NMC Case Report Journal 2017; 4: 5–9
DOI: 10.2176/nmccrj.cr.2016-0106

Case Report

Coexistence of Quasi-moyamoya Disease and POEMS Syndrome in a Patient with Intracranial Hemorrhage: A Case Report and Literature Review

Izumi Yamaguchi,[1] Junichiro Satomi,[1] Nobuaki Yamamoto,[2] Shotaro Yoshioka,[1] Yoshiteru Tada,[1] Kenji Yagi,[1] Yasuhisa Kanematsu,[1] and Shinji Nagahiro[1]

POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) syndrome is a rare paraneoplastic syndrome elicited by plasma cell dyscrasia. Its clinical manifestations are multiple and stroke is not a recognized feature. A 44-year-old woman with a 3-month history of bilateral lower extremity sensorimotor disturbance was admitted to our hospital. Examinations revealed polyneuropathy, organomegaly, hypothyroidism, monoclonal gammopathy, pelvic plasmacytoma, and elevated serum vascular endothelial growth factor (VEGF) levels. A diagnosis of POEMS was made. Her condition was improved by radiation therapy of her pelvic plasmacytoma and she continued to be seen on an outpatient basis. Five years after her first admission she was re-admitted with sudden-onset right hemiparesis. A brain computed tomography (CT) scan revealed a left intracranial hemorrhage and magnetic resonance (MR) angiography and cerebral angiography showed occlusion of the proximal portion of the bilateral middle cerebral artery and narrowing of the bilateral internal carotid artery at the terminal portion; moyamoya vessels were seen. This is the first report of a patient whose intracranial hemorrhage was attributable to quasi-moyamoya disease associated with POEMS syndrome. We suggest that the POEMS syndrome be ruled out in the differential diagnosis of patients presenting with atypical stroke, multivessel stenotic lesions (moyamoya vessels), and polyneuropathy.

Keywords: POEMS syndrome, VEGF, quasi-moyamoya disease

Introduction

POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) syndrome is a rare paraneoplastic syndrome due to plasma cell dyscrasia.[1)] Major clinical manifestations of this syndrome are captured by the acronym POEMS; they include polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes.[2)] Stroke is not a recognized feature of this syndrome. This is the first report of a patient with sudden-onset intracranial hemorrhage attributable to quasi-moyamoya disease associated with POEMS syndrome.

[1]Department of Neurosurgery, Institute of Biomedical Sciences, Tokushima University Graduate School, Tokushima, Japan
[2]Department of Clinical Neuroscience, Institute of Biomedical Sciences, Tokushima University Graduate School, Tokushima Japan

Received: April 18, 2016; Accepted: June 13, 2016

Case Report

A 44-year-old woman with a 3-month history of lower limb hypesthesia and paralysis was admitted to our hospital. The medical history of the patient was unremarkable. Physical examination revealed cervical lymph node swelling and pretibial edema. Neurological examination showed lower limb motor weakness, sensory loss, and absent distal reflexes. As electrophysiologic tests disclosed a polyneuropathy pattern we suspected chronic inflammatory demyelinating polyneuropathy. Abdominal computed tomography (CT) showed a pelvic tumor (Fig. 1A), hepatomegaly, splenomegaly, para-aortic lymph node swelling and ascites. CT-guided biopsy of the tumor revealed plasmacytoma (Fig. 2). The serum vascular endothelial growth factor (VEGF) level was 814 pg/ml. Serum immunoelectrophoresis showed monoclonal gammopathy (IgGλ); the hormonal values were indicative of hypothyroidism. Under a diagnosis of POEMS syndrome, she underwent radiation therapy (46 Gy delivered in 23 fractions) for pelvic plasmacytoma. Pelvic plasmacytoma gradually became smaller and changed into osteosclerotic lesion (Fig. 1B). Hepatomegaly, splenomegaly, para-aortic lymph node swelling, and monoclonal gammopathy were improved. The serum VEGF level decreased to 406 pg/ml. Her condition improved and she was discharged. During this period, magnetic resonance (MR) angiography taken for headache revealed a narrowing of the proximal portion of the bilateral middle cerebral artery and the terminal portion of the internal carotid artery (Fig. 3A). She had no cerebral ischemic symptom and no family history of moyamoya disease. MR angiography was not followed up since headache was mild and improved.

