Case Report

Multiple Cerebral Aneurysms Associated With Neurofibromatosis Type 1

Yuki Takeshima, MD,* Yasuyuki Kaku, MD, PhD,* Toru Nishi, MD, PhD,* Akitake Mukasa, MD, PhD,† and Shigeo Yamashiro, MD, PhD*

Neurofibromatosis type 1 (NF1) is a rare disease with an incidence of approximately one in every 3000 births. *NF1* is mainly recognized as a tumor suppressor. Vasculopathy in NF1 is well described in the literature, but the association between NF1 and cerebral aneurysm has not been determined. We report a case of a 67-year-old female with NF1 accompanied by 8 cerebral aneurysms. Two of the patient's unruptured aneurysms, the large distal anterior cerebral artery (ACA) aneurysm and anterior communicating artery aneurysm, were initially treated with microsurgical clipping. The peripheral ACA aneurysm gradually increased in size and ruptured after 5 years. Coil embolization was performed for the ruptured aneurysm. Four of the 5 remaining unruptured aneurysms were treated surgically. The patient is currently well, without neurological deficit, and coil embolization is scheduled for the last remaining aneurysm. NF1 is a probable risk factor for multiple cerebral aneurysms due to vessel wall vulnerability. Therapeutic indications for patients with NF1 who show multiple cerebral aneurysms include strict follow-up and aggressive treatment to avoid subarachnoid hemorrhage.

Key Words: Multiple cerebral aneurysms—neurofibromatosis type 1—subarachnoid hemorrhage—therapeutic indication

Introduction

Neurofibromatosis type 1 (NF1) is an inherited autosomal dominant trait that results from a mutation in the NF1 gene on the long arm of chromosome 17 (17q1.2) that codes for neurofibromin.[1] NF1 has an incidence of approximately 1 in 3000 births. It is characterized by alterations in skin pigmentation (café-au-lait spots), iris Lisch nodules, and multiple benign neurofibromas. Individuals with NF1 frequently have learning disabilities, skeletal abnormalities, central nervous system tumors, or malignant peripheral nerve sheath tumors.[2] Vasculopathy in NF1 is well described in the literature, but the association between NF1 and cerebral aneurysm has not been determined.

Here, were present a unique case of NF1 in a patient presenting with 8 cerebral aneurysms, and review the cerebral aneurysms associated with NF1.

Abbreviation: ACA, anterior cerebral artery; Acom, anterior communicating artery; CT, computed tomography; CTA, computed tomographic angiography; ECM, extracellular matrix; IC-AchA, internal carotid-anterior choroidal artery; IC-PC, internal carotid-posterior communicating artery; MCA, middle cerebral artery; MMPs, matrix metalloproteinases; MRI, magnetic resonance imaging; NF1, neurofibromatosis type 1; ROS, reactive oxygen species; SAH, subarachnoid hemorrhage; VMSC, vascular smooth muscle cell

From the *Division of Neurosurgery, Department of Cerebrovascular Medicine and Surgery, Saiseikai Kumamoto Hospital, Kumamoto, Japan; and †Department of Neurosurgery, Graduate School of Life Sciences, Kumamoto University, Japan.

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Address correspondence to: Yasuyuki Kaku, MD, PhD, Division of Neurosurgery, Saiseikai Kumamoto Hospital, 5-3-1, Chikami, Minami-ku, Kumamoto city, Kumamoto 861-4193, Japan. E-mail: kakuyasuyukisyn@gmail.com.

