Review Article doi: 10.2176/nmc.ra.2019-0059

Neurol Med Chir (Tokyo) 59, 361–370, 2019 Online July 6, 2019

Influence of Inflammatory Disease on the Pathophysiology of Moyamoya Disease and Quasi-moyamoya Disease

Takeshi MIKAMI,[1] Hime SUZUKI,[1] Katsuya KOMATSU,[1] and Nobuhiro MIKUNI[1]

[1]*Department of Neurosurgery, Sapporo Medical University, Sapporo, Hokkaido, Japan*

Abstract

Moyamoya disease is a unique cerebrovascular disease that is characterized by progressive bilateral stenotic alteration at the terminal portion of the internal carotid arteries. These changes induce the formation of an abnormal vascular network composed of collateral pathways known as moyamoya vessels. In quasi-moyamoya disease, a similar stenotic vascular abnormality is associated with an underlying disease, which is sometimes an inflammatory disease. Recent advances in moyamoya disease research implicate genetic background and immunological mediators, and postulate an association with inflammatory disease as a cause of, or progressive factor in, quasi-moyamoya disease. Although this disease has well-defined clinical and radiological characteristics, the role of inflammation has not been rigorously explored. Herein, we focused on reviewing two main themes: (1) molecular biology of inflammation in moyamoya disease, and (2) clinical significance of inflammation in quasi-moyamoya disease. We have summarized the findings of the former theme according to the following topics: (1) inflammatory biomarkers, (2) genetic background of inflammatory response, (3) endothelial progenitor cells, and (4) noncoding ribonucleic acids. Under the latter theme, we summarized the findings according to the following topics: (1) influence of inflammatory disease, (2) vascular remodeling, and (3) mechanisms gleaned from clinical cases. This review includes articles published up to February 2019 and provides novel insights for the treatment of the moyamoya disease and quasi-moyamoya disease.

Key words: inflammation, moyamoya disease, macrophage

Introduction

Moyamoya disease was defined in 1969 by Suzuki and Takaku[1)] as a unique cerebrovascular disease characterized by chronic progressive bilateral stenosis of the terminal portion of the internal carotid arteries (ICAs), leading to the formation of an abnormal vascular network composed of collateral pathways at the base of the brain. Although this disease is idiopathic, it is also sometimes associated with an underlying disease. In that case, it is called quasi-moyamoya disease.[2,3)] Although the epidemiology, clinical features, and genetics of quasi-moyamoya disease have been studied,[4)] little is known about its etiology and mechanism of progression.

Received March 26, 2019; Accepted May 28, 2019

In quasi-moyamoya disease, some of the underlying diseases are associated with acute or chronic inflammation including atherosclerosis, autoimmune disease, meningitis, and irradiation.[5,6)] These local or systemic inflammatory diseases sometimes precede the clinical progression of quasi-moyamoya disease. Therefore, multiple inflammatory pathways of these inflammatory diseases might promote the onset or progress of moyamoya disease and quasi-moyamoya disease. Recently, chronic inflammation has attracted attention as a common pathological basis of various diseases. Low-level chronic inflammation reaction, called smoldering, is associated with chronic inflammation in the progress of various diseases. The chronic inflammation induces fibrosis or angiogenesis due to the disruption of the adaptative responses, and sometimes leads to organ failure. Current cerebrovascular disease research has adopted a more integrative approach toward inflammatory diseases.[7,8)] In this review article, the influence of acute or chronic inflammation on the pathophysiology of moyamoya disease and quasi-moyamoya disease is discussed.

Methods

For this review, a systematic search of the English language literature was performed using the PubMed/Medline database with the keywords moyamoya disease and various combinations of words such as pathology, inflammation, genetics, cytokines, and angiogenesis. Considering an association between moyamoya disease or quasi-moyamoya disease and inflammatory disease, this review included two main themes: (1) molecular biology of inflammation in moyamoya disease, and (2) clinical significance of inflammation in quasi-moyamoya disease. We summarized the findings of the former theme according to the following topics: (1) inflammatory biomarkers, (2) genetic background of inflammatory response, (3) endothelial progenitor cells (EPCs), and (4) noncoding ribonucleic acids (RNAs). Under the latter theme, we summarized the findings according to the following topics: (1) influence of inflammatory disease, (2) vascular remodeling, and (3) mechanisms gleaned from clinical cases.

The definitions of moyamoya disease and quasi-moyamoya disease overlap conceptually. Basically, when moyamoya disease is clinically associated with a complicated inflammatory disease, it is defined as quasi-moyamoya disease in this article. Therefore, the association between moyamoya disease (not quasi-moyamoya disease) and an inflammatory disease cannot be explained in a clinical setting. According to this definition, it is transcribed into quasi-moyamoya disease in this article when underlying disease are apparent, and differentiate it from moyamoya disease that is without underlying disease. Atherosclerotic disease is also included in quasi-moyamoya disease. However, when an inflammatory disease was found incidentally, it was transcribed into moyamoya disease. In terms of basic research, we transcribed all it into moyamoya disease.

Molecular biology of inflammation in moyamoya disease

Inflammatory biomarkers Inflammatory response ultimately leads to the hyperplasia of intimal vascular smooth muscle cells and neovascularization by proliferation of endothelial cells, that causes lumen stenosis and collateral formation. The two major pathways conceptualized to be influential in the inflammatory response for the initiation or progression of moyamoya disease are: (1) anti-inflammatory cytokine pathway, and (2) pro-inflammatory cytokine pathway activating the ring finger protein 213 (*RNF213*) (Fig. 1). The immune responses associated with angiogenesis are promoted by M2 macrophages that are induced by anti-inflammatory cytokines including Interleukin (IL)-4, IL-10, IL-13, interferon (IFN)-α, and transforming growth factor (TGF)-β. Fujimura et al.[9] reported that serum CD163 and CXCL5 levels of moyamoya disease patients were significantly higher than those of controls, suggesting that moyamoya disease pathology was associated with M2 macrophages. Angiogenetic mediators are activated through these anti-inflammatory cytokines. TGF β from Treg/Th17 cells with unique CD4+

