

A case of neurofibromatosis type 1 complicated with repeated intracerebral hemorrhage  
due to quasi-moyamoya disease

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Running title: A case of neurofibromatosis type 1 and quasi-moyamoya disease

## **Abstract**

Moyamoya disease is a unique occlusive disease of the bilateral internal carotid arteries with moyamoya vessels. A inherited or acquired disorders and conditions may present in conjunction with MMD. This condition is known as quasi-moyamoya disease. We report a case of quasi-moyamoya disease complicated with repeated intracerebral hemorrhage during long-term follow-up for cerebral ischemia. A 35 year-old woman who had a diagnosis of neurofibromatosis type 1 visited our hospital because of incidentally found cerebral infarction. Angiography showed occlusive changes in the distal portion of the bilateral internal carotid artery and multiple massive collateral arteries from occluded internal carotid artery. Since revascularization from external carotid artery systems developed, she was treated conservatively and followed annually with radiological study. During follow-up, she suffered from minor intracerebral hemorrhages. At age 55, she died of massive intracerebral hemorrhages. Although the intracerebral hemorrhage is not common in quasi-moyamoya disease, it has a potential to be fatal. Long-term follow-up with radiological study and proper surgical treatment are required.

**Key words;** moyamoya disease, quasi-moyamoya disease, neurofibromatosis type 1, cerebral infarction, intracerebral hemorrhage

## **Introduction**

Moyamoya disease (MMD) is characterized by the progressive occlusion of the internal carotid artery (ICA) or its terminal branches, accompanied by the formation of extensive collateral vessels (moyamoya vessels) at the base of the brain. This disease has been reported in association with various disease entities including atherosclerosis, autoimmune disease, meningitis, brain neoplasm, neurofibromatosis type 1 (NF-1), Down syndrome, irradiation to the head [1-3]. These conditions are distinguished from MMD according to the diagnostic criteria of the Research Committee on Moyamoya Disease (Spontaneous Occlusion of the Circle of Willis) of Ministry of Health and Welfare of Japan (RCMJ), and named as quasi-moyamoya disease [4, 5, 6].

NF-1 is a multisystemic genetic disorder that displays important cutaneous manifestation such as café-au-lait spots, freckles and neurofibromas. The incidence of NF-1 is approximately one in 2,500 births, affecting all races. The gene for NF-1 is located on the long arm of chromosome 17, and more precisely, in the 17q11.2 band. This gene codes for neurofibromin, a protein that acts during nervous tissue growth remodeling [7]. The susceptibility locus of familial MMD has been mapped to 17q25.3 in Japanese families, and the gene was identified as RNF213 [8]. Interestingly, the RNF213 locates near the NF-1 gene and occasionally cerebrovascular abnormalities including moