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Understanding the importance of cerebrovascular involvement in Kawasaki disease

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Kawasaki disease (KD) is a systemic vasculitis in infants and young children. However, its natural history has not been fully elucidated because the first case was reported in the late 1960s and patients who have recovered are just now entering middle age. Nevertheless, much evidence has raised concerns regarding the subclinical vascular changes that occur in post-KD patients. KD research has focused on coronary artery aneurysms because they are directly associated with fatality. However, aneurysms have been reported in other extracardiac muscular arteries and their fate seems to resemble that of coronary artery aneurysms. Arterial strokes in KD cases are rarely reported. Asymptomatic ischemic lesions were observed in a prospective study of brain vascular lesions in KD patients with coronary artery aneurysms. The findings of a study of single-photon emission computed tomography suggested that asymptomatic cerebral vasculitis is more common than we believed. Some authors assumed that the need to consider the possibility of brain vascular lesions in severe cases of KD regardless of presence or absence of neurological symptoms. These findings suggest that KD is related with cerebrovascular lesions in children and young adults. Considering the fatal consequences of cerebral vascular involvement in KD patients, increased attention is required. Here we review our understanding of brain vascular involvement in KD.

Key words: Kawasaki disease, Stroke, Central nervous system, Vasculitis

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Why do we focus on cerebral vascular involvement in KD?

Kawasaki disease (KD) is a self-limiting systemic vasculitis that occurs in infants and young children that preferentially involves medium-sized muscular arteries, particularly the coronary arteries.[1] Coronary artery aneurysm, the most severe complication of KD, develops in 15%–25% of untreated patients and may lead to lethal manifestations including myocardial ischemia, infarction, and sudden death.[2] Since the introduction of intravenous immunoglobulin (IVIG) therapy, the risk of coronary artery aneurysm has remarkably decreased, but it still occurs in 4%–6% of patients.[3,4] KD is among the leading causes of acquired heart disease in developed countries.[4] However, research focuses on the coronary artery because coronary arterial lesions are directly associated with fatality. However, KD is a systemic vascular disease. Aneurysms have been reported in other extracardiac muscular arteries such as the celiac, mesenteric, femoral, iliac, renal, and branchial.[5] Extracardiac artery aneurysms reportedly occur in younger infants and those with severe acute vasculitis. The fate of extracardiac artery aneurysms resembles that of coronary artery aneurysms. Larger extracardiac artery aneurysms seem to cause stenotic lesions in the late period.[5] Arterial strokes are very rarely reported in KD.[6] Based on these findings, some authors suggested that noninvasive imaging modalities to confirm extracardiac artery aneurysms should be

performed in severe cases of KD with coronary aneurysms.[5] Attention to cerebral vascular involvement in KD patients is also needed considering its fatal consequences. Autopsy cases showed endoarteritis and periarteritis in the parenchymal and pial arteries despite such lesions being less extensive than those seen in other areas such as the coronary and iliac arteries.[7] However, until now, there has been little interest in cerebral vasculitis, which may lead to stroke in KD patients. Since KD was first recognized in the late-1960s, patients who have recovered will now be middle-aged or younger. Therefore, the follow-up of these patients has been insufficient to reveal the disease's natural history.[8] This report aims to review brain vascular involvement in KD focusing on cerebral vasculitis. Here we summarize case reports of arterial strokes, discuss the evidence of cerebral vasculitis, and suggest future research directions.

Review of arterial stroke in KD patients

1. Ischemic stroke

To our knowledge, only 16 cases of cerebral ischemic stroke have been reported in pediatric patients with KD. In the literature, cerebral infarction onset associated with KD ranges from 3 days to 4 months.[6] Most cases developed during the acute to subacute phase of KD.[6] Among them, we summarize only those studies published in English (Table 1).[6,9-19] However, too few cases were reported to identify the clinical predictors of stroke in KD patients. Nevertheless, a prolonged fever or severe KD presentation seems to be noteworthy in connection with ischemic stroke. All patients but one suffered from a fever lasting more than a week (median 10.5 days). In some patients, a devastating course developed. This analysis shows that we must monitor for cerebrovascular involvement as well as cardiovascular complications in KD patients with prolonged fever or severe progression.