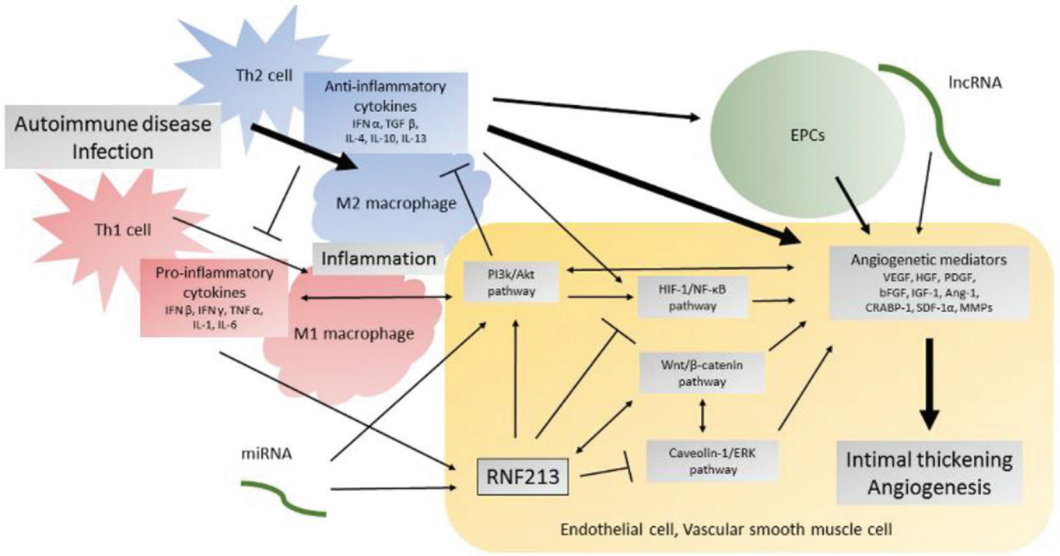

Fig. 1 Conceptualized overview of the association between inflammation and angiogenesis. The regulatory roles of *RNF213*, pro-inflammatory cytokines, anti-inflammatory cytokines, PI3K/Akt pathway, HIF-1/NF-κB pathway, Wnt/β-catenin pathway, caveolin-1/ERK pathway, and angiogenic mediators are shown. Two major pathways are conceptualized: (1) anti-inflammatory cytokine pathway, and (2) pro-inflammatory cytokines pathway with *RNF213*.

T-helper cell subsets has been recently shown to contribute to abnormal angiogenesis in moyamoya disease through regulation of vascular endothelial growth factor (VEGF) signaling.[10] Elevation of numerous angiogenetic mediators such as VEGF, basic fibroblast growth factor (bFGF), platelet-derived growth factor (PDGF), hepatocyte growth factor (HGF), matrix metalloproteinases (MMPs), hypoxia-inducible factor 1 (HIF-1) and cellular retinoic acid-binding protein-1 (CRABP-1) has been reported in moyamoya disease.[11–22] These are postulated to play a crucial role in angiogenesis and intimal proliferation by reciprocally influencing endothelial cells, and perhaps causing the initiation or progression of moyamoya disease. The pro-inflammatory cytokines such as IFN-β, IFN-γ, tumor necrosis factor (TNF)-α, IL-1, and IL-6 activating the *RNF213*-dependent pathway work differently from the anti-inflammatory cytokine pathways.

Genetic background of inflammatory response

In 2011, the *RNF213* gene variant, c.14576G>A (p.R4810K, rS112735431), was identified as the susceptibility gene for moyamoya disease in East Asian populations. The p.R4810K variant exists in 0.5–2.0% of the general population in East Asia.[23,24] Liu et al.[25] screened for the p.R4810K variant and reported that the frequency differed depending the country; this variant was estimated to exist in approximately 16.16 million people in the East Asian countries. However, the actual number of patients exhibiting these symptoms is much less, indicating that other factors such as inflammatory and immune response might play an indirect role in the onset of moyamoya disease. Interestingly, the frequency of p.R4810K carriers was significantly higher in quasi-moyamoya disease than in controls,[26,27] supporting the role of the gene variant *RNF213* p.R4810K in quasi-moyamoya disease. On the other hand, Miyawaki et al.[28] reported that *RNF213* c.14576G>A variant is not associated with quasi-moyamoya disease, although it could be due to a small sample size.

Pro-inflammatory cytokines including IFN-β, IFN-γ, and TNF-α, synergistically activated the transcription of *RNF213* both *in vitro* and *in vivo*.[29,30] Although these pro-inflammatory cytokines are anti-angiogenic, they have an suppressive effect through the induction of *RNF213* (Fig. 2).[30] PI3 kinase-Akt (PI3K/Akt) pathway in endothelial cell contributes to the transcriptional activation of *RNF213*. Although the inhibition of the PI3K/Akt pathway has been shown to reduce the severity of inflammation in autoimmune diseases,[31] some types of moyamoya diseases triggered by inflammatory disease might be involved in the PI3K/Akt pathway. β-Catenin is crucial in the vascular endothelial cell proliferation and migration during neovascularization after myocardial infarction.[32] VEGF was identified as a target gene of the β-catenin signaling.[33] This suggests that the Wnt signal pathway is possibly associated with angiogenesis. Recently, Scholz et al.[34] reported that *RNF213* in vascular endothelial cells was involved in angiogenesis regulation via the Wnt signaling pathway. Caveolin-1, critical for an inflammatory response,[35,36] is also a key mediator of moyamoya disease. Levels of caveolin-1 in the serum were lower in moyamoya disease, and were markedly decreased in those with the *RNF213* variant.[37] Caveolin-1 is associated with angiogenesis,[38,39] and there is bidirectional crosstalk between the caveolin-1/ERK and Wnt/β-catenin pathways.[40] HIF-1 plays distinct roles in regulating the inflammatory response along with NF-κB.[41] Expression of HIF-1 is regulated by the PI3K/Akt pathway.[42] Triggered by inflammatory cytokines due to autoimmune diseases or infections, each signal transduction pathway is mutually activated through *RNF213*.