Five years later, she was readmitted with a chief complaint of sudden-onset right hemiparesis. A brain CT scan showed left intracranial hemorrhage (Fig. 3B). MR angiography and cerebral angiography revealed progression of vessel stenosis, development of leptomeningeal anastomosis and moyamoya vessels (Fig. 3C–F). Moyamoya vessels were less than a typical moyamoya disease, and collateral circulation from the external carotid artery was not detected. Cerebral microbleeds were not detected. Single photon emission tomography (SPECT) using N-isopropyl-4 iodoamphetamine (123I-IMP) obtained on the 13th hospital day showed reduction of the cerebral blood flow (CBF) in the left frontoparietal

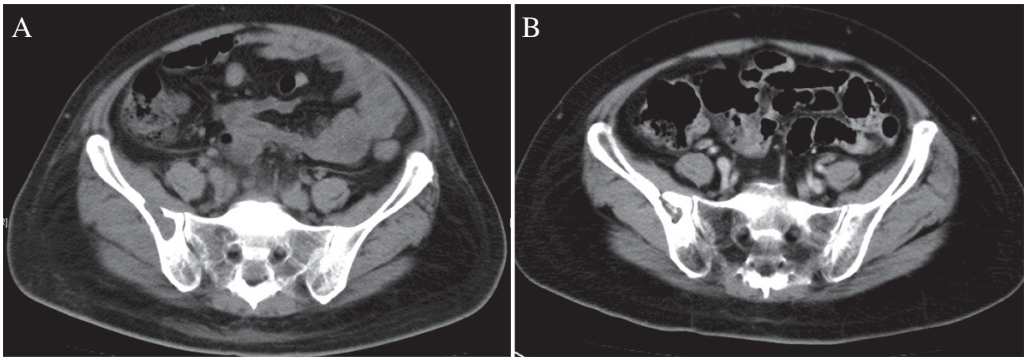

Fig. 1 Abdominal CT (A) Osteolytic lesion was detected in right pelvis. (B) Pelvic tumor became smaller and changed into osteosclerotic lesion.

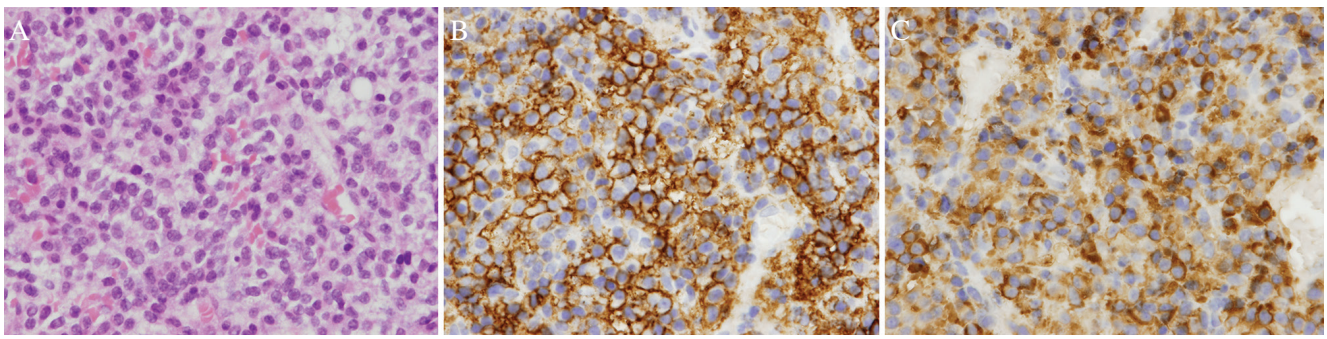

Fig. 2 Pathological features of plasmacytoma (A) Diffuse proliferation of plasma cells (Hematoxylin and eosin 40×) (B) CD138 positivity (40×) (C) Lambda light-chain positivity (40×).

cortex, left regional temporo-occipital cortex, and right cerebellum (Fig. 3G). Complete blood cell count, basic metabolic panel and coagulation parameters revealed normal findings. The serum VEGF level was 27.9 pg/ml. No recurrence of monoclonal gammopathy was observed after initial therapy. Disease progression of POEMS syndrome was thought to be negative in laboratory data. Although we thought that her hemorrhage was due to hemodynamic stress she was treated conservatively because the appropriate treatment of quasi-Moyamoma disease remains to be determined.[3] She was transferred to a rehabilitation center and in the course of two-year follow-up she suffered no rebleeding.

Discussion

POEMS syndrome and cerebrovascular disease

POEMS syndrome have been also called Crow-Fukase syndrome, Takatsuki syndrome or PEP (plasma cell dyscrasia, endocrinopathy, and polyneuropathy) syndrome. POEMS syndrome is a very rare disease; a 2003 survey showed an incidence of approximately 0.3/100,000 Japanese.[1] Of 99 patients with POEMS syndrome contained in the Mayo Clinic database, 18 had experienced venous (n = 10) and/or arterial (n = 11) thrombotic events manifesting as myocardial infarction, stroke, and Budd-Chiari syndrome.[4] The literature on POEMS syndrome associated with cerebrovascular disease documents 23 patients and most of these presented with major vessel stenosis or occlusion (Table 1).[2,5–15] The 5-year risk for stroke in patients with POEMS syndrome is 13.4%. According to Dupont et al.[2] POEMS syndrome is accompanied by multivessel stenosis and typically leads to vascular anomalies. The elevation of plasma and serum VEGF levels is a characteristic of POEMS syndrome and included in its diagnostic criteria. Plasma VEGF levels of 200 pg/ml were 95% specific and 68% sensitive for a diagnosis of POEMS syndrome.[1]

Quasi-moyamoya disease and moyamoya disease

In quasi-moyamoya disease, vessel stenosis or occlusion is accompanied by an abnormal vascular network associated with an underlying disease.[16] The annual incidence of quasi-moyamoya disease is 0.11/100,000; its prevalence is 0.34/100,000.[17] Underlying diseases are atherosclerosis (29%), Down syndrome (15.1%), von Recklinghausen disease (14%), brain tumor/irradiation (7.5%), autoimmune disease (7.5%), and hyperthyroidism(7.5%).[18] The ring finger protein (RNF213) is a susceptibility gene for moyamoya disease.[19] Although the homozygous c.14576G>A variant of RNF213 predicts the early onset and severe form of moyamoya disease, patients with non-atherosclerotic quasi-moyamoya disease did not harbor the variant.[20,21] The genetic background of moyamoya and quasi-moyamoya disease may be different.

Angiogenesis in POEMS syndrome

The biological effects of VEGF are angiogenesis and an increase in vessel permeability. Elevated levels of VEGF, interleukin (IL)-12, IL-1β, tumor necrosis factor (TNF)-α, and IL-6 have been reported in POEMS syndrome patients; VEGF is the cytokine that is consistently elevated and best correlated with disease activity.[1] Although the pathogenesis of POEMS syndrome is not well understood, vascular hyperpermeability induced by VEGF is thought to be responsible

