes, excluding emboli of cardiac origin. Transient cerebral arteriopathy is a recently described entity that is increasingly recognized as an important cause. The cerebral arterial wall is thought to be affected by an inflammatory process related to certain infections. The authors report a 2.5-year-old girl with sudden left hemiplegia and aphasia. The neuroimaging showed occlusion of the right middle cerebral artery and ischemic damages. Laboratory revealed positive cytomegalovirus immunoglobulin M and G in cerebrospinal fluid and in early and late sera. Treatment with ganciclovir, anticytomegalovirus immunoglobulin, and prednisolone, followed by oral aspirin, resulted in clinical improvement. The follow-up neuroimaging showed stabilization of the arterial lesions without residual stenosis. To our knowledge, this is the first report of a cytomegalovirus-associated transient cerebral arteriopathy in an immunocompetent child. Our report demonstrates the propensity for cytomegalovirus to be involved in pediatric cerebral vascular disease.

Keywords

stroke, childhood, cytomegalovirus, arteriopathy, infection

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Transient cerebral arteriopathy is a unilateral monophasic arteriopathy frequently recognized in children with arterial ischemic stroke. Transient cerebral arteriopathy typically results in lenticulostriate infarcts as a result of a nonprogressive unilateral intracranial arteriopathy of the distal internal carotid artery and proximal middle cerebral artery or the anterior cerebral artery. The confirmatory diagnosis of transient cerebral arteriopathy requires follow-up cerebrovascular imaging, indicating stabilization or improvement in the arterial lesions, with or without residual stenosis.[1] In regard to the pathognomonic mechanism of transient cerebral arteriopathy, the cerebral arterial wall is thought to be affected by an inflammatory process related to certain infections. The previously reported infectious agents associated with transient cerebral arteriopathy include varicella-zoster virus, enterovirus, human immunodeficiency virus (HIV), and *Borrelia burgdorferi*.[2] However, the association of transient cerebral arteriopathy with a cytomegalovirus infection has never been reported. Here, the authors report a child with transient cerebral arteriopathy associated with a cytomegalovirus infection, which can be a causative agent.

Case Study

A girl, aged 2 years and 6 months, had previously been in good health. She presented to our emergency department with a chief complaint of the sudden onset of left hemiplegia and aphasia, heralded by left-sided headaches. Over the previous 2 weeks, she experienced 3 episodes of transient left-sided weakness, which had resolved spontaneously in less than an hour on each occasion. She received Japanese B encephalitis vaccine 3 days

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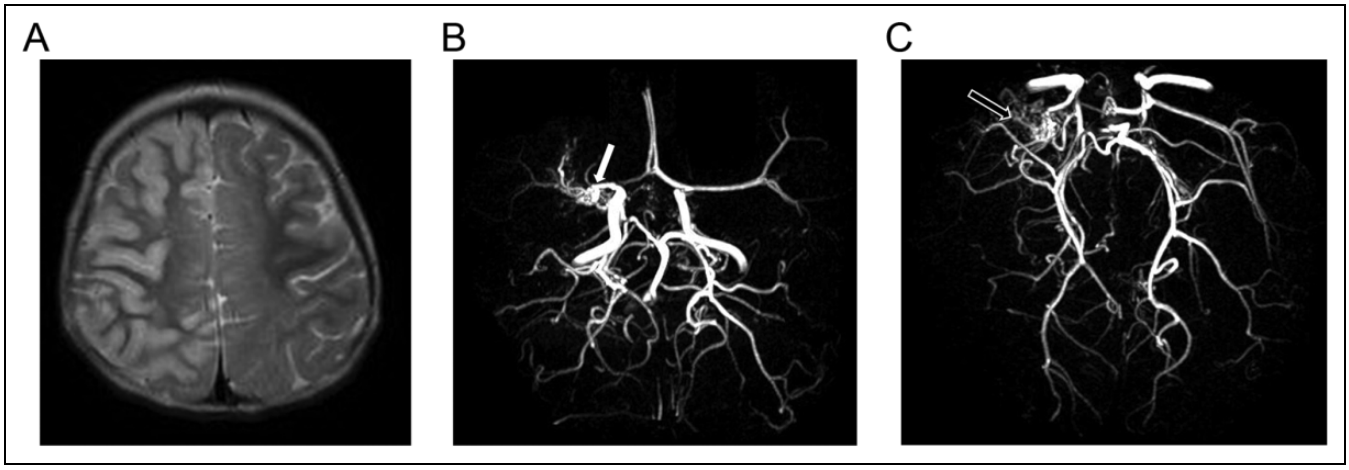

Figure 1. A, T2-weighted magnetic resonance imaging showing hypersignal of the right middle cerebral artery territory. B, Magnetic resonance angiography showing an occlusion of the right middle cerebral artery (white arrow). C, Note a "puff-of-smoke" network of vessels, reminiscent of Moyamoya disease, was also depicted in the territory supplied by right lateral lenticulostriate arteries (black arrow).

prior to this episode. The relevant feature in her past history was a mild febrile episode associated with a transient maculopapular skin rash and elevated serum hepatic transaminase levels 1 month previously: aspartase aminotransferase = 85 IU/L (normal reference: 10-42 IU/L) and alanine aminotransferase = 102 IU/L (normal reference: 10-40 IU/L). She was fully conscious and afebrile, and there were no respiratory or digestive signs. Her neurological examination on admission revealed an expressive aphasia, left facial droop, and hemiparesis, with her leg being weaker than her arm.

A brain computerized tomography scan revealed diffusely edematous changes with enhanced meninges in the right fronto–parieto–temporal lobes and the left parietal lobe. A cranial magnetic resonance imaging showed infarction in the region of the right middle cerebral artery (Figure 1A). The magnetic resonance angiography showed loss of signal in the proximal middle cerebral artery, suggestive of occlusion (Figure 1B). In addition, the magnetic resonance angiography showed stenoses of bilateral supraclinoid internal carotid arteries and a reminiscent feature of Moyamoya disease in the right basal ganglion, which was demonstrated by "puff-of-smoke" network of vessels (Figure 1C). Routine investigations for a possible underlying cause of the childhood ischemic stroke, including tests for a possible thrombotic tendency (factor V Leiden mutations, homocysteine, protein S and C, antithrombin III levels, antiphospholipid antibodies, and lactic acid), inborn errors of metabolism (plasma amino acids and urine organic acids), or congenital heart disease (echocardiogram), were all normal. A lumbar puncture showed 45 nucleated cells per mm^3 with 80% lymphocytes and normal glucose and protein. Tests for a viral infection were performed, including detection of viral material in the cerebrospinal fluid using polymerase chain reaction (PCR) techniques and detection of antibodies (immunoglobulin G and M). Serum cytomegalovirus immunoglobulin M and immunoglobulin G tests were positive in early and late sera. Cytomegalovirus immunoglobulin M was positive in cerebrospinal fluid; however, no cytomegalovirus DNA was detected by PCR either in the cerebrospinal fluid or in the blood. Cytomegalovirus antigen pp65 was not found in cerebrospinal fluid or serum samples. Polymerase chain reaction was negative for human immunodeficiency virus, varicella-zoster virus, herpes simplex virus type 1 and 2, and enterovirus. The cryptococcal antigen was not detected.

Treatment with anticytomegalovirus immunoglobulin for 3 days and ganciclovir for 2 weeks in addition to prednisolone resulted in gradual improvement in clinical symptoms. She is currently on long-term aspirin therapy and has made a good functional recovery with no recurrent events. The parents refused a further survey via conventional cerebral arteriography. Follow-up magnetic resonance angiography performed 3 months later showed stabilization of the previous vascular lesions and further improvement at the 6-month follow-up. Magnetic resonance angiography showed partial recanalization of the right middle cerebral artery with increased distal flow and improvement in the internal carotid artery stenosis. Twelve months later, her neurological examination was normal and a follow-up magnetic resonance angiography was unchanged.

Discussion

Transient cerebral arteriopathy is emerging as one of the main arteriopathies underlying childhood stroke. The most plausible pathogenesis underlying transient cerebral arteriopathy is a transient vasculitis induced by a preceding viral infection. Among the previously reported infectious origins in transient cerebral arteriopathy, varicella-zoster virus accounts for the most common (approximately one-third) identifiable pathogen. Herein, we describe a child with a prior cytomegalovirus infection and ischemic stroke who fulfilled the criteria of a transient cerebral arteriopathy.[2] Furthermore, the fact that the child's arteriopathy is in complete remission after antiviral therapy and treatment with prednisolone also favors a diagnosis of

cytomegalovirus-associated transient cerebral arteriopathy. To our knowledge, this is the first reported case of transient cerebral arteriopathy manifestly associated with a cytomegalovirus infection. Our report highlights that a cytomegalovirus infection should be considered in children diagnosed with transient cerebral arteriopathy.

