Moyamoya vasculopathy

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Conventionally, we distinguish between moyamoya disease (MMD, the idiopathic form) and moyamoya syndrome (MMS), also known as “moyamoya like,” “quasi moyamoya,” “akin moyamoya” and “secondary moyamoya” (the acquired form). MMS is mainly associated with other diseases and risk factors such as intracranial atherosclerosis, cerebral vasculitis, Down syndrome, neurofibromatosis type I (NF-1), and sickle cell anemia. Predisposing factors, with unknown link, are autoimmune diseases such as vasculitis, or Basedow-Graves thyroid disease. MMS is a cerebrovascular condition that predisposes affected patients to stroke in association with progressive stenosis of the intracranial internal carotid arteries and their proximal branches.[1] The incidence of MMS is higher in Western countries and in females (female/male ratio 1.57e4.25:1).[2] In the pediatric population, MMS is associated with congenital diseases such as Down syndrome and NF-1, whereas intracranial atherosclerotic disease and thyroid disease are predominant in elderly patients.[3] In patients with MMS, the development of moyamoya vessels is less pronounced than in patients with MMD and steno-occlusive lesions are unilateral in most patients.[4] Recently, there are several reports that do not distinguish between MMD and MMS, but analyze them together as MMV.[5, 6]

Angiopathy, vasculopathy, and arteriopathy

Angiopathy is a disease of the arteries, veins, and capillaries. There are two types of angiopathy: microangiopathy and macroangiopathy. In microangiopathy, the walls of small blood vessels become so thick and weak that they bleed, leak protein, and slow the flow of blood. For example, diabetics may develop microangiopathy with thickening of capillaries in many areas, including the eye. In macroangiopathy, fat and blood clots build up in the large blood vessels, stick to the vessel walls, and block the flow of blood. Macroangiopathy in the heart is coronary artery disease. Peripheral vascular disease is macroangiopathy that affects vessels in the legs.

Vasculopathy (vascular disease) is a general term used to describe any disease affecting blood vessels. This ranges from diseases of arteries, veins and lymph vessels to blood disorders that affect circulation. It includes vascular abnormalities caused by degenerative, metabolic and inflammatory conditions, embolic diseases, coagulative disorders, and functional disorders such as posterior or reversible encephalopathy syndrome. The etiology of vasculopathy is generally unknown and the condition is frequently not pathologically proven. Vasculitis, on the other hand,

is a more specific term and is defined as inflammation of the wall of a blood vessel. However, the term vasculopathy is also used for “vasculitis” that has not been pathologically established. Cerebral arteriopathies are disorders that affect the arteries in the brain. There are several different types of these blood vessel abnormalities, including moyamoya disease, arterial dissection, and vasculitis. About a quarter of cerebral arteriopathies have no known cause.
Neither name is strictly defined. In moyamoya disease, it may be better to use arteriopathy, considering that it is a disease of the arteries. However, arteriopathy is generally used in children, and both angiopathy and vasculopathy are general and comprehensive technical terms.

Vessel wall imaging

Vessel wall imaging refers to 2D or 3D black blood MRI sequences with cerebrospinal fluid suppression that allow intracranial blood vessel walls to be delineated. Typically, MMD shows concentric, non-enhancing steno-occlusive lesions with wall shrinkage.66 When MMD segments do enhance they have a mild concentric and homogenous pattern. Ryoo et al. reported concentric enhancement in 93.3% of a symptomatic MMD segment, suggesting that this finding could be an indicator of evolving intimal hyperplasia, neovascularization, and active inflammation.[7]
The problem lies in differentiating MMD from atherosclerotic stenosis. According to the 2021 version of the diagnostic criteria of moyamoya disease in Japan, Atherosclerosis associated (AS)-MMV has been removed from moyamoya syndrome. The reason described in the new criteria is that MMD and AS-MMV are completely different in terms of their etiology and pathophysiology, even though they shared similar clinical and radiological features.[8,9]
Mossa-Basha et al reported that the likelihood of a correct diagnosis in MMV patients significantly increased from 31.6% to 86.8% when HRMRI was combined with luminal imaging, and this increase was significant for both MMD and AS-MMV.[10]
Recently, several studies have reported that AS-MMV could be distinguished from MMD using high-resolution MR (HRMR) imaging Vascular changes are similar to those in MMD but in ICAD the steno-occlusive lesions are not always limited to supraclinoid ICA and proximal ACA and/or MCA. Several studies have also reported cases of MCA atherosclerotic stenosis associated with moyamoya vessels. The development of moyamoya collaterals may serve as an endogenous bypass procedure and have a protective role from hypoperfusion. Tanaka et al. showed that in MMS, secondary to intracranial atherosclerosis, moyamoya vessels are more developed in the presence of multiple steno-occlusive lesions involving the ACA and MCA and in poorly developed leptomeningeal collateral vessels from the ACA.[11]
The major findings on luminal imaging include narrowing of one or more vessels, possible development of moyamoya vessels, regular downstream antegrade flow or retrograde flow from leptomeningeal collaterals evaluable by DSA. On HR-MRI, the typical atherosclerosis plaque is an eccentric, heterogeneous, and positive remodeling lesion and shows eccentric wall enhancement. HRMR should be used in daily clinical practice, as it can help identify patients

with MMD who are at risk of rapid disease progression and future cerebrovascular events.[12] (Figure 1)

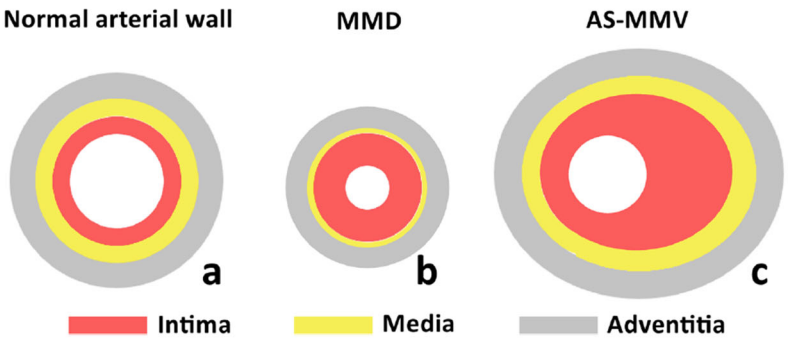

Figure1. 動脈壁の模式図（文献 12 より）
a：正常な動脈壁　b：もやもや病の動脈壁．内膜の過形成と中膜の萎縮により外径の縮小と同心円状の内腔狭窄を示す　c: 動脈硬化による moyamoya vasculopathy．血管内皮下に脂質と泡沫細胞が沈着し、内膜の偏心性肥厚、早期には positive remodeling が起こる。

Yu LB et al. prospectively studied 116 patients who had angiographically proven MMD and Quasi-MMD (unilateral cerebral artery steno-occlusion lesion combined with moyamoya vessels). Detailed analysis of 204 affected hemispheres showed that several combinations of different vasculopathies were observed in the ICA and MCA of the same hemisphere, such as ICAD-ICAD, ICAD-MMD, dissection-ICAD, and dissection-MMD. They discussed the mixed vasculopathies in the affected ICA or MCA indicated the complicated etiologies in moyamoya vasculopathies, and misdiagnosis might occur if only luminal imaging was used
for evaluation.[13] The diagnostic performance of pattern of vessel wall thickening was inferior to that of outer diameter and RI. The possible reasons are as follows: (1) some patients with MMD may coexist with atherosclerosis, which could lead to the presence of eccentric thickening; (2) at the early stage of AS-MMV, the eccentric thickening of the vessel wall is not evident enough to meet the diagnostic criteria (the thickest part of the wall was 2 times of the thinnest part). (3) The pattern of vessel wall thickening cannot be evaluated in patients with occlusive MCA. Based on the above analysis, the application of the pattern of vessel wall thickening in differentiating MMD from AS-MMV is limited.

