Association between \textit{RNF213} c.14576G\textgreater{}A Variant (rs112735431) and Peripheral Pulmonary Artery Stenosis in Moyamoya Disease

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\textbf{Keywords}  
\textit{RNF213} · Polymorphism · Homozygote · Moyamoya disease · Peripheral pulmonary artery stenosis

\textbf{Abstract}

\textbf{Background:} Moyamoya disease (MMD) and peripheral pulmonary artery stenosis (PPAS) are relatively rare and demonstrate steno-occlusive vascular lesions in different organs. Genetic studies identified \textit{RNF213} polymorphism c.14576G\textgreater{}A (rs112735431) as a susceptibility variant for East Asian MMD. \textit{RNF213} polymorphism c.14576G\textgreater{}A is further associated with various vascular lesions of other organs. In this study, we aimed to clarify the incidence and clinical manifestations of PPAS in MMD patients and analyze the correlation between \textit{RNF213} genotype and PPAS. \textbf{Methods:} This retrospective case-control study investigated the association between \textit{RNF213} polymorphism and PPAS in 306 MMD/quasi-MMD patients, reviewing the medical charts and imaging records of consecutive patients with MMD admitted from January 2015 to December 2020. \textbf{Results:} PPAS was observed in 3 MMD/quasi-MMD patients (0.98\%, 3/306). \textit{RNF213} polymorphism c.14576G\textgreater{}A was determined for all 306 MMD/quasi-MMD patients. The incidence of PPAS in \textit{RNF213}-wildtype, \textit{RNF213}-heterozygote, and \textit{RNF213}-homozygote MMD/quasi-MMD patients was 0\% (0/101), 0.5\% (1/200), and 40\% (2/5), respectively. The association between PPAS and homozygote polymorphism of \textit{RNF213} c.14576G\textgreater{}A was statistically significant in MMD/quasi-MMD patients (\textit{p} = 0.0018). In all cases, pulmonary artery hypertension due to PPAS was evident during their childhood and young adolescent stages. Surgical indications for MMD were discouraged in 1 case due to her severe cardiopulmonary dysfunction. \textbf{Conclusions:} The homozygote variant of \textit{RNF213} polymorphism c.14576G\textgreater{}A can be a potential predisposing factor for PPAS in MMD/quasi-MMD patients. Despite the relatively rare entity, PPAS should be noted to determine surgical indications for MMD/quasi-MMD patients.
Introduction

Moyamoya disease (MMD) is a cerebrovascular disease characterized by chronic and progressive steno-occlusive lesions at the terminal portion of internal carotid arteries and the development of “Moyamoya vessels” [1, 2]. Although intracranial carotid arteries are preferentially affected in MMD, extracranial vascular involvement, such as stenotic lesions in pulmonary, coronary, and renal arteries, has been reported [3–6].

Genetic studies identified a single-nucleotide polymorphism c.14576G>A (rs112735431) in the RNF213 gene as a susceptibility variant for East Asian MMD [7, 8]. In particular, the homozygote variant of RNF213 c.14576G>A is associated with early and severe onset of MMD [9]. Recent studies revealed that RNF213 polymorphism c.14576G>A is associated with non-MMD stenocclusive lesions in intracranial [10, 11] and coronary arteries [12]. In addition, MMD cases with pulmonary artery stenosis (PPAS) had homozygote polymorphism of RNF213 c.14576G>A [3–5]. This observation raised the hypothesis that RNF213 polymorphism c.14576G>A plays essential roles in the development of PPAS in MMD patients. In this study, we aimed to clarify the incidence and clinical manifestations of PPAS in MMD patients and analyze the correlation between RNF213 genotype and PPAS.

Materials and Methods

This is a retrospective case-control study. This study adhered to the Declaration of Helsinki and was approved by the Ethics Committee of Tohoku University (Approval No. 2016-1-212 and 2018-1-675) and Kohnan Hospital (Approval No. 2020-0520-03). Written informed consent was obtained from all the participants or their guardians.

Diagnosis of MMD/Quasi-MMD and PPAS

We retrospectively reviewed the medical charts and imaging records of consecutive patients with MMD who visited our institution from January 2015 to December 2020. Diagnosis of MMD and quasi-MMD was based on the diagnostic criteria of the Research Committee on Spontaneous Occlusion of the Circle of Willis of the Ministry of Health, Labor and Welfare of Japan [1, 2]. The patients were diagnosed as quasi-MMD, if the patients showed angiographic findings equivalent to MMD but also had comorbidities, such as autoimmune diseases (for instance, rheumatoid arthritis, systemic lupus erythematosus, anti-phospholipid antibody syndrome, and Sjögren syndrome), neurofibromatosis type 1, meningitis, intracranial tumors, Down syndrome, and sickle cell anemia. A total of 533 MMD/quasi-MMD (523 MMD and 10 quasi-MMD) patients were enrolled in this study. Examination of cardiopulmonary systems was conducted when patients manifested signs of cardiopulmonary dysfunction. PPAS was diagnosed based on the clinical findings, including cardiopulmonary symptoms and the findings of imaging studies such as CT pulmonary angiography, ventilation-perfusion scan, and conventional pulmonary angiography. Peripheral pulmonary artery hypertension (PAH) was defined by a mean pulmonary artery pressure ≥25 mm Hg and a pulmonary arterial wedge pressure ≤15 mm Hg at rest at right heart catheterization. Indication of balloon pulmonary angioplasty for PPAS was to decrease pulmonary arterial pressure, to relieve of PAH symptoms, and to de-escalate PAH-specific drugs.