Several potential mechanisms may explain the occurrence of stroke in KD. In most cases, cerebral infarction occurred in the middle cerebral artery (MCA) territory in KD patients. Most cases of MCA territory infarction have been attributed to cardiogenic embolism, internal carotid artery occlusion, or internal carotid artery dissection.[20] Embolism induced by myocardial infarct likely provokes the cerebral infarction in the course of KD.[21] IVIG-associated thrombosis also has been suggested as a cause of stroke in KD.[13] Complete occlusion of the internal carotid artery was reported in an 18-month-old girl 10 days after the onset of fever and the day after she received IVIG.[6] Thrombotic complication is one of the well-known complications of immunoglobulin therapy.[22] IVIG-associated thrombosis may be related with an increased blood viscosity, procoagulant activity of immunoglobulin itself, and immunoglobulin-induced arterial vasospasm.[6] The authors of this case suggested evaluating hydration status before IVIG treatment.[6] A 30-month-old girl with hemiplegia showed ongoing inflammatory processes of the cerebral vessels as the cause of her stroke and no abnormal findings of magnetic resonance angiography (MRA).[16] However, in this patient, stroke occurred shortly after aspirin therapy was stopped.[16] Therefore, in addition to vascular inflammation, acquired thrombophilia related to inflammatory syndrome with hyperthrombocytosis might have been a mechanism of stroke in this patient.[16]

An arteritic complication was also suggested as a possible mechanism of stroke in a male infant with cerebral infarct because complete occlusion of the MCA and systemic aneurysms (including coronary aneurysm) were noticed simultaneously.[23] In this patient, stroke occurred 45 days after KD symptom onset and he was not treated with IVIG.[23] This case suggested that cerebral infarction involving large-sized blood vessels might be associated with arterial occlusion resulting from a nonspecific inflammation burst and prothrombotic inflammatory state of the large vessels.[19] Cerebral vasculitis affecting medium- and small-sized vessels has been suggested as a cause of stroke in KD.[19] A 4-year-old female patient presented with rapidly catastrophic KD in which tetraplegia developed 15 days after KD onset.[19] Multiple supra- and infratentorial microhemorrhages were observed, but neuroimaging revealed normal arteries of the circle of Willis.[19] Based on these findings, the authors suggested diffuse brain vasculitis as a cause of ischemic damage in this patient.[19]

2. Hemorrhagic stroke

Only 5 cases have been reported to date on hemorrhagic stroke as a possible complication of KD.[24-28] Among them, we summarize 3 cases were published in English (Table 2).[24-26] All 3 cases were caused by aneurysm rupture that occurred from 7 months to a decade after KD onset.[24-26] Aneurysm rupture appears a more long-term complication of KD compared with ischemic stroke. Among the 3 cases, a saccular aneurysm at the bifurcation of the major arteries in 2 cases and a stalk-like aneurysm located at the trunk of the major artery in 1 case.[24-26] Histopathologic findings of a 12-year-old male patient seemed to mimic the acute inflammatory changes observed in the coronary arteries in KD because of hypertrophy and invasion of the inflammatory cells resulting in endothelial wall thickness.[24] This patient had KD at 3 years of age and had a stroke 9 years later.[24] On the other hand, there was only mild invasion of inflammatory cells but complete absence of the elastic lamina in a 20-year-old man.[26] The authors suggested that all the vasculitis changes during infancy completely destroy elastic lamina and tunica intima which caused the aneurysmal formation.[26] The pathological findings of the 2 cases suggested that inflammation of cerebral arteries might be associated with aneurysm formation in KD.[24,26] Although it is difficult to draw any conclusions from the 2 cases, these findings show why attention must be paid to inflammation of the cerebral vessels in KD.