RNF213 knock-in mice did not induce moyamoya disease spontaneously, and the characteristic angioarchitecture of moyamoya disease as indicated by the

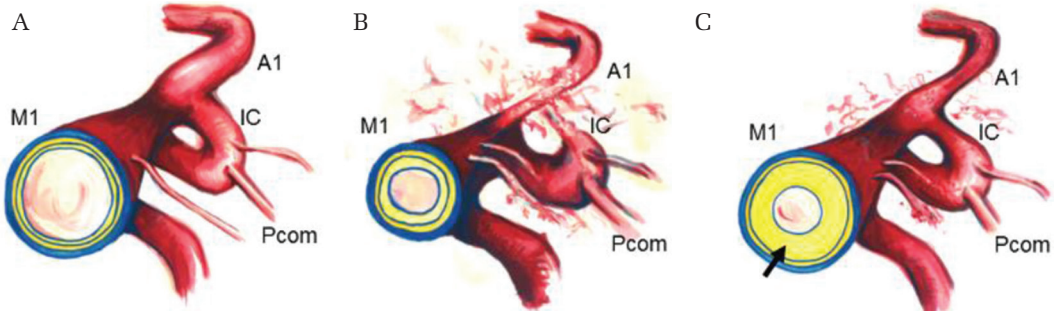

Fig. 2 Schematic of the progression pattern of arterial stenosis in quasi-moyamoya disease. (A) The terminal portion of the ICA in normal artery. (B) The arterial diameter is reduced by constrictive remodeling as shown in moyamoya disease and a majority of quasi-moyamoya diseases. (C) In some types of quasi-moyamoya diseases, the intimal thickening is remarkable with limited vascular constriction.

magnetic resonance angiography was missing in these mice.[43] Moreover, wild-type mice showed temporary hyperplasia of the intimal and medial layers after common carotid artery ligation; however, *RNF213* knock-in mice did not exhibit these changes.[44] On the basis of these findings, Fujimura et al.[45] hypothesized that *RNF213* deficiency might cause vascular fragility and hemodynamic stress vulnerability, which consequently leads to the development of moyamoya disease. In other words, the *RNF213* gene may not be directly involved in the development of moyamoya disease. However, these studies suggest that inflammation due to the autoimmune response might influence *RNF213* and promote the progression of moyamoya disease.

Endothelial progenitor cells The circulating EPCs are derived from the bone marrow, and contribute to postnatal physiological and pathological neovascularization.[46,47] Opposing opinions exist in the moyamoya disease field regarding the EPCs. Rafat et al.[22] first reported an increase of circulating EPCs in adult patients of moyamoya disease. A decrease of EPCs after revascularization surgery was also indicated in moyamoya disease.[48] EPCs secrete angiogenetic factors including VEGF, HGF, angiopoietin-1 (Ang-1), insulin-like growth factor-1 (IGF-1), stromal-derived factor-1α (SDF-1α), bFGF, and PDGF,[49–51] factors which were also increased in moyamoya disease in addition to an increase in circulating EPCs.[22,52] Conversely, Kim et al.[53] reported a decrease in EPCs in pediatric moyamoya disease. The EPC function was also significantly lower in moyamoya disease.[54] Choi et al.[55] also indicated the impaired functional recovery of *in vivo* EPCs in moyamoya disease compared with control. These two opposing results indicate that angiogenesis is either facilitated or decreased in moyamoya disease. However, they all point to abnormal angiogenesis being associated with the pathogenesis of moyamoya disease. This is supported by the success of revascularization surgery in moyamoya disease in which restoration of blood flow to the brain helps in angiogenesis, and improves collateral circulation.

Noncoding RNAs MicroRNAs (miRNAs) are short non-coding RNAs, fewer than 22 nucleotides in length, that regulate gene expression by targeting mRNA for cleavage or translational repression.[56] miRNAs play an essential role in regulating proliferation, survival, differentiation, and aging of cells.[56] They are also involved in inflammation, neurogenesis, and angiogenesis.[57] miRNAs have emerged as important regulators of Toll-like receptor (TLR) signaling in reducing excessive inflammation, increasing tissue repair, and returning to homeostasis after infection and tissue injury.[58] Dai et al.[59] reported that miR-106b and miRNA-126 were upregulated while miRNA-125a-3p was downregulated in moyamoya disease, and the *RNF213* and BRCC3-associated miRNA might contribute to the development of moyamoya disease. In addition, an increase in the expression of miRNA-196a2 and miRNA Let-7c was reported, and these might be potential biomarkers for moyamoya disease.[60,61]

Long noncoding RNAs (lncRNAs) are longer than 200 nucleotides without the protein-coding ability,[62] and play a role in chromatin remodeling, transcriptional control, and post-transcriptional processing.[63] The regulation of lncRNAs might contribute to inflammatory response.[64–66] The lncRNAs are also associated with moyamoya disease pathology through inflammatory cascade including the mitogen-activated protein kinase (MAPK) signaling pathway.[67,68]

Clinical significance of inflammation in quasi-moyamoya disease

Influence of inflammatory disease The frequency with which an inflammatory disease occurs in association with quasi-moyamoya disease is 1.7–4.7% in adults, and 0.54–1.5% in infants.[5] In this study, approximately half of the quasi-moyamoya disease patients had atherosclerosis; therefore, the autoimmune disease cluster has relatively low numerical data. According to the Japanese national survey by Hayashi et al.,[4] diseases except for atherosclerosis accounted for 17.2% of inflammatory diseases in quasi-moyamoya disease. Of these, hyperthyroidism was at 7.5%, meningitis at 2.2%, and other autoimmune diseases were at 17.2% of the total. Thus, hyperthyroidism was the most common autoimmune disease associated with the quasi-moyamoya disease. Other than these, systemic lupus erythematosus, antiphospholipid antibodies syndrome, polyarteritis nodosa, Kawasaki disease, Sjogren's syndrome, Addison's disease, dermatomyositis, granulomatosis with polyangitis, multiple sclerosis, myasthenia gravis, polymyositis, primary systemic vasculitis, rheumatoid arthritis, systemic sclerosis, thyroiditis, and acute limbic encephalitis with anti-LGI1 antibody have been reported.[4,5,69] The associated mechanisms between quasi-moyamoya disease and each individual autoimmune disease are difficult to discern, because at present it is difficult to distinguish correlation form causation. However, the association between chronic systemic inflammation due to autoimmune response and quasi-moyamoya disease can be established.

Compared with moyamoya disease, the clinical characteristics of quasi-moyamoya disease associated with hyperthyroidism are seen primarily in females, involve ischemia, and a relatively higher onset age.[70,71] Moreover, the disease progresses more rapidly than in quasi-moyamoya disease.[72,73] Ischemic attacks often

aggravate the thyroid function. In most cases, the ischemic symptoms induced by thyrotoxicosis were ameliorated after hyperthyroidism was controlled.[71] High levels of thyroid hormones might lead to the progression of quasi-moyamoya disease by augmenting vascular sensitivity to the sympathetic nervous system.[74] T-cell-mediated autoimmune response can also accelerate the pathology. Therefore, the treatment of hormonal abnormality and immunosuppressive therapy prior to surgical treatment are reported to be effective in the management of quasi-moyamoya disease associated with autoimmune diseases.[75,76] Because vascular sensitivity should be improved by suppressing immunological stimulation, then, controlled appearance of symptoms of the quasi-moyamoya disease. Tendler et al.[77] suggested that cellular proliferation and vascular dysregulation in quasi-moyamoya disease and immunological stimulation in hyperthyroidism had a common pathological mechanism involving T-cell dysregulation. This mechanism is associated with not only vascular sensitivity but also vascular morphological alterations in quasi-moyamoya disease with hyperthyroidism,[78] and procedures such as surgical revascularization are recommended in cases with morphological alterations. Hyperthyroidism itself is associated with surgical risk; therefore, for the management of quasi-moyamoya disease, surgical revascularization should be considered after the control of hyperthyroidism.

Quasi-moyamoya disease due to meningitis is rare, and estimated to be 2.2% of all the quasi-moyamoya diseases.[4] The reported causes of infection are as follows; *Propionibacterium acnes*,[79] *Streptococcus pneumoniae*,[75,80,81] *β*-hemolytic group A *Streptococcus*,[82] *Mycobacterium tuberculosis,*[83–86] *Haemophilus influenzae*,[87,88] *Leptospira*,[89] *Mycoplasma pneumoniae*,[90] *Neisseria meningitidis* with Cytomegalovirus,[91] human immunodeficiency virus (HIV),[92–94] *syphilis* with HIV,[95] measles virus,[96] varicella-zoster virus,[97] and Epstein–Barr virus.[91] Vascular events associated with meningitis generally occur within the first 2 weeks after the onset.[98,99] In some cases with quasi-moyamoya disease associates with meningitis, a late-onset morphological alteration of the circle of the Willis after meningitis was observed;[75,80,84,86–88] the elevated autoimmune antibodies indicate an autoimmune trigger for the onset of quasi-moyamoya disease.[75] Liu et al.[100] reported that cerebrospinal fluid in quasi-moyamoya disease had a positive immune response to leptospirosis, and quasi-moyamoya disease was associated with immune reactive vasculitis. We reported a case of the quasi-moyamoya disease that developed 9 years after non-herpetic acute limbic encephalitis with a familial history of moyamoya disease.[101] It was positive for the anti-LGI1 antibody, and we postulated that inflammation due to the autoimmune process contributed to the progress of quasi-moyamoya disease. Thus, chronic inflammation through the autoimmune process, rather than acute inflammation itself, can be a trigger for quasi-moyamoya disease in acute inflammatory disease. In addition to meningitis, systemic acute inflammatory disease might be associated with the development of moyamoya disease. Suzuki et al.[102] studied the incidence of infections in patients with moyamoya disease; they found 82.6% of the children and 61.6% of the adults with moyamoya disease had head and face infections such as tonsillitis, otitis media, maxillary sinusitis, and infections of unknown origin.

Vascular remodeling Pathologically, the vascular lesions in idiopathic moyamoya disease are multilayered intimal fibrous thickenings with neither significant disruption of the internal elastic lamina nor inflammatory infiltration.[103] No lipid pool, inflammatory cells, or macrophage infiltration to the subintimal layer were found, as typically observed in atherosclerosis.[104] Based on this, moyamoya disease has been defined as non-inflammatory intracranial vascular disease. Contrary to the above, Masuda et al.[105] demonstrated smooth muscle proliferation, macrophage infiltration, and the presence of T-cells in moyamoya vessel walls of autopsy specimens. In the quasi-moyamoya disease associated with von Recklinghausen disease, inflammatory cells infiltrate the region surrounding the disease lesion. This indicates that some types of quasi-moyamoya diseases are associated with an inflammatory disease.

From the view point of radiological aspects, Kaku et al.[106] reported that both outer and inner diameters of the ICAs shrink during the remodeling process in moyamoya disease, which is different from the atherosclerotic disease that shows an outward remodeling pattern. The vascular shrinkage in moyamoya disease is found specifically in the horizontal segment of the middle cerebral artery (M1).[107] In a subgroup of quasi-moyamoya diseases, the arterial shrinkage was not remarkable, and the outer diameter of the circle of Willis was not reduced on 3D constructive interference in steady-state sequence.[106] However, this was not common in quasi-moyamoya disease. Yamamoto et al.[108] suggest that quasi-moyamoya disease includes two different pathological subgroups: the constrictive subgroup and non-constrictive subgroup. Thus, a section of the former subgroup of quasi-moyamoya disease shows limited intimal hyperplasia and strong vascular constrictive changes (Fig. 2). The latter subgroup of quasi-moyamoya disease might show excessive fibrosis.

Mechanisms gleaned from clinical cases Two mechanisms have been proposed to be involved

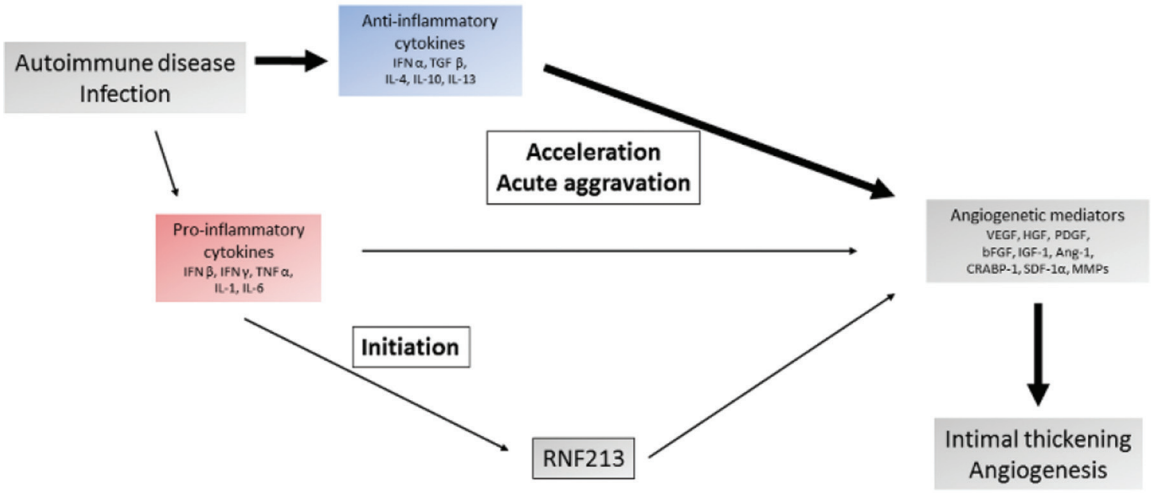

Fig. 3 Conceptualized schema of the mechanisms involved in the inflammatory diseases associated with the moyamoya disease. One mechanism highlights the initiation pathway in which pro-inflammatory cytokines influence *RNF213*. The other mechanism indicates that anti-inflammatory or pro-inflammatory cytokines influence the angiogenetic mediators for acceleration or acute aggravation of the moyamoya disease.

in the inflammatory diseases associated with the quasi-moyamoya disease (Fig. 3). One of the mechanisms involves the anti-inflammatory mediators in the blood or cerebrospinal fluid which influence the acceleration or acute aggravation of the quasi-moyamoya disease. In this pathway, anti-inflammatory cytokines directly affect the vascular reactivity and autoregulation, leading to progress. From the pathophysiological perspective, remission of the symptoms of moyamoya disease could be achieved by the treatment of the inflammatory disease. Based on this, pro-inflammatory cytokines might influence on fulminant progression partly.[109] Specifically, this applies to the quasi-moyamoya disease with hyperthyroidism.[71–74]

The second mechanism involves an increase in the inflammatory cytokines in the inflammatory diseases that influence *RNF213* and lead to the onset of quasi-moyamoya disease. Presence of high frequency of *RNF213* p.R4810K in quasi-moyamoya disease supports this hypothesis. Late-onset cases fall under this type.[75,80,84,86,88,101] This pathway might work as an initiator of the disease, and the clinical course is relatively slow after the onset. This mechanism might be applied not only to quasi-moyamoya disease but also to moyamoya disease widely. Although these concepts are estimates from clinical cases, they play important roles in concurrently controlling both quasi-moyamoya disease and associated diseases. Moyamoya disease and quasi-moyamoya disease is a rare disease, and studying additional cases in the future will provide essential insights for its treatment.

Conclusion

Although inflammation is not a direct cause of quasi-moyamoya disease, it may influence *RNF213*, leading to angiogenesis. It is important to induce curative angiogenesis reflected in the treatment, and increase collateral circulation. To this end, it is essential to increase the expression of the angiogenetic factors, and enhance interaction between vascular cells and neurons; this can pave the way for identifying novel treatments in the future.

Conflicts of Interest Disclosure

The authors declare no conflict of interest.

References

1) Suzuki J, Takaku A: Cerebrovascular "moyamoya" disease. Disease showing abnormal net-like vessels in base of brain. *Arch Neurol* 20: 288–299, 1969
2) Research Committee on the Pathology and Treatment of Spontaneous Occlusion of the Circle of Willis; Health Labour Sciences Research Grant for Research on Measures for Infractable Diseases: Guidelines for diagnosis and treatment of moyamoya disease (spontaneous occlusion of the circle of Willis). *Neurol Med Chir* (*Tokyo*) 52: 245–266, 2012
3) Houkin K, Mikami T: Moyamoya disease and moyamoya syndrome. In Wanebo J, Khan N, Zabramski J, Spetzler R (eds): Moyamoya Disease: Diagnosis and Treatment: Thieme Medical Publishers, 2013

4) Hayashi K, Horie N, Izumo T, Nagata I: Nationwide survey on quasi-moyamoya disease in Japan. *Acta Neurochir* (*Wien*) 156: 935–940, 2014
5) Mejia-Munne JC, Ellis JA, Feldstein NA, Meyers PM, Connolly ES: Moyamoya and inflammation. *World Neurosurg* 100: 575–578, 2017
6) Houkin K, Mikami T: Moyamoya disease and moyamoya syndrome. In Wanebo J, Khan N, Zabramski J, Spetzler R (eds): Moyamoya Disease: Diagnosis and Treatment. New York, Thieme, 2014, pp. 3–9
7) Acosta SA, Lee JY, Nguyen H, Kaneko Y, Borlongan CV: Endothelial progenitor cells modulate inflammation-associated stroke vasculome. *Stem Cell Rev* 15: 256–275, 2019
8) Yoshida Y, Hiwasa T, Machida T, et al.: Elevation of autoantibody in patients with ischemic stroke. *Neurol Med Chir* (*Tokyo*) 58: 303–310, 2018
9) Fujimura M, Fujimura T, Kakizaki A, et al.: Increased serum production of soluble CD163 and CXCL5 in patients with moyamoya disease: involvement of intrinsic immune reaction in its pathogenesis. *Brain Res* 1679: 39–44, 2018
10) Weng L, Cao X, Han L, et al.: Association of increased Treg and Th17 with pathogenesis of moyamoya disease. *Sci Rep* 7: 3071, 2017
11) Hoshimaru M, Takahashi JA, Kikuchi H, Nagata I, Hatanaka M: Possible roles of basic fibroblast growth factor in the pathogenesis of moyamoya disease: an immunohistochemical study. *J Neurosurg* 75: 267–270, 1991
12) Malek AM, Connors S, Robertson RL, Folkman J, Scott RM: Elevation of cerebrospinal fluid levels of basic fibroblast growth factor in moyamoya and central nervous system disorders. *Pediatr Neurosurg* 27: 182–189, 1997
13) Suzui H, Hoshimaru M, Takahashi JA, et al.: Immunohistochemical reactions for fibroblast growth factor receptor in arteries of patients with moyamoya disease. *Neurosurgery* 35: 20–24; discussion 24–25, 1994
14) Yoshimoto T, Houkin K, Takahashi A, Abe H: Angiogenic factors in moyamoya disease. *Stroke* 27: 2160–2165, 1996
15) Hojo M, Hoshimaru M, Miyamoto S, et al.: Role of transforming growth factor-beta1 in the pathogenesis of moyamoya disease. *J Neurosurg* 89: 623–629, 1998
16) Aoyagi M, Fukai N, Sakamoto H, et al.: Altered cellular responses to serum mitogens, including platelet-derived growth factor, in cultured smooth muscle cells derived from arteries of patients with moyamoya disease. *J Cell Physiol* 147: 191–198, 1991
17) Nanba R, Kuroda S, Ishikawa T, Houkin K, Iwasaki Y: Increased expression of hepatocyte growth factor in cerebrospinal fluid and intracranial artery in moyamoya disease. *Stroke* 35: 2837–2842, 2004
18) Kim SK, Yoo JI, Cho BK, et al.: Elevation of CRABP-I in the cerebrospinal fluid of patients with Moyamoya disease. *Stroke* 34: 2835–2841, 2003
19) Takagi Y, Kikuta K, Nozaki K, et al.: Expression of hypoxia-inducing factor-1 alpha and endoglin in intimal hyperplasia of the middle cerebral artery of patients with moyamoya disease. *Neurosurgery* 60: 338–345; discussion 345, 2007
20) Fujimura M, Watanabe M, Narisawa A, Shimizu H, Tominaga T: Increased expression of serum matrix metalloproteinase-9 in patients with moyamoya disease. *Surg Neurol* 72: 476–480; discussion 480, 2009
21) Kang HS, Kim JH, Phi JH, et al.: Plasma matrix metalloproteinases, cytokines and angiogenic factors in moyamoya disease. *J Neurol Neurosurg Psychiatry* 81: 673–678, 2010
22) Rafat N, Beck GCh, Peña-Tapia PG, Schmiedek P, Vajkoczy P: Increased levels of circulating endothelial progenitor cells in patients with moyamoya disease. *Stroke* 40: 432–438, 2009
23) Liu W, Morito D, Takashima S, et al.: Identification of *RNF213* as a susceptibility gene for moyamoya disease and its possible role in vascular development. *PLoS One* 6: e22542, 2011
24) Kamada F, Aoki Y, Narisawa A, et al.: A genome-wide association study identifies *RNF213* as the first moyamoya disease gene. *J Hum Genet* 56: 34–40, 2011
25) Liu W, Hitomi T, Kobayashi H, Harada KH, Koizumi A: Distribution of moyamoya disease susceptibility polymorphism p.R4810K in *RNF213* in East and Southeast Asian populations. *Neurol Med Chir* (*Tokyo*) 52: 299–303, 2012
26) Zhang Q, Liu Y, Yu L, et al.: The association of the *RNF213* p.R4810K polymorphism with quasi-moyamoya disease and a review of the pertinent literature. *World Neurosurg* 99: 701–708.e1, 2017
27) Morimoto T, Mineharu Y, Kobayashi H, et al.: Significant association of the *RNF213* p.R4810K polymorphism with quasi-moyamoya disease. *J Stroke Cerebrovasc Dis* 25: 2632–2636, 2016
28) Miyawaki S, Imai H, Shimizu M, et al.: Genetic analysis of *RNF213* c.14576G>A variant in nonatherosclerotic quasi-moyamoya disease. *J Stroke Cerebrovasc Dis* 24: 1075–1079, 2015
29) Ohkubo K, Sakai Y, Inoue H, et al.: Moyamoya disease susceptibility gene *RNF213* links inflammatory and angiogenic signals in endothelial cells. *Sci Rep* 5: 13191, 2015
30) Kobayashi H, Matsuda Y, Hitomi T, et al.: Biochemical and functional characterization of *RNF213* (Mysterin) R4810K, a susceptibility mutation of moyamoya disease, in angiogenesis *in vitro* and *in vivo*. *J Am Heart Assoc* 4: pii: e002146, 2015
31) Hawkins PT, Stephens LR: PI3K signalling in inflammation. *Biochim Biophys Acta* 1851: 882–897, 2015
32) Blankesteijn WM, van Gijn ME, Essers-Janssen YP, Daemen MJ, Smits JF: Beta-catenin, an inducer of uncontrolled cell proliferation and migration in malignancies, is localized in the cytoplasm of vascular endothelium during neovascularization after myocardial infarction. *Am J Pathol* 157: 877–883, 2000
33) Easwaran V, Lee SH, Inge L, et al.: beta-Catenin regulates vascular endothelial growth factor expression in colon cancer. *Cancer Res* 63: 3145–3153, 2003