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Clinical Presentation

A 67-year-old female patient presented with repeated rhinorrhagia. She had multiple "café-au-lait" spots on her femurs and a strong family history of NF1. Her past medical history was significant for hypertension. No abnormalities were found upon otolaryngologic assessment, but magnetic resonance imaging accidentally revealed multiple unruptured cerebral aneurysms, at which point the patient was referred to our hospital. Computed tomographic angiography demonstrated a total of 8 cerebral aneurysms: on the left side, in the internal carotid-anterior choroidal artery (IC-AchA), A2-3 segment and A4 segments; and on the right side, in the internal carotid artery-top, internal carotid-posterior communicating artery, M1 segment, middle cerebral artery bifurcation, and anterior communicating artery (Acom) (Fig 1). Microsurgical clipping was attempted on an irregular large distal anterior cerebral artery (ACA) and Acom aneurysm, which were presumed to have a high risk of rupture. Under general anesthesia, a bifrontal craniotomy was performed according to standard practice. Neck clipping was performed on each aneurysm using Yasargil clips. Postoperatively, regular imaging evaluations showed the peripheral ACA aneurysm (A4-5 portion) to be growing gradually (Fig 2). We recommended aggressive treatment, but the patient did not provide consent and requested observation.

Five years following surgery, the patient presented with a 3-day history of headaches. No neurologic deficit was detected on examination, but computed tomography of the head revealed a left frontal lobe hematoma adjacent to the interhemispheric fissure with no subarachnoid hemorrhage (SAH) (Fig 3a). SAH was diagnosed due to the rupture of the growing peripheral ACA aneurysm (WFNS Grade I, Hunt and Kosnik Grade I, Fisher Group 2), and treatment via coil embolization was considered. Endovascular treatment was performed under general anesthesia. Briefly, a guiding catheter was placed in the left common carotid artery. Subsequently, a microcatheter was guided into the peripheral ACA aneurysm using the guidewire, and the coil embolization was performed (Fig 3b). The left IC-AchA aneurysm could have been treated at the same time; however, we treated the ruptured aneurysm only.

Following treatment and rehabilitation, the patient requested treatment of the remaining aneurysms due to concerns over further ruptures. Four of the 5 aneurysms (right internal carotid-posterior communicating artery, M1, IC top, and middle cerebral artery bifurcation) were successfully treated with Yasargil clips using the right pterional approach (Fig 4), with no neurological deficits. A further coil embolization will be scheduled to treat the left IC-AchA aneurysm. Written informed consent was obtained from the patient, including consent to participate and to publish the findings.

Discussion

Vascular involvement is well described in patients with NF1,[3] and its prevalence in a large series of such patients ranged from 0.4 to 6.4%.[4-6] The most frequent manifestation is renal artery stenosis, which is associated with renovascular hypertension.[5] Cerebrovascular abnormalities in NF1 typically present as stenosis or occlusion of the cerebral arteries[7]; however, cerebral aneurysms have also been reported.[8-43] Table 1 summarizes 45 cases of NF1 with cerebral aneurysms in the literature. The mean age of their occurrence is 41 (range 1-67) years with a prevalence in females (male: female = 17:26, unknown: 2). Eighteen cases (40%) had multiple cerebral aneurysms. Among the 77 identified cerebral aneurysms, 62 (80.5%) were in the anterior circulation, and 15 (19.5%) were in the posterior circulation. Twenty-one lesions (27.3%) manifested as fusiform/dissecting aneurysms. In the normal human population, on the other hand, the frequency of multiple intracranial aneurysms has been reported to range from 20 to 30%,[44-48] and the presence of more than 4 aneurysms is quite rare.[49] Fusiform/dissecting aneurysms represent 3%-13%,[50] and