Table 1. Literature review of studies of ischemic stroke associated with Kawasaki disease (English publications only)

Study	Sex/age[a]	Clinical findings before stroke	Stroke onset[b]/ associated symptoms	Lesions brain/ coronary artery & others	KD treatment	Stroke treatment
Hosaki et al. (1978)[9]	M/4 mo	?	45 Days/hemiplegia	Occlusion of the right MCA/ aneurysms of coronary artery & brachial artery	Corticosteroid & antibiotics	Anticoagulant
Laxer et al. (1984)[10]	F/26 mo	Fever 10 days+5/5 features of KD[c]; seizures with fever	18 Days/desquamation of fingers & toes, hemiplegia	Occlusion of the right MCA/ ?	Corticosteroid & antibiotics	?
Lapointe (1984)[23]	M/4 mo	Fever 21 days+4/5 features of KD; diarrhea	45 Days/focal motor seizures, mental changes, hemiplegia, bilateral pulsation mass at groin & axilla	Occlusion of the right MCA/ right common carotid artery complete occlusion	Corticosteroid, antibiotics, azathioprine	?
Templeton and Dunne (1987)[11]	?/6 mo	Fever 3 wk+?	26 Days/2nd febrile illness, desquamation, focal motor seizures, hemiparesis	Occlusion of the right MCA/ aneurysms of coronary artery & left internal iliac arteries	?	Died one day after stroke
Suda et al. (2003)[12]	M/8 mo	Fever 20 days+4/5 features of KD	20 Days/fever persisted, hemiplegia	Occlusion of the left MCA/ aneurysms of coronary artery	IVIG & aspirin when diagnosed with stroke	Intracoronary thrombolysis & anticoagulant (heparin)
Wada et al. (2006)[13]	M/3 yr	Fever >6 days+4/5 features of KD	10 Days/hemiplegia	Occlusion of the left MCA/ none	IVIG (1 g/kg for 2 days) & aspirin, 6th day of illness	?
Fujiwara et al. (1992)[14]	M/22 mo	Fever 59 days+5/5 features of KD; mild liver dysfunction; DIC (13rd–20th day of illness)	59 Days/stroke proven only in images without neurological symptoms	Occlusion of the left MCA/ aneurysms of coronary, axillary, & internal iliac arteries	IVIG (250 mg/kg for 5 days) & aspirin, 6th day of illness; DIC treatment	Anticoagulant
Muneuchi et al. (2006)[15]	M/4 yr	Fever 11 days+5/5 features of KD	21 Days/stroke proven only in images without neurological symptom	Right PICA stenosis/left coronary artery dilatation	Aspirin, 3rd day of illness; IVIG (totally 6 g/kg), 5th day of illness; methylprednisolone pulse therapy with heparin (11th day of illness)	Anticoagulant (warfarin)
Gitiaux et al. (2012)[19]	F/4 yr	Fever >12 days+5/5 features of KD; multiorgan failure with shock (9th day of illness)	15 Days (after sedation cessation)/deteriorated consciousness, tetraplegia, ophthalmoplegia, loss of visual reactivity	Diffuse ischemic damage with microhemorrhage (vasculitis)/none	IVIG (2 g/kg) & aspirin, 6th day of illness; corticosteroid (10 mg/kg for 4 days), 8th day of illness; inotropes	Immunosuppressive therapy
Tassinari et al. (2013)1[6]	F/31 mo	Fever 9 days+5/5 features of KD	120 Days (after aspirin withdrawal)/irritability & inconsolable crying, hemiplegia, and facial palsy	Ischemic lesion of right lenticular nucleus & corona radiate. But normal MRA/ none	IVIG (2 g/kg) & aspirin, 7th day of illness	Aspirin
Sabatier et al. (2013)[6]	F/18 mo	Fever 10 days+5/5 features of KD	11 Days (the day after IVIG administration)/hemiplegia, left ptosis	Occlusion of the left MCA/ right common carotid artery complete occlusion	IVIG (2 g/kg) & aspirin, 10th day of illness	Anticoagulant (enoxaparin & aspirin)
Prangwatanagul and Limsuwan (2017)[17]	M/15 mo	Fever 4 days+4/5 features of KD	5 Days (just after fever subsided)/hemiplegia, facial palsy, periungual desquamation	Occlusion of the right MCA/ coronary artery aneurysm	Antibiotics & acyclovir	?
Nikkhah (2018)[18]	M/4 yr	Fever 8 days+2/5 features of KD	3 Days/hemiplegia, facial palsy, aphagia	Occlusion of the left MCA/ bright spot on right coronary artery	IVIG (2 g/kg) & aspirin, 6th day of illness	?