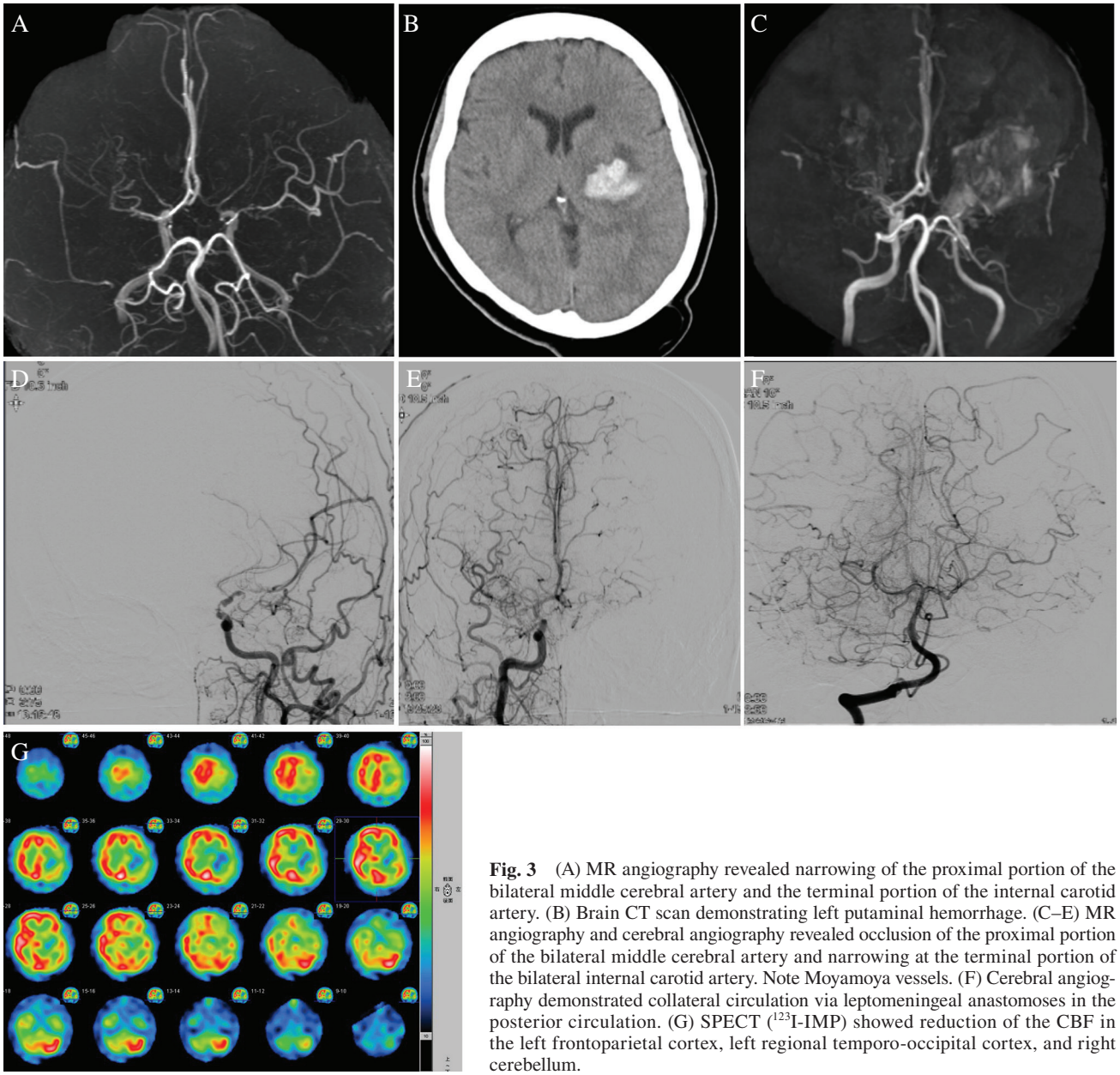

Fig. 3 (A) MR angiography revealed narrowing of the proximal portion of the bilateral middle cerebral artery and the terminal portion of the internal carotid artery. (B) Brain CT scan demonstrating left putaminal hemorrhage. (C–E) MR angiography and cerebral angiography revealed occlusion of the proximal portion of the bilateral middle cerebral artery and narrowing at the terminal portion of the bilateral internal carotid artery. Note Moyamoya vessels. (F) Cerebral angiography demonstrated collateral circulation via leptomeningeal anastomoses in the posterior circulation. (G) SPECT (^{123}I-IMP) showed reduction of the CBF in the left frontoparietal cortex, left regional temporo-occipital cortex, and right cerebellum.

for its characteristic symptoms such as edema, pleural effusion, ascites, angioma, and organomegaly.[22)]

The two thrombotic mechanisms in POEMS syndrome are hypercoagulability elicited by proinflammatory cytokines (IL-1β, TNF-α), thrombocytosis, polyglobulia, hyperviscosity, hyperfibrinogemia, and angiogenesis of vasa vasorum accelerated by VEGF leading to intramural hemorrhage.[2,5–7,9,11–13,15,23)]

Polyneuropathy is a required symptom for a diagnosis of POEMS. Elevated systemic levels of VEGF induce hypertrophy and proliferation of endothelial cells with secondary microangiopathy. The consequent reduction in the oxygen supply elicits a robust expression of HIF-1α (hypoxia inducible factor-1α) by all nerve constituents; a secondary increase in the local VEGF expression results in a self-perpetuating toxic gain of VEGF function.[24)] We think that this mechanism leads to major cerebral vessel stenosis and occlusion and that VEGF-induced angiogenesis results in the production of moyamoya vessels.

In our patient, fragile moyamoya vessels may have ruptured due to hemodynamic stress resulting in intracranial hemorrhage. Based on the above observations, we suggest that VEGF is one of the most important factors in the pathogenesis of POEMS syndrome.

Similarity of moyamoya disease and POEMS syndrome

Moyamoya vessels are thought of as the collateral circulation that develops to compensate for cerebral ischemia due to stenosis. Pathological findings on a sural nerve biopsy in a POEMS

Table 1 Summary of previously reported patients with POEMS syndrome and cerebrovascular disease

Reference	Number of cases	Age	Sex	Vascular structure
Lesprit et al.[5]	1	53	F	Right ICA occlusion, left ICA stenosis
Forster et al.[14]	1	59	M	NA
Erro et al.[15]	1	63	F	Right ICA occlusion
Kang et al.[9]	3	42	M	NA
		48	F	Proximal left MCA stenosis
		52	F	Left ICA stenosis
Rössler et al.[10]	1	32	F	Right A1/M1 stenosis, left ICA occlusion
Garcia et al.[7]	2	49	M	Right M1 stenosis, left M1 occlusion
		50	F	Bilateral ICA/M1/A1/PCA stenosis
Lee et al.[11]	1	41	M	Bilateral M1 occlusion and ICA stenosis
Huang et al.[8]	1	42	F	NA
Dupont et al.[2]	9	46 (34–67)	M7/F2	Left M1 occlusion
				Right M1 stenosis, left M1 occlusion
				Right ICA occlusion
				No major occlusion
				Left ICA occlusion (dissection s/o)
				NA
				NA
				NA
				NA
Sommer et al.[13]	1	54	F	NA
Dacci et al.[6]	1	49	M	NA
Akyol et al.[12]	1	47	F	Bilateral M1 occlusion, left ICA stenosis

A1: first anterior cerebral artery segment, ICA: internal carotid artery, M1: first MCA segment, MCA: middle cerebral artery, NA: not available, PCA: posterior cerebral artery.

syndrome patient showed narrowing or occlusion of the vasa-nervorum, hypercellularity, and proliferation of endothelial cells.[24,25] These findings may point to identical mechanisms underlying vessel occlusion. In response to vessel stenosis or occlusion due to hypoxia and a decreased vascular blood flow, angiogenic agents such as VEGF, basic fibroblast growth factor (bFGF), hepatocyte growth factor (HGF), transforming growth factor-β_1 (TGF-β_1), and granulocyte-colony stimulating factor (G-CSF) are overexpressed in moyamoya disease.[26] The presence of VEGF in the dura is an interesting finding that hints at the expansion of pathological mechanisms beyond the cerebral vasculature.[27] In patients with atypical stroke presenting with multi-vessel stenotic lesions (moyamoya vessels) and polyneuropathy, POEMS syndrome must be ruled out. The observations made in our patient suggest the possible coexistence of POEMS syndrome and quasi-moyamoya disease. Stroke can precede the manifestation of the typical clinical features of POEMS syndrome.[6] As it is a life-threatening condition, appropriate treatment must be delivered immediately.