Results

The Association between RNF213 Genotype and PPAS in MMD/Quasi-MMD Patients

A total of 306 MMD/quasi-MMD patients (300 MMD and 6 quasi-MMD) agreed for genetic testing, which revealed heterozygote and homozygote polymorphism in 1 and 2 MMD/quasi-MMD patients with PPAS, respectively (Table 1). The incidence of PPAS was higher in MMD/quasi-MMD patients with homozygote polymorphism of RNF213 c.14576G>A (40%, 2/5) than in those without polymorphism or with heterozygote polymorphism of RNF213 c.14576G>A (0% [0/101] and 0.5% [1/200], respectively) (Table 1). Statistical analysis demonstrated the significant association between homozygote polymorphism of RNF213 c.14576G>A and PPAS in MMD/quasi-MMD patients (p = 0.0018), whereas there is no significant association between PPAS and heterozygote polymorphism of RNF213 c.14576G>A (p = 1.000).
Clinical Manifestations in MMD/Quasi-MMD Patients with PPAS

Clinical characteristics of 3 MMD/quasi-MMD patients with PPAS are summarized in Table 2. These 3 patients had a family history of MMD/quasi-MMD, of which 2 cases suffered from transient ischemic attacks (cases 1 and 3) and 1 patient had a history of subarachnoid hemorrhage (case 2). Only case 3 underwent revascularization for MMD/quasi-MMD before the manifestation of cardiopulmonary dysfunction. All 3 cases suffered from peripheral PAH due to PPAS when they were children or young adolescents. A prostacyclin agonist was administered, and balloon pulmonary angioplasty was performed in all 3 cases. We conservatively treated MMD in cases 1 and 2, considering the surgical risk due to severe cardiopulmonary dysfunction. Neither ischemic nor hemorrhagic events recurred so far. A representative case (case 1) is shown in Figure 1.

Discussion

This study revealed a significant association between homozygote variant of RNF213 polymorphism c.14576G>A and PPAS in MMD/quasi-MMD patients. The homozygote variant of RNF213 polymorphism c.14576G>A can be a potential predisposing factor for PPAS in MMD/quasi-MMD patients.

All the MMD cases with PPAS in the previous literature studies [3–5] and the present study harbored homozygote polymorphism of RNF213 c.14576G>A, except for 1 quasi-MMD case with heterozygote polymorphism in the present study. Likewise, a recent prospective study revealed the association among extracranial arteriopathies and RNF213 polymorphism, especially the homozygote variant [6]. However, it did not include MMD patients associated with PPAS probably due to small number of enrolled cases. These data support the hypothesis that RNF213 polymorphism c.14576G>A, especially the homozygote variant, can be the predisposing factor for various steno-occlusive vascular lesions [15].

RNF213 mediates various aspects of cellular homeostasis. Experimental studies have revealed the physiological roles of RNF213 in nonmitochondrial oxygen consumption [16], lipid metabolism [17], and antigen uptake, processing, and presentation [18]. Given the observations that knock-in of the RNF213 polymorphism c.14576G>A variant itself could not lead to the development of MMD [19], environmental stimuli could potenti ate the endothelial dysfunction and proangiogenic activity. Intrinsic chronic inflammatory state can be one of the important environ-
mental stimuli, as evidenced by high prevalence of co-existing autoimmune diseases [13, 20] and increased levels of circulating inflammatory factors [21–23]. Experimental studies showing the impaired T-cell response and enhanced angiogenic activities in Rnf213-mutant mice also support this idea [18, 24, 25]. Despite the need of the further investigations, RNF213 appears to modulate metabolism and immune systems, which may affect vascular pathology.

Neurosurgical indications should be carefully determined if PAH is evident in MMD patients. Tokunaga et al. [3] reported 1 MMD case who passed away postoperatively due to the severe pneumonia associated with PPAS. This case suggests neurosurgical interventions are challenging once PAH is evident. In the present study, surgical treatment for an ischemic-onset MMD patient (case 1) was not performed due to severe cardiopulmonary dysfunction. Fortunately, this case remained free from further ischemic attacks after antiplatelet therapy. A thorough follow-up of both MMD and PAH is warranted because the progression of PPAS can affect cerebral ischemia. These observations suggest the necessity of careful management in MMD/quasi-MMD patients with PPAS.

This retrospective study holds several limitations. First, the incidence of PPAS might be underestimated because cardiopulmonary system examination was performed only when the patients developed any symptoms, including cardiac murmur. Second, sampling bias may exist due to the availability of genetic testing and the lack of asymptomatic MMD/quasi-MMD patients in the present study. A future prospective study which screens PPAS in all the MMD/quasi-MMD cases is required to validate the findings of the current study.
Conclusion

There was a significant association between homozygote variant of RNF213 polymorphism c.14576G>A and PPAS in MMD/quasi-MMD patients. The homozygote variant of RNF213 polymorphism c.14576G>A can be a potential predisposing factor for PPAS in MMD/quasi-MMD patients. Despite the relatively rare entity, PPAS should be noted to determine surgical indications for MMD/quasi-MMD patients.

Statement of Ethics

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Conflict of Interest Statement

The authors have no conflicts to declare.

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