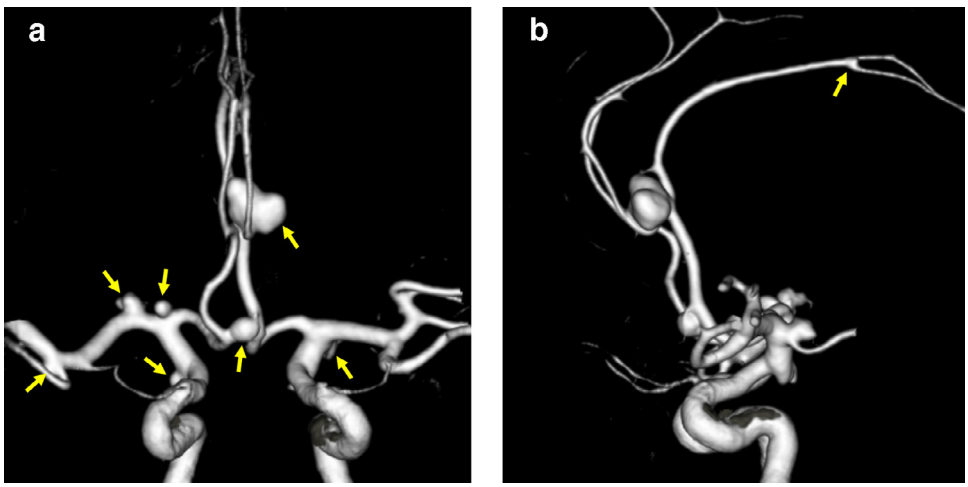

Figure 1. *Computed tomographic angiography showing eight cerebral aneurysms* (arrows). *(a) Anteroposterior view; (b) Lateral view.*

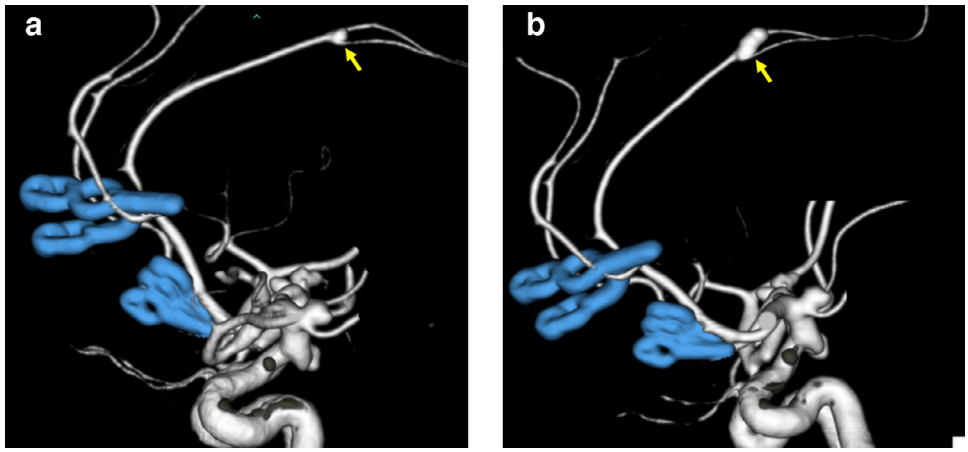

Figure 2. *Computed tomographic angiography revealing a peripheral ACA aneurysm (A4-5 portion,* arrow*) gradually growing after: (a) 3 years; and (b) 4 years and 6 months following the initial operation. ACA, anterior cerebral artery.*