34) Scholz B, Korn C, Wojtarowicz J, et al.: Endothelial RSPO3 controls vascular stability and pruning through non-canonical WNT/Ca(2+)/NFAT signaling. *Dev Cell* 36: 79–93, 2016
35) Zemans R, Downey GP: Role of caveolin-1 in regulation of inflammation: different strokes for different folks. *Am J Physiol Lung Cell Mol Physiol* 294: L175–L177, 2008
36) Yuan K, Huang C, Fox J, et al.: Elevated inflammatory response in caveolin-1-deficient mice with *Pseudomonas aeruginosa* infection is mediated by STAT3 protein and nuclear factor kappaB (NF-kappaB). *J Biol Chem* 286: 21814–21825, 2011
37) Bang OY, Chung JW, Kim SJ, et al.: Caveolin-1, Ring finger protein 213, and endothelial function in moyamoya disease. *Int J Stroke* 11: 999–1008, 2016
38) Liu J, Wang XB, Park DS, Lisanti MP: Caveolin-1 expression enhances endothelial capillary tubule formation. *J Biol Chem* 277: 10661–10668, 2002
39) Jasmin JF, Malhotra S, Singh Dhallu M, Mercier I, Rosenbaum DM, Lisanti MP: Caveolin-1 deficiency increases cerebral ischemic injury. *Circ Res* 100: 721–729, 2007
40) Gortazar AR, Martin-Millan M, Bravo B, Plotkin LI, Bellido T: Crosstalk between caveolin-1/extracellular signal-regulated kinase (ERK) and β-catenin survival pathways in osteocyte mechanotransduction. *J Biol Chem* 288: 8168–8175, 2013
41) Taylor CT, Doherty G, Fallon PG, Cummins EP: Hypoxia-dependent regulation of inflammatory pathways in immune cells. *J Clin Invest* 126: 3716–3724, 2016
42) Zhang Z, Yao L, Yang J, Wang Z, Du G: PI3K/Akt and HIF-1 signaling pathway in hypoxia-ischemia (Review). *Mol Med Rep* 18: 3547–3554, 2018
43) Kanoke A, Fujimura M, Niizuma K, et al.: Temporal profile of the vascular anatomy evaluated by 9.4-tesla magnetic resonance angiography and histological analysis in mice with the R4859K mutation of *RNF213*, the susceptibility gene for moyamoya disease. *Brain Res* 1624: 497–505, 2015
44) Sonobe S, Fujimura M, Niizuma K, et al.: Temporal profile of the vascular anatomy evaluated by 9.4-T magnetic resonance angiography and histopathological analysis in mice lacking *RNF213*: a susceptibility gene for moyamoya disease. *Brain Res* 1552: 64–71, 2014
45) Fujimura M, Sonobe S, Nishijima Y, et al.: Genetics and biomarkers of moyamoya disease: significance of *RNF213* as a susceptibility gene. *J Stroke* 16: 65–72, 2014
46) Asahara T, Masuda H, Takahashi T, et al.: Bone marrow origin of endothelial progenitor cells responsible for postnatal vasculogenesis in physiological and pathological neovascularization. *Circ Res* 85: 221–228, 1999
47) Shi Q, Rafii S, Wu MH, et al.: Evidence for circulating bone marrow-derived endothelial cells. *Blood* 92: 362–367, 1998
48) Zhang W, Wang X, Wang Z, Shang J, Wang H, Yin G: Effectiveness of superficial temporal artery-to-middle cerebral artery anastomosis in treating moyamoya disease by reducing endothelial progenitor cells. *World Neurosurg* 93: 365–370, 2016
49) Ii M, Nishimura H, Iwakura A, et al.: Endothelial progenitor cells are rapidly recruited to myocardium and mediate protective effect of ischemic preconditioning via "imported" nitric oxide synthase activity. *Circulation* 111: 1114–1120, 2005
50) Jujo K, Ii M, Losordo DW: Endothelial progenitor cells in neovascularization of infarcted myocardium. *J Mol Cell Cardiol* 45: 530–544, 2008
51) Rosell A, Morancho A, Navarro-Sobrino M, et al.: Factors secreted by endothelial progenitor cells enhance neurorepair responses after cerebral ischemia in mice. *PLoS One* 8: e73244, 2013
52) Ni G, Liu W, Huang X, et al.: Increased levels of circulating SDF-1α and CD34+ CXCR4+ cells in patients with moyamoya disease. *Eur J Neurol* 18: 1304–1309, 2011
53) Kim JH, Jung JH, Phi JH, et al.: Decreased level and defective function of circulating endothelial progenitor cells in children with moyamoya disease. *J Neurosci Res* 88: 510–518, 2010
54) Jung KH, Chu K, Lee ST, et al.: Circulating endothelial progenitor cells as a pathogenetic marker of moyamoya disease. *J Cereb Blood Flow Metab* 28: 1795–1803, 2008
55) Choi SA, Chong S, Kwak PA, et al.: Impaired functional recovery of endothelial colony-forming cells from moyamoya disease in a chronic cerebral hypoperfusion rat model. *J Neurosurg Pediatr* 23: 204–213, 2018
56) Bartel DP: MicroRNAs: genomics, biogenesis, mechanism, and function. *Cell* 116: 281–297, 2004
57) Zeng L, He X, Wang Y, et al.: MicroRNA-210 overexpression induces angiogenesis and neurogenesis in the normal adult mouse brain. *Gene Ther* 21: 37–43, 2014
58) O'Neill LA, Sheedy FJ, McCoy CE: MicroRNAs: the fine-tuners of Toll-like receptor signalling. *Nat Rev Immunol* 11: 163–175, 2011
59) Dai D, Lu Q, Huang Q, et al.: Serum miRNA signature in moyamoya disease. *PLoS One* 9: e102382, 2014
60) Zhao S, Gong Z, Zhang J, et al.: Elevated serum MicroRNA Let-7c in moyamoya disease. *J Stroke Cerebrovasc Dis* 24: 1709–1714, 2015
61) Park YS, Jeon YJ, Lee BE, et al.: Association of the miR-146aC>G, miR-196a2C>T, and miR-499A>G polymorphisms with moyamoya disease in the Korean population. *Neurosci Lett* 521: 71–75, 2012
62) Kowalczyk MS, Higgs DR, Gingeras TR: Molecular biology: RNA discrimination. *Nature* 482: 310–311, 2012
63) Mercer TR, Dinger ME, Mattick JS: Long non-coding RNAs: insights into functions. *Nat Rev Genet* 10: 155–159, 2009
64) Li Z, Chao TC, Chang KY, et al.: The long noncoding RNA THRIL regulates TNFα expression through its interaction with hnRNPL. *Proc Natl Acad Sci USA* 111: 1002–1007, 2014