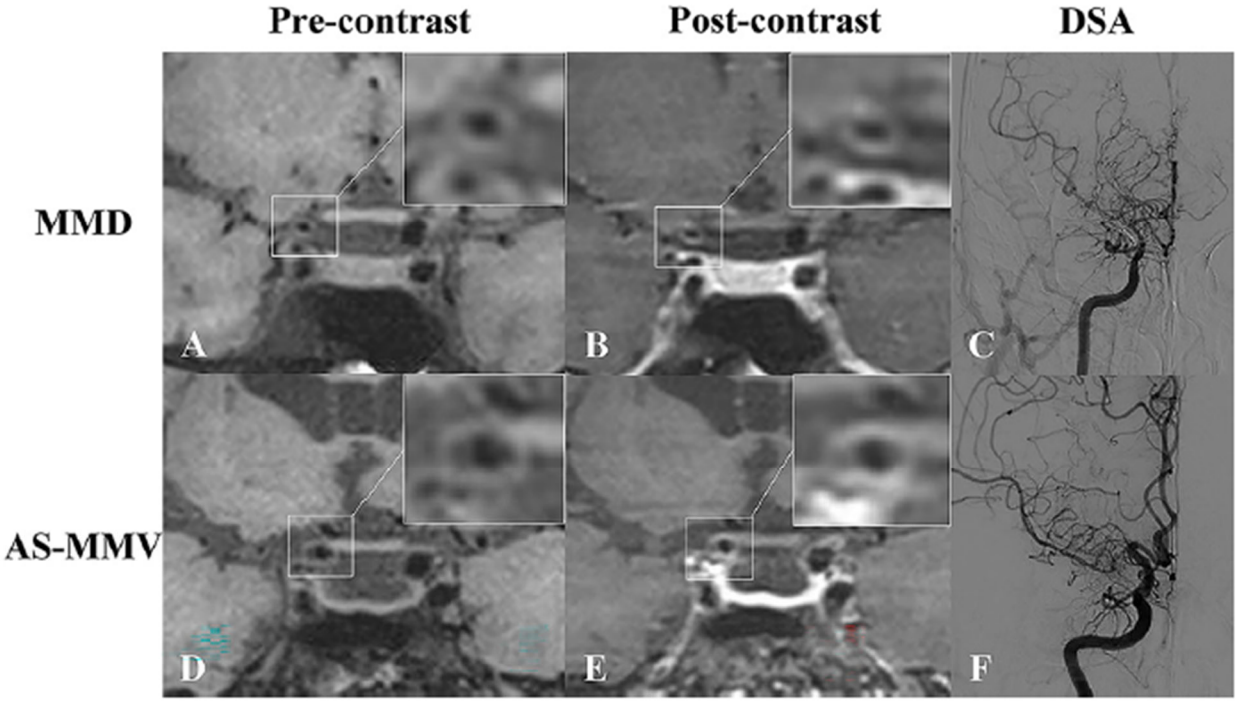

Figure12.　MMD と AS-MMV の血管壁の特徴（文献 12）
A, B: MMD では造影前と造影後の T1WI では、HRMRI で右遠位 ICA ないに偏心性壁肥厚を伴わない外径減少を伴う内腔狭小化がみられる
D, E: 動脈硬化性 MMV では、造影前および造影後 T1WI で、偏心性壁肥厚を伴う内服狭小、血管壁の信号の不均一性がみられ、HRMRI では右遠位 ICA 内の外径の減少は見られなかった。
C, F) 両者において DSA では同じ Suzuki Stage を示していた

Moyamoya disease and RNF213 vasculopathy

RNF213-related vasculopathy was proposed as a new disease entity in 2019,[14]
The R4810K variant was identified in 95% of patients with familial MMD, 80% with sporadic MMD, and 1.8% of control individuals in a Japanese population.[15] In vitro and in vivo experiments revealed that RNF213 is related to angiogenesis and vascular inflammation; however, the exact physiologic functions of RNF213 remain unknown.[16] The penetrance rate of MMD in heterozygotes is as low as one per 150–300, whereas the penetrance rate of MMD in homozygotes was calculated to be over 78%.[17]
There is increasing evidence for RNF213 p.(R4810K) being related to vasculopathy with a spectrum of clinical presentations that include MMD but also other intracranial and systemic vasculopathies.[18] Extracranial involvement of MMD has been described in case reports of coronary, pulmonary, and renal artery stenosis in 7.9% of pediatric MMD patients, although genetic information was unavailable. R4810K is associated with a high penetrance of systemic vasculopathy in homozygous patients, and a low penetrance of MMD in heterozygous patients, suggestive of a gene-dosage effect. MMD requires redefinition, from childhood and cerebral vasculopathy to a broader spectrum vasculopathy affecting both cerebral and systemic vessel

systems.[19] Both genetic and environmental factors may play important roles in the development and phenotype of RNF213 vasculopathy, through complex mechanisms. (Figure 3)
RNF213 variants may not be the only determinants of MMD. Very recent clinical studies showed that RNF213 variants are associated not only with MMD but also with intracranial atherosclerosis and systemic vascular diseases, such as peripheral pulmonary artery stenosis and renal artery stenosis. Moreover, not all the patients with MMD have this genetic variant.

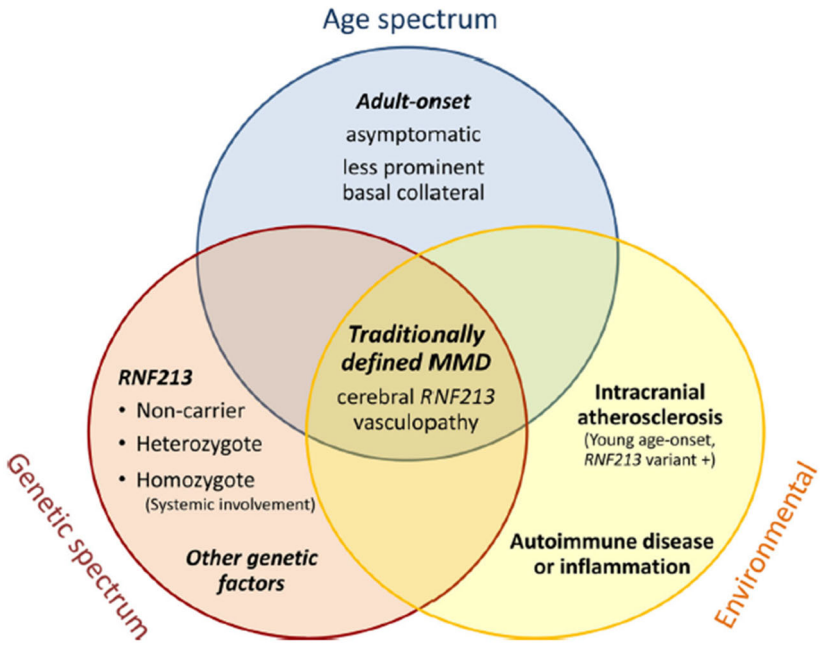

Figure 3 RNF213 vasculopathy のスペクトラム（文献 19 より）

MMD and autoimmune disorders

Recent findings increasingly point towards an aberrant immune response to infection as a potential trigger for MMD onset. A number of moyamoya cohort studies suggested autoimmune conditions and infection as potential environmental triggers. Seventy-five cases of MMD associated with leptospiral cerebral arteritis had already been described in 1980. A second cohort study describing the incidence of infections in 100 MMD patients dates from 1983 and found that 87 patients had experienced infections of the face, head and/or throat before the onset of MMD, including otitis media and tonsilitis.[20] Since the link with Graves' disease, less-common autoimmune disorders such as polyarteritis nodosa, myasthenia gravis, systemic lupus erythematosus, antiphospholipid antibody syndrome, Addison's disease, dermatomyositis, Sjögren's syndrome, Kawasaki's disease, acute limbic encephalitis with anti-LGI1 antibody, granulomatosis, multiple sclerosis, systemic sclerosis, primary systemic vasculitis, rheumatoid arthritis, polymyositis, and thyroiditis have also been related to MMD.

A recent study by Roy et al. suggested that RNF213 could function as a key regulator of cerebral endothelial integrity. When RNF213 was depleted from human cerebral ECs, the

authors reported morphological changes associated with increased blood–brain barrier permeability and abnormally high secretion of proinflammatory cytokines. These results suggest that blood–brain barrier disruption may play a role in MMA and that endothelial dysfunction is the initiating event leading to MMD pathogenesis, as it is in numerous other cerebrovascular diseases.[21]

The recently discovered function of RNF213 as a key antimicrobial protein strengthens a role for infectious or autoimmune stimuli as second hit for MMD onset.[22, 23] (Figure 4)

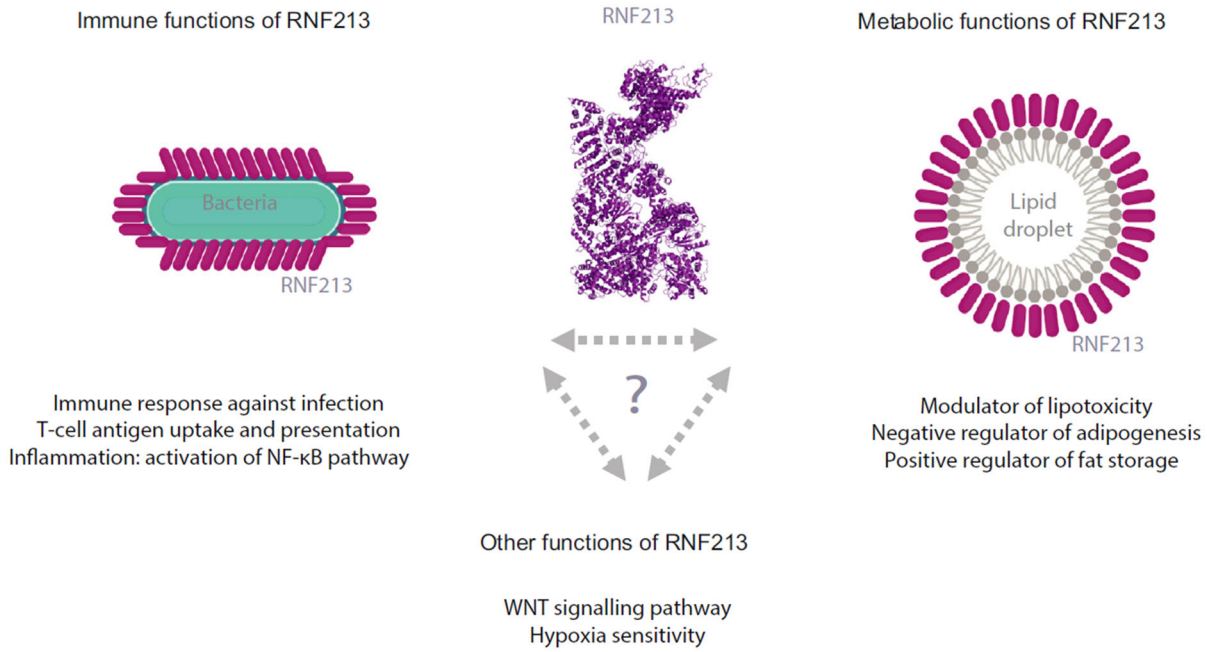

Figure 4 多機能タンパク質である RNF213 (文献 22 より)
RNF213 が細菌や脂質滴の表面に局在するのは、免疫系や脂質代謝における様々な機能と関連していると考えられる。RNF213 の代謝機能には、脂質毒性の調節、脂肪形成の負の調節、脂肪蓄積の正の調節などがある。免疫関連機能には、感染に対する応答における役割、抗原の取り込みと提示における役割、NF-κB 経路の活性化における役割などがある。さらに、RNF213 は WNT シグナル伝達や低酸素感知にも関与している。RNF213 のこれらの様々な機能は、まだ発見されていない
方法で相互に関連している可能性が高い。

Although the etiology of MMD/MMS is not clear, Komiyama proposed the concept of cephalic neurocristopathy based on the fact that stenotic and obstructive changes are developmentally limited to arteries derived from neural crest cells (embryological anterior circulation).[24,25,26] The possibility that not only genetic factors including RNF213 but also epigenetics and environmental factors are involved in the pathogenesis of this disease has been shown. It is time to review the diagnosis and pathogenesis of MMD/MMS from multiple perspectives.

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