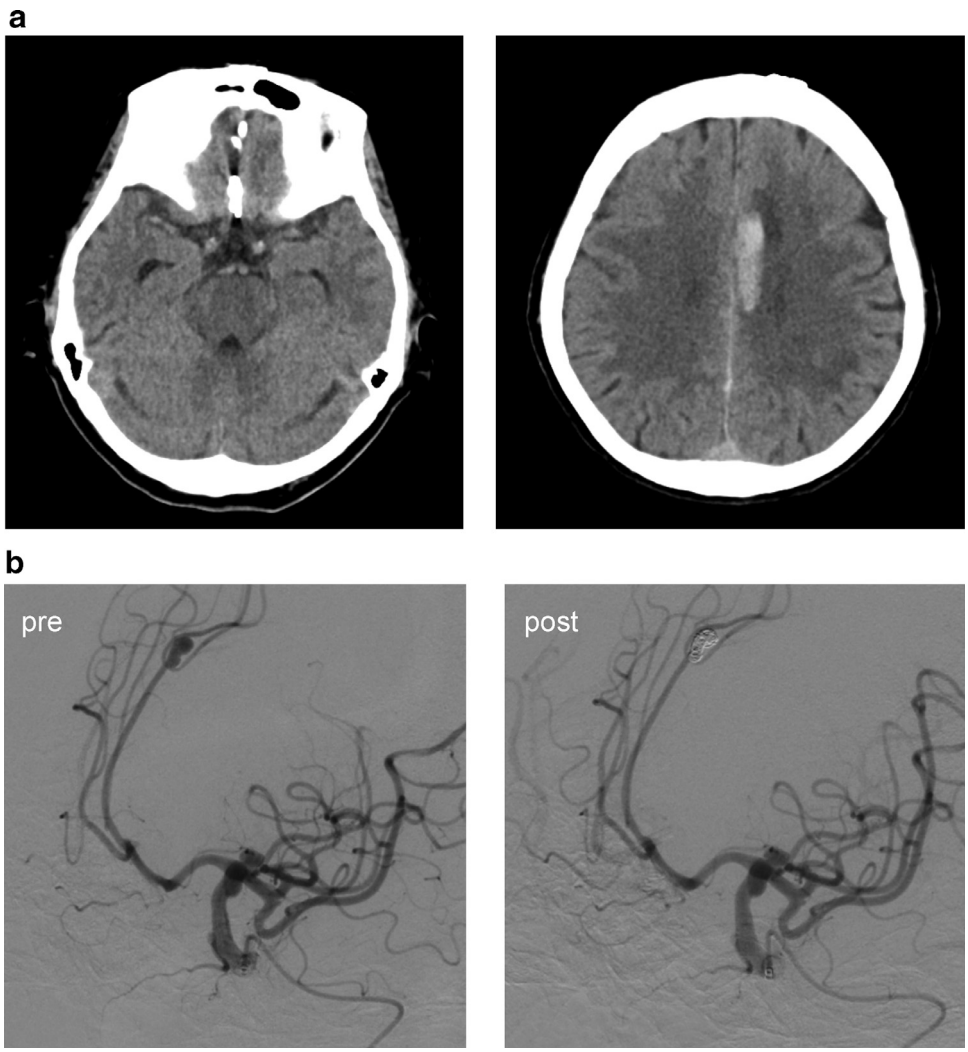

Figure 3. *(a) Computed tomography scan showing a left frontal lobe hematoma adjacent to the interhemispheric fissure with no subarachnoid hemorrhage (SAH) in the basal cistern. (b) Oblique view of the internal carotid angiography showing the peripheral ACA AN (left) and postcoil embolization of the ACA AN (right). ACA, anterior cerebral artery; AN, aneurysm.*

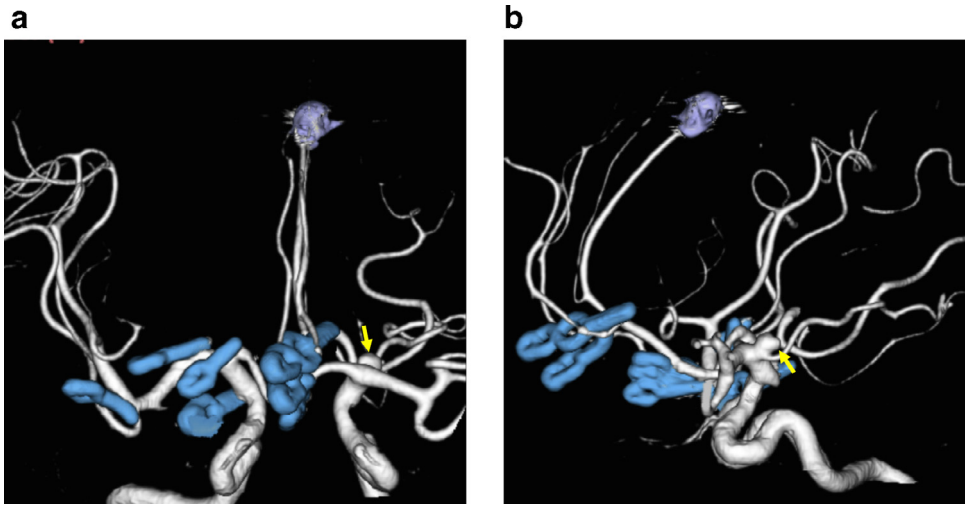

Figure 4. *Computed tomographic angiography showing the 7 treated aneurysms, with the remaining left internal carotid-anterior choroidal artery aneurysm* (arrow). *(a) Anteroposterior view; (b) Lateral view.*

approximately 85% of saccular aneurysms are present in anterior circulation.[51] Based on the above observations, features of cerebral aneurysms in NF1 are as follows; (1) predominance in females, (2) frequently manifested as multiple aneurysms, (3) tendency to favor posterior circulation, and (4) a high proportion of fusiform/dissecting aneurysms.

Considering these results, there are some important points in the treatment of cerebral aneurysms associated with NF1. First, it is necessary to check angiography carefully lest we overlook other aneurysms, arterial occlusion/stenosis, and other vascular abnormalities. Additionally, we have to keep in mind the vessel wall vulnerabilities[52,53] as can be seen in the fusiform/dissecting aneurysms.

Although a single-center autopsy study has demonstrated a lack of association between NF1 and cerebral aneurysms,[54] only 25 NF1 cases were assessed. NF1 is a comparatively rare disease, and a large database is necessary for its accurate evaluation. Terry et al[55] has conducted a case-controlled study using the US Nationwide Inpatient Sample and revealed a significantly increased risk of stroke, especially intracerebral hemorrhage, in hospitalized patients with NF1. In addition, both adult and pediatric patients with NF1 are more likely to have cerebrovascular abnormalities, such as moyamoya arteriopathy and unruptured aneurysms.

Neurofibromin, a large protein encoded by *NF1*, functions as a $p21^{Ras}$ (Ras) GTPase-activating protein that downregulates the Ras pathway. Neurofibromin plays an important part in controlling cell proliferation, migration, and the suppression of apoptosis, and prevents cells from acquiring the ability to invade, metastasize, and induce disordered angiogenesis.[56] In addition, neurofibromin is involved in regulating the functions of bone marrow-derived cells, epithelioid cells, and vascular smooth muscle cells in vitro and in vivo in response to multiple growth factors associated with vessel wall homeostasis.[57,58]

Genetic studies have demonstrated that matrix metalloproteinases (MMPs) and reactive oxygen species (ROS), secreted by vascular smooth muscle cells and macrophages, are molecular triggers for aneurysmal formation.[59] MMPs play an important role in extracellular matrix (ECM) remodeling by degrading various elements of the ECM, which contributes to organ development and regeneration, angiogenesis, and wound healing. Aneurysm walls show decreased levels of elastin and increased levels of collagen. Furthermore, MMP-2 and MMP-9 degrade elastin and are linked with aneurysm formation. According to a previous report by Longo et al,[60] MMP-2 and MMP-9 knockout mice did not form aneurysms in response to aortic injury.

In a murine model, Li et al[61] showed that the heterozygous inactivation of *NF1* ($NF1^{+/-}$) contributes to aneurysm formation via increased inflammatory cell infiltration, MMP activation, and ROS production. This results in the proliferation and migration of VMSCs in the intima area of the vessels. The authors also revealed that heterozygous inactivation of *NF1* ($NF1^{+/-}$) in myeloid cells alone leads to aneurysm formation. These findings suggest that the NF1 mutation may induce vascular vulnerability, leading to aneurysm formation.

It is also assumed that acquired degenerative changes are highly associated with the formation of multiple cerebral aneurysms, in addition to congenital factors. McDowell et al[62] have reported that females, a longer smoking history, aneurysms in the posterior circulation, higher body mass index, and black ethnicity are independently associated with the development of multiple aneurysms.