Conclusion

This is the first report of a patient with sudden-onset intracranial hemorrhage whose underlying morbidities were co-existing quasi-moyamoya disease and POEMS syndrome. In patients with atypical stroke who harbor multivessel stenotic lesions (moyamoya vessels) and manifest polyneuropathy, POEMS syndrome should be included in the differential diagnosis.

Conflicts of Interest Disclosure

The authors declare no conflicts of interest.

References

1) Dispenzieri A: POEMS syndrome: 2014 update on diagnosis, risk-stratification, and management. *Am J Hematol* 89: 214–223, 2014
2) Dupont SA, Dispenzieri A, Mauermann ML, Rabinstein AA, Brown RD, Jr. Cerebral infarction in POEMS syndrome: incidence, risk factors, and imaging characteristics. *Neurology* 73: 1308–1312, 2009
3) Miyamoto S, Yoshimoto T, Hashimoto N, Okada Y, Tsuji I, Tominaga T, Nakagawara J, Takahashi JC; JAM Trial Investigators: Effects of extracranial-intracranial bypass for patients with hemorrhagic moyamoya disease: results of the Japan Adult Moyamoya Trial. *Stroke* 45: 1415–1421, 2014
4) Dispenzieri A, Kyle RA, Lacy MQ, Rajkumar SV, Therneau TM, Larson DR, Greipp PR, Witzig TE, Basu R, Suarez GA, Fonseca R, Lust JA, Gertz MA: POEMS syndrome: definitions and long-term outcome. *Blood* 101: 2496–2506, 2003
5) Lesprit P, Authier FJ, Gherardi R, Bélec L, Paris D, Melliere D, Schaeffer A, Godeau B: Acute arterial obliteration: a new feature of the POEMS syndrome? *Medicine* (*Baltimore*) 75: 226–232, 1996
6) Dacci P, Lessi F, Dalla Bella E, Morbin M, Briani C, Lauria G: Ischemic stroke as clinical onset of POEMS syndrome. *J Neurol* 260: 3178–3181, 2013
7) Garcia T, Dafer R, Hocker S, Schneck M, Barton K, Biller J: Recurrent strokes in two patients with POEMS syndrome and Castleman's disease. *J Stroke Cerebrovasc Dis* 16: 278–284, 2007
8) Huang J, Wang L, Zhou W, Jin J: Hyaline vascular Castleman disease associated with POEMS syndrome and cerebral infarction. *Ann Hematol* 86: 59–61, 2007
9) Kang K, Chu K, Kim DE, Jeong SW, Lee JW, Roh JK: POEMS syndrome associated with ischemic stroke. *Arch Neurol* 60: 745–749, 2003
10) Rössler M, Kiessling B, Klotz JM, Langohr HD: Recurrent cerebral ischemias due to cerebral vasculitis within the framework of incomplete POEMS syndrome with Castleman disease. *Der Nervenarzt* 75: 790–794, 2004
11) Lee MR, Choi HJ, Lee EB, Baek HJ: POEMS syndrome complicated by extensive arterial thromboses. *Clin Rheumatol* 26: 1989–1992, 2007
12) Akyol A, Nazliel B, Batur Caglayan HZ, Oner Y, Sucak GT: Recurrent transient ischemic attacks in a patient with POEMS syndrome. *Case Rep Neurol Med* 2014: 158471, 2014
13) Sommer B, Schaumberg J: Therapeutic challenges in a patient with POEMS syndrome and recurrent stroke: presentation of a case and review of the literature. *Acta Neurol Belg* 112: 9–13, 2012
14) Forster A, Muri R: Recurrent cerebrovascular insult—manifestation of POEMS syndrome?. *Schweiz Med Wochenschr* 128: 1059–1064, 1998
15) Erro ME, Lacruz F, Aymerich N, Ayuso T, Soriano G, Gállego J, Villanueva JA. Acute carotid obliteration: a new vascular manifestation in POEMS syndrome. *Eur J Neurol* 10: 383–384, 2003