65) Heward JA, Lindsay MA: Long non-coding RNAs in the regulation of the immune response. *Trends Immunol* 35: 408–419, 2014
66) Pearson MJ, Philp AM, Heward JA, et al.: Long intergenic noncoding RNAs mediate the human chondrocyte inflammatory response and are differentially expressed in osteoarthritis cartilage. *Arthritis Rheumatol* 68: 845–856, 2016
67) Gao F, Yu L, Zhang D, Zhang Y, Wang R, Zhao J: Long noncoding RNAs and their regulatory network: potential therapeutic targets for adult moyamoya disease. *World Neurosurg* 93: 111–119, 2016
68) Wang W, Gao F, Zhao Z, et al.: Integrated analysis of LncRNA-mRNA co-expression profiles in patients with moyamoya disease. *Sci Rep* 7: 42421, 2017
69) Houkin K, Ito M, Sugiyama T, et al.: Review of past research and current concepts on the etiology of moyamoya disease. *Neurol Med Chir* (*Tokyo*) 52: 267–277, 2012
70) Malik S, Russman AN, Katramados AM, Silver B, Mitsias PD: Moyamoya syndrome associated with Graves' disease: a case report and review of the literature. *J Stroke Cerebrovasc Dis* 20: 528–536, 2011
71) Ohba S, Nakagawa T, Murakami H: Concurrent Graves' disease and intracranial arterial stenosis/occlusion: special considerations regarding the state of thyroid function, etiology, and treatment. *Neurosurg Rev* 34: 297–304; discussion 304, 2011
72) Chen JB, Lei D, He M, et al.: Clinical features and disease progression in moyamoya disease patients with Graves disease. *J Neurosurg* 123: 848–855, 2015
73) Lee R, Sung K, Park YM, Yu JJ, Koh YC, Chung S: A case of moyamoya disease in a girl with thyrotoxicosis. *Yonsei Med J* 50: 594–598, 2009
74) Liu JS, Juo SH, Chen WH, Chang YY, Chen SS: A case of Graves' diseases associated with intracranial moyamoya vessels and tubular stenosis of extracranial internal carotid arteries. *J Formos Med Assoc* 93: 806–809, 1994
75) Czartoski T, Hallam D, Lacy JM, Chun MR, Becker K: Postinfectious vasculopathy with evolution to moyamoya syndrome. *J Neurol Neurosurg Psychiatry* 76: 256–259, 2005
76) Im SH, Oh CW, Kwon OK, Kim JE, Han DH: Moyamoya disease associated with Graves disease: special considerations regarding clinical significance and management. *J Neurosurg* 102: 1013–1017, 2005
77) Tendler BE, Shoukri K, Malchoff C, et al.: Concurrence of Graves' disease and dysplastic cerebral blood vessels of the moyamoya variety. *Thyroid* 7: 625–629, 1997
78) Ni J, Gao S, Cui LY, Li SW: Intracranial arterial occlusive lesion in patients with Graves' disease. *Chin Med Sci J* 21: 140–144, 2006
79) Yamada H, Deguchi K, Tanigawara T, et al.: The relationship between moyamoya disease and bacterial infection. *Clin Neurol Neurosurg* 99: S221–S224, 1997
80) Pinardi F, Stracciari A, Spinardi L, Guarino M: Postpneumococcal moyamoya syndrome case report and review of the postinfective cases. *BMJ Case Rep* 2013: pii: bcr2012006726, 2013
81) Pugin D, Copin JC, Goodyear MC, Landis T, Gasche Y: Persisting vasculitis after pneumococcal meningitis. *Neurocrit Care* 4: 237–240, 2006
82) Cardenas JF, Chapman K: Sydenham's chorea as a presentation of moyamoya disease. *Semin Pediatr Neurol* 17: 30–34, 2010
83) Stoeter P, Voigt K: [Moyamoya syndrome of tuberculous cerebral arteritis]. *Rofo* 124: 516–519, 1976 (German)
84) Kitahara M, Kaneko U, Fujiwara S, Suzuki J: [A case showing angiographically moyamoya vessels combined with intracranial calcification]. *No Shinkei Geka* 14: 367–372, 1986 (Japanese)
85) Kashiwagi S, Abiko S, Harada K, Yamashita K, Ito H: [Ischemic cerebrovascular complication in tuberculous meningitis; a case of Fröhlich syndrome and hemiparesis]. *No Shinkei Geka* 18: 1141–1145, 1990 (Japanese)
86) Nakayama Y, Tanaka A, Nagasaka S, Ikui H: [Intracerebral hemorrhage in a patient with moyamoya phenomenon caused by tuberculous arteritis: a case report]. *No Shinkei Geka* 27: 751–755, 1999 (Japanese)
87) Palacio S, Hart RG, Vollmer DG, Kagan-Hallet K: Late-developing cerebral arteropathy after pyogenic meningitis. *Arch Neurol* 60: 431–433, 2003
88) Kerr L, Filloux FM: Cerebral infarction as a remote complication of childhood Haemophilus influenzae meningitis. *West J Med* 157: 179–182, 1992
89) Matsushima Y, Qian L, Aoyagi M: Comparison of moyamoya disease in Japan and moyamoya disease (or syndrome) in the People's Republic of China. *Clin Neurol Neurosurg* 99: S19–S22, 1997
90) Greco F, Castellano Chiodo D, Sorge A, Perrini S, Sorge G: [Multiple arterial ischemic strokes in a child with moyamoya disease and *Mycoplasma pneumoniae* infection]. *Minerva Pediatr* 58: 63–68, 2006 (Italian)
91) Tanigawara T, Yamada H, Sakai N, Andoh T, Deguchi K, Iwamura M: Studies on cytomegalovirus and Epstein–Barr virus infection in moyamoya disease. *Clin Neurol Neurosurg* 99: S225–S228, 1997
92) Hsiung GY, Sotero de Menezes M: Moyamoya syndrome in a patient with congenital human immunodeficiency virus infection. *J Child Neurol* 14: 268–270, 1999
93) Galati V, Grilli E, Sallustio F, Petrosillo N: An adult HIV patient with unilateral moyamoya syndrome. *Clin Neurol Neurosurg* 112: 76–78, 2010
94) Sharfstein SR, Ahmed S, Islam MQ, Najjar MI, Ratushny V: Case of moyamoya disease in a patient with advanced acquired immunodeficiency syndrome. *J Stroke Cerebrovasc Dis* 16: 268–272, 2007
95) Morgello S, Laufer H: Quaternary neurosyphilis in a Haitian man with human immunodeficiency virus infection. *Hum Pathol* 20: 808–811, 1989
96) Takasugi H, Maemoto T, Kitazawa K, Honda A: [A case of Down syndrome with moyamoya syndrome presenting extensive multiple cerebral infarction