KD, Kawasaki disease; MCA, middle cerebral artery; PICA, posterior inferior cerebellar artery; IVIG, intravenous immunoglobulin; DIC, disseminated intravascular coagulation; MRA, magnetic resonance angiography; ?, unknown.
[a]Age at KD diagnosis. [b]Stroke after KD symptoms onset. [c]Five principal clinical features: bilateral non-purulent conjunctivitis, oral mucosal changes such as strawberry tongue and cracked lips, peripheral extremity changes, rash, and cervical lymphadenopathy >1.5 cm.

Table 2. Literature review of studies of hemorrhagic stroke associated with Kawasaki disease (English publications only)

Study	Sex	Age of KD	Symptoms of stroke	Lesion	Onset of stroke[a]	Other arterial lesion	Fever duration	KD treatment	Stroke treatment
Tanaka et al. (2007)[24]	M	3 yr	Headache	Meningeal hemorrhage by rupture of left PCA aneurysm	9 yr	Right PCA, right posterior communicating artery	3 Days	Unknown	Surgery
Ahn et al. (2010)[25]	M	6 mo	Seizure	Intracerebral & meningeal hemorrhage by rupture of left middle cerebral artery aneurysm	7 mo	None	5 Days	IVIG & aspirin	Surgery
Ishida et al. (2014)[26]	M	Unknown	Headache	Intracerebral and meningeal hemorrhage by rupture of right middle cerebral artery aneurysm	Unknown	Unknown	Unknown	Unknown	Surgery

KD, Kawasaki disease; MCA, middle cerebral artery; PCA, posterior cerebral artery; IVIG, intravenous immunoglobulin; MRA, magnetic resonance angiography.
[a]Stroke after KD symptom onset.

Asymptomatic cerebral vasculitis may be more common than expected

To discuss this issue, we must review a prospective systematic review of KD patients with coronary artery lesions.[15] Muneuchi et al.[15] prospectively evaluated brain lesions using magnetic resonance imaging (MRI) and MRA in 24 patients with coronary artery lesions at 0.1–21.2 years after the onset of KD. The median age at KD onset was 1.2 years, and no patients had significant neurological symptoms or signs.[15] Of 24 patients, approximately half (11 of 24) had a giant aneurysm in the coronary artery, while 17 (70%) were treated with aspirin and IVIG. An ischemic lesion was observed in one of 24 patients (4%) on brain images.[15] MRI on the 21st day of the illness revealed an ischemic lesion on the cerebellum with severe stenosis of the right posterior inferior cerebellar artery in a 4-year-old boy.[15] He was unresponsive to 2 trials of IVIG and had a giant aneurysm. Interestingly, he had no obvious neurological symptoms or signs throughout the KD course.[15] The authors assumed the need to consider the possibility of brain vascular lesions in severe cases of KD with or without neurological symptoms.[15] Considering the long-term consequences of cerebrovascular lesions, the incidence of 4% seen in this study is not low.