16) 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
17) Hayashi K, Horie N, Suyama K, Nagata I: An epidemiological survey of moyamoya disease, unilateral moyamoya disease and quasi-moyamoya disease in Japan. *Clin Neurol Neurosurg* 115: 930–933, 2013
18) Hayashi K, Horie N, Izumo T, Nagata I: Nationwide survey on quasi-moyamoya disease in Japan. *Acta Neurochir* (*Wien*) 156: 935–940, 2014
19) Kamada F, Aoki Y, Narisawa A, Abe Y, Komatsuzaki S, Kikuchi A, Kanno J, Niihori T, Ono M, Ishii N, Owada Y, Fujimura M, Mashimo Y, Suzuki Y, Hata A, Tsuchiya S, Tominaga T, Matsubara Y, Kure S: A genome-wide association study identifies RNF213 as the first Moyamoya disease gene. *J Hum Genet* 56: 34–40, 2011
20) Miyawaki S, Imai H, Shimizu M, Yagi S, Ono H, Nakatomi H, Shimizu T, Saito N: Genetic Analysis of RNF213 c.14576G>A Variant in Non-atherosclerotic Quasi-Moyamoya Disease. *J Stroke Cerebrovasc Dis* 24: 1075–1079, 2015
21) Miyatake S, Miyake N, Touho H, Nishimura-Tadaki A, Kondo Y, Okada I, Tsurusaki Y, Doi H, Sakai H, Saitsu H, Shimojima K, Yamamoto T, Higurashi M, Kawahara N, Kawauchi H, Nagasaka K, Okamoto N, Mori T, Koyano S, Kuroiwa Y, Taguri M, Morita S, Matsubara Y, Kure S, Matsumoto N: Homozygous c.14576G>A variant of RNF213 predicts early-onset and severe form of moyamoya disease. *Neurology* 78: 803–810, 2012
22) Watanabe O, Arimura K, Kitajima I, Osame M, Maruyama I: Greatly raised vascular endothelial growth factor (VEGF) in POEMS syndrome. *Lancet* 347: 702, 1996
23) Soubrier M, Guillon R, Dubost JJ, Serre AF, Ristori JM, Boyer L, Sauvezie B: Arterial obliteration in POEMS syndrome: possible role of vascular endothelial growth factor. *J Rheumatol* 25: 813–815, 1998
24) Scarlato M, Previtali SC, Carpo M, Pareyson D, Briani C, Del Bo R, Nobile-Orazio E, Quattrini A, Comi GP: Polyneuropathy in POEMS syndrome: role of angiogenic factors in the pathogenesis. *Brain* 128: 1911–1920, 2005
25) Saida K, Kawakami H, Ohta M, Iwamura K: Coagulation and vascular abnormalities in Crow-Fukase syndrome. *Muscle & Nerve* 20: 486–492, 1997
26) Weinberg DG, Arnaout OM, Rahme RJ, Aoun SG, Batjer HH, Bendok BR: Moyamoya disease: a review of histopathology, biochemistry, and genetics. *Neurosurg Focus* 30: E20, 2011
27) Sakamoto S, Kiura Y, Yamasaki F, Shibukawa M, Ohba S, Shrestha P, Sugiyama K, Kurisu K: Expression of vascular endothelial growth factor in dura mater of patients with moyamoya disease. *Neurosurg Rev* 31: 77–81, 2008

Corresponding author:
Junichiro Satomi, Department of Neurosurgery, Institute of Biomedical Sciences, Tokushima University Graduate School, 3-18-15, Kuramoto-cho, Tokushima, 770-8503, Japan.
✉junichirosatomi@gmail.com