during measles infection]. *No To Hattatsu* 32: 39–43, 2000 (Japanese)
97) Ueno M, Oka A, Koeda T, Okamoto R, Takeshita K: Unilateral occlusion of the middle cerebral artery after varicella-zoster virus infection. *Brain Dev* 24: 106–108, 2002
98) Weststrate W, Hijdra A, de Gans J: Brain infarcts in adults with bacterial meningitis. *Lancet* 347: 399, 1996
99) Igarashi M, Gilmartin RC, Gerald B, Wilburn F, Jabbour JT: Cerebral arteritis and bacterial meningitis. *Arch Neurol* 41: 531–535, 1984
100) Liu XM, Ruan XZ, Cai Z, Yu BR, He SP, Gong YH: Moyamoya disease caused by leptospiral cerebral arteritis. *Chin Med J* (*Engl*) 93: 599–604, 1980
101) Takahashi Y, Mikami T, Suzuki H, et al.: Development of moyamoya disease after non-herpetic acute limbic encephalitis: a case report. *J Clin Neurosci* 53: 250–253, 2018
102) Suzuki J, Kodama N: Moyamoya disease—a review. *Stroke* 14: 104–109, 1983
103) Hosoda Y, Ikeda E, Hirose S: Histopathological studies on spontaneous occlusion of the circle of Willis (cerebrovascular moyamoya disease). *Clin Neurol Neurosurg* 99: S203–S208, 1997
104) Ikeda E, Hosoda Y: Distribution of thrombotic lesions in the cerebral arteries in spontaneous occlusion of the circle of Willis: cerebrovascular moyamoya disease. *Clin Neuropathol* 12: 44–48, 1993
105) Masuda J, Ogata J, Yutani C: Smooth muscle cell proliferation and localization of macrophages and T cells in the occlusive intracranial major arteries in moyamoya disease. *Stroke* 24: 1960–1967, 1993
106) Kaku Y, Morioka M, Ohmori Y, et al.: Outer-diameter narrowing of the internal carotid and middle cerebral arteries in moyamoya disease detected on 3D constructive interference in steady-state MR image: is arterial constrictive remodeling a major pathogenesis? *Acta Neurochir* (*Wien*) 154: 2151–2157, 2012
107) Mikami T, Noshiro S, Komatsu K, et al.: Vascular remodeling of the circle of Willis in moyamoya disease. *Neurol Res* 37: 880–885, 2015
108) Yamamoto S, Koh M, Kashiwazaki D, et al.: Is quasi-moyamoya disease a uniform disease entity? a three-dimensional constructive interference in steady state imaging study. *J Stroke Cerebrovasc Dis* 25: 1509–1516, 2016
109) Naldini A, Carraro F: Role of inflammatory mediators in angiogenesis. *Curr Drug Targets Inflamm Allergy* 4: 3–8, 2005

Address reprint requests to: Takeshi Mikami, MD, PhD, Department of Neurosurgery, Sapporo Medical University, South 1 West 16, Chuo-ku, Sapporo, Hokkaido 060-8543, Japan.
e-mail: tmikami@sapmed.ac.jp