Some viral infections are able to produce a cerebral vasculitis, leading to infarction. Herpes simplex virus 1 and 2 are the best known; however, varicella-zoster virus can be a more frequent cause. The family of herpesviruses consists of a large group of double-stranded DNA viruses that includes herpes simplex virus 1, herpes simplex virus 2, cytomegalovirus, Epstein-Barr virus, varicella-zoster virus as well as human herpes virus 6 and 7. Similar to varicella-zoster virus, cytomegalovirus, as one of the members of the herpesvirus family, has the capacity to remain latent in tissue after an acute infection.[2] Subsequently, cytomegalovirus productively infects vascular endothelial cells, causing vasculitis of leukocytoclastic or necrotizing form with fibrinoid necrosis. Conversely, cytomegalovirus is also known to alter the phenotype of the endothelium in vitro from anticoagulant to procoagulant by elevation in both platelet-derived growth factor and transforming growth factor, thus promoting the adherence of neutrophils and platelets to the endothelium. These growth factors can also induce vascular cell wall proliferation.[3] Therefore, a cytomegalovirus virus infection can simultaneously cause vascular injury and thrombosis, leading to infarctions. Intriguingly, our patient's magnetic resonance angiography also depicted a Moyamoya arteriopathy pattern in her right basal ganglion. Older children with transient cerebral arteriopathy generally have large-vessel disease; however, features of a Moyamoya-like pattern of arteriopathy have been described in the angiogram of a postvaricella-infected boy.[4]

In the present case, the causal relationship between transient cerebral arteriopathy and cytomegalovirus infection is defined by the detection of seroconversion against cytomegalovirus in the patient's early and late sera and positive immunoglobulin M in the cerebrospinal fluid. Cytomegalovirus is a ubiquitous herpesvirus with the capacity to cause various clinical syndromes. Although postnatal cytomegalovirus infection is common, clinically apparent cytomegalovirus infection is uncommon in healthy children. Most immunocompetent children infected by cytomegalovirus can manifest a self-limited course of either hepatitis or an infectious mononucleosis-like syndrome (cytomegaloviral mononucleosis). The immunocompromised hosts are particularly at risk for life-threatening complication of an acute cytomegalovirus infection, such as encephalitis and pneumonitis. In addition, a cytomegalovirus infection appears to have a specific tropism for vascular endothelium. Indeed, cytomegalovirus-associated vasculitis has been reported; however, it is an extremely rare condition. Vasculitis caused by cytomegalovirus occurs predominantly in immunocompromised patients and represent a broad spectrum of disease involving the gastrointestinal tract, skin, lung, eyes, heart, kidneys, central nervous system, and peripheral nervous system.[5] On rare occasions, cytomegalovirus infection can also cause vasculitis in nonimmunocompromised patients and can be either a causative agent or an opportunistic infection. The underlying state of host immunocompetence probably plays a pivotal role in determining the outcome of cytomegalovirus-associated vasculitis.[5] Such postulation can further explain the self-limited course of arteriopathy in our patient.

Infection with cytomegalovirus has been associated with several childhood neurologic conditions, including infantile spasms, Guillain-Barre syndrome, encephalitis, and myelitis. Similarly, cytomegalovirus-associated vasculitis can complicate a variety of neurologic defects.[6] A severe case of cytomegalovirus-associated vasculitis resulting in widespread infarction of the brain and spinal cord was described in a patient with an underlying lymphoma.[7] The arteriopathy can be explained either by direct cytomegalovirus infection of the cerebral vascular wall or by an indirect immunological effect of systemic cytomegalovirus infection. In accordance with past hypotheses,[5,6] the present case showing the presence of pleocytosis and the positive immunoglobulin M for cytomegalovirus in the cerebrospinal fluid makes the former mechanism more plausible. The exact mechanism of varicella-zoster virus-associated transient cerebral arteriopathy is unclear; however, transaxonal migration of reactivated varicella-zoster virus from the trigeminal ganglion along the trigeminal nerve to the cerebral arteries, leading to vasculitis, is likely. We postulate a similar mechanism in which cytomegalovirus spread to the affected arterial wall occurs through the ophthalmic branch of the trigeminal nerve.

In conclusion, the present case highlights the need to include cytomegalovirus infections as possible causative factors in the differential diagnosis and classification of children with transient cerebral arteriopathy. We suggest the necessity for performing an extensive infectious disease evaluation for possible viral pathogens of the cerebral involvements when the cause of the childhood stroke remains indefinite.

Author Contribution

Wei-Tsun Kao contributed to conception of report, acquisition of data, or analysis and interpretation of data, comments upon the manuscript, and drafting the manuscript for intellectual content. Wei-Chen Lin contributed to analysis and interpretation of imaging. Yong-Hao Tseng contributed to acquisition of the data and comments upon the manuscript. Tai-Heng Chen contributed to conception and design, acquisition of data, revising the manuscript critically for important intellectual content, comments upon the manuscript, and final approval of the version to be published.

Declaration of Conflicting Interests

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Ethical Approval

The study was obtained a waiver of ethical review approved by the Institutional Review Board of Kaohsiung Medical University Hospital, Kaohsiung, Taiwan.

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