We then considered the brain vascular involvement in patients without coronary artery lesion. No coronary artery lesion has been reported in some patients with ischemic stroke.[6,13] A study of single-photon emission computed tomography (SPECT) by Ichiyama et al.[29] might answer this question. To investigate brain perfusion in the acute stage of KD, they performed SPECT in 21 children with acute stage KD and performed follow-up SPECT and MRI about 1 month after the first SPECT.[29] SPECT imaging demonstrated localized cerebral hypoperfusion in 6 of 21 children (28.6%), but none had any abnormal neurological symptoms or signs.[29] No coronary lesions were reported in any of these 6 patients.[29] The maximum C-reactive protein level or fever duration was not related with SPECT abnormalities.[29] The follow-up SPECT and MRI performed 1 month after the first SPECT revealed no abnormalities.[29] SPECT has been used as a diagnostic tool for cerebral vasculitis.[30] Vasculitic central nervous system (CNS) involvement has been seen with hypoperfusion in SPECT.[30] Based on these findings, Ichiyama et al.[29] suggested that cerebral vasculitis might have been caused by transient localized cerebral hypoperfusion observed on SPECT in patients of this study. The interesting findings of this study are that approximately 30% of patients showed evidence of cerebral vasculitis without coronary lesions and neurological signs.[29] The 2 studies mentioned above[15,29] suggested that asymptomatic involvement of the cerebral vessels or cerebral vasculitis may be more common than expected. Thus, should all KD patients be subjected to further neurological evaluations? There is insufficient data to answer this. However, considering the fact that clinically significant neurological complications are very rare, additional neurological examinations or tests may not be necessary in all KD patients.

Cerebrospinal fluid study evaluating CNS inflammation in KD

From this perspective, we studied the intracranial inflammatory response in patients with acute-phase KD with evaluating the cerebrospinal fluid (CSF) cytokine levels.[31] We hypothesized that the CSF levels of proinflammatory cytokines are elevated if cerebral vasculitis accompanies acute stage KD.[31] Inflammatory cytokines including tumor necrosis factor (TNF)-α and interleukin (IL)-6 might play a critical role in the pathogenesis of KD[32] and the development of inflammation within the cerebral blood vessels.[32,33] These cytokines were secreted by infiltrated immune cells within the vessels.[34] Vascular changes such as endoarteritis, periarteritis, and perivascular cuffing with mild lymphocytic infiltration have been observed in some pial arteries in autopsy cases.[7] Pentraxin-3 (PTX3) is synthesized at the sites of vascular inflammation and serves as a biomarker of vasculitis in many diseases.[35] The whole-blood transcript levels of PTX3-encoding genes and the extent of KD vasculitis have been reported.[36] PTX3 is capable of inducing vascular endothelial dysfunction.[37] Based on these findings, we hypothesized that elevated CSF levels of TNF-α, IL-6, and PTX3 may suggest CNS vascular involvement. To verify our hypothesis,

we measured the levels of the aforementioned mediators in patients with KD and compared them to those of the febrile control groups.[31] Contrary to our expectations, PTX3 and TNF-α were rarely detected in KD patients, while the levels of IL-6 did not differ from those of nonspecific viral illness.[31] Our study seems to show that intracranial inflammation including vasculitis might not be insignificant in patients with KD.[31] We found no evidence of intracranial inflammation related with vascular involvement.

However, Korematsu et al.[38] reported that CSF IL-6, soluble TNF-α receptor 1, and the IL-6 CSF/serum ratio were elevated in patients with KD. They revealed that some patients with KD had a higher degree of independent CNS inflammation.[38] Thus, how can we interpret these conflicting results? The major differences between our study[31] and that of Korematsu et al.[38] were onset age, disease severity, and the presence of neurological symptoms. The mean patient age in the study of Korematsu et al.[38] was 2.6±2.1 years; all patients had mildly disturbed consciousness, while some had a coronary aneurysm. In contrast, all patients in our study were very young (median, 2.3 months), did not have coronary aneurysm, and underwent lumbar puncture to find the febrile focus.[31] Those findings suggest that intracranial inflammation may be related with coronary artery inflammation severity. To prove this issue, further studies involving larger number of patients with a wide spectrum are needed. The intracranial inflammation status is unknown in most KD patients.

There is growing concern about the predisposition of KD patients to endothelial damage or cardiovascular disease in later life. Some authors advise that individuals with a history of KD receive cardiovascular counseling and make an effort to minimize traditional modifiable cardiovascular risk factors.[39] Stroke might be a complication of KD. A few studies have suggested that asymptomatic cerebral vasculitis might be more common than originally thought.[29] Therefore, pediatricians should be aware of the possibility of vascular involvement beyond the heart in KD, particularly in the cerebral vessels.

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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