Table. 1. *Cases of cerebral aneurysms associated with NF1 from the literature*

Case	Author (year)	Age	Sex	Site of cerebral aneurysms	Total number of cerebral aneurysms	Symptoms and Signs	Associated anomalies
1	Bergouigman (1951)	17	M	Acom	1	Convulsion	Abnormal vascularity of the brain
2	Bergouigman (1951)	60	F	Rt.IC-PC	1	SAH	
3	Gibbons (1967)	32	F	Acom	1	SAH, hypertension	Pheocromocytoma
4	Momose (1973)	50	F	?	?	SAH	bil.ICA stenosis or occlusion (moyamoya-like)
5	Rosenbusch (1977)	24	F	bil.ICA (cavernous)	2	Hypertension	Coarctation, renal artery occlusion, mesenteric artery occlusion
6	Leone (1982)	52	F	Lt.posterior choroidal artery	1	SAH	bil.ICA stenosis
7	Debure (1984)	36	F	Lt.ICA	1	Hypertension	
8	Hasegawa (1984)	51	M	Rt.IC-PC, Rt.IC-Ach, Acom	3	Hypertension, headache	Catecholamine-secreting malignant schwannoma
9	Chono (1985)	60	F	Acom	1	SAH	bil.ICA stenosis, bil M1 occlusion, Lt.PCA stenosis, basal moyamoya
10	Kamiyama (1985)	56	F	Rt.VA-PICA, Lt.ICA (C2-C3, fusiform)	2	Bruit	Two Rt.ICA extracranial aneurysms, extracranial Lt.VA dAVF
11	Sobata (1988)	28	F	Rt.IC-Oph	1	Hematoma	Lt. ICA stenosis (C3), Lt.VA occlusion, moyamoya phenomenon
12	Frank (1989)	18	F	Rt.ICA (petrous, fusiform)	1	None	
13	Ueda (1990)	51	M	Rt.distal ACA (fusiform)	1	SAH, hypertension	Lt.VA aneurysm (V3)
14	Gomori (1991)	37	M	bil.MCA, basilar tip	3	Headache, hypertension	Renal artery stenosis
15	Muhonen (1991)	52	F	Lt.ICA (cavernous), Lt.PCA	2	Necked mass	Lt.VA aneurysm (extracranial), Rt.ICA (C5) stenosis/occlusion
16	Muhonen (1991)	19	M	Rt.ICA (cavernous, fusiform)	1	Diplopia, headache	
17	Muhonen (1991)	36	M	Rt.MCA × 2 (saccular and fusiform)	2	SAH, headache	Trifurcation of the Rt.MCA
18	Benatar (1994)	27	M	Rt.ICA (fusiform), BA (fusiform)	2	Leftside weakness, headache	Lt.ICA aneurysm (fusiform, extracranial)
19	Poli (1994)	42	F	Rt.Sylvian artery, Acom, Rt.VA	3	SAH, hypertension	Renal artery stenosis
20	Uranishi (1995)	60	F	Lr.IC top (fusiform), Lt.VA-PICA	2	Ischemia	
21	Uranishi (1995)	40	F	Rt.IC-PC	1	SAH	Extracranial Lt.VA dAVF
22	Sasaki (1995)	55	M	Rt.Heubner's artery (fusiform)	1	ICH	Rt.ICA (C1) stenosis/occlusion
23	Kirchhof (1996)	29	F	BA (fusiform)	1	SAH	
24	Fukunaga (1997)	64	F	Rt.MCA, BA	2	Hypertension	
25	Schievink (1997)	30	F	Lt.MCA, Lt.anterior temporal artery	2	SAH	MCA trifurcation, sphenoid wing dysplasia
26	Zhao (1998)	55	F	Rt.ICA (C1-C2)	1	SAH, fourth nerve palsy	
27	Siquera (1998)	28	M	PCA (fusiform)	1	SAH	Moyamoya arteriopathy
28	Oyama (1998)	30	M	Rt.MCA × 2, Lt.MCA, Lt.ICA × 2	5	SAH, hypertension	AVM

(*Continued*)

Table. 1 (*Continued*)

Case	Author (year)	Age	Sex	Site of cerebral aneurysms	Total number of cerebral aneurysms	Symptoms and Signs	Associated anomalies
29	Oyama (1998)	62	F	Acom	1	SAH, hypertension	
30	Sampei (1999)	41	M	Lt.VA dissecting aneurysm	1	SAH	Extracranial VA dAVF
31	Mitsui (2001)	49	M	BA (fusiform)	1	Wallenberg syndrome	
32	Fujimoto (2004)	55	F	Acom, Rt.ICA (cavernous)	2	SAH	PPTA, Rt.MCA fenestration
33	Rosser (2005)	1	?	Lt.ICA (cavernous)	1	None	
34	Rosser (2005)	11	?	Rt. ICA (fusiform), bil.MCA (fusiform)	3	None	
35	Schievink (2005)	36	F	Rt.IC (cavernous, fusiform), Lt.ICA (supraclinoid) × 4	5	Left arm paresthesia	
36	Schievink (2005)	56	F	Rt.IC top	1	bil.arm paresthesia	
37	Baldauf (2005)	34	F	Acom	1	SAH	
38	Roth (2007)	51	M	megadolicobasilar artery	1	Locked-in syndrome	
39	Roth (2007)	62	M	megadolicobasilar artery	1	Locked-in syndrome	
40	Serrantino-Garcia (2007)	35	M	Acom	1	SAH	
41	Bassou (2008)	43	M	Diffuse fusiform ectasia of the cerebral arteries	-	Seizure	
42	Becker (2010)	58	F	Lt.ICA, Acom	2	Headache	
43	Conforti (2014)	25	M	bil.ICA (cavernous, fusiform)	2	Tolosa-Hunt syndrome	
44	Takeshima (2017)	36	F	Rt.distal SCA dissecting aneurysm	1	SAH	
45	Present case (2018)	67	F	Rt.IC top, Rt.IC-PC, Rt.M1, Rt.MCA, Lt. IC-Ach, Lt.A2-3, Lt.A4, Acom	8	SAH, hypertension	

ACA, anterior cerebral artery; Acom, anterior communicating artery; BA, basilar artery; bil, bilateral; ICA, internal carotid artery; IC-Ach, internal carotid-anterior choroidal artery; ICH, intracerebral hemorrhage; IC-PC, internal carotid-posterior communicating artery; lt, left; MCA, middle cerebral artery; NF1, neurofibromatosis type 1; PCA, posterior cerebral artery; rt, right; SAH, subarachnoid hemorrhage; SCA, superior cerebellar artery; VA, vertebral artery; VA-PICA, vertebral artery-posterior inferior cerebellar artery.

In our case, the risk factors were a history of hypertension and increased body mass index. We hypothesize that the 8 aneurysms found in our patient were associated with NF1, and the risk factors may have created a cumulative effect.

The presence of multiple cerebral aneurysms is associated with unfavorable outcomes after rupture when compared with single aneurysm cases.[45] Therefore, aggressive treatment was necessary in this case. As the aneurysms could not all be treated in a single session, we selected to treat the 2 high-risk aneurysms surgically first (Acom and distal ACA), and planned a multistage treatment for the remaining aneurysms. However, when multiple craniotomies and surgical approaches are necessary in general, they are accompanied with risks resulting from multiple rounds of general anesthesia, brain retraction injury, and surgical manipulation of the brain.[63] There is a possibility that these risks influenced our patient's decision to request observation.

Endovascular treatment is another option. Endovascular coiling can obliterate multiple aneurysms at the same time. Nonetheless, there are complication risks for each aneurysm. This is the reason why we treated the ruptured peripheral ACA aneurysm alone when coil embolization was performed.

There are some limitations for endovascular treatment of cerebral aneurysm. It can be difficult to position the microcatheter into the lesion due to a distal or tortuous access route. Furthermore, endovascular coiling remains a controversial option for the treatment of aneurysms, such as wide-neck aneurysms. Multiple clipping and coiling treatment modalities[64,65] may be desirable for multiple cerebral aneurysms due to their relative simplicity and increased safety.

In this case study, we learned the following: (1) the formation of cerebral artery aneurysms and NF1 may be associated and (2) if patients have several risk factors for cerebral aneurysms, such as NF1, close monitoring and therapeutic interventions are needed to avoid SAH.

Conclusions

Acquired degenerative changes and congenital factors have been associated with the formation of multiple cerebral aneurysms. In addition, NF1 could be a risk factor due to the vulnerability of the vessel walls. Patients with NF1 who have multiple cerebral aneurysms require strict follow-up and aggressive treatment to avoid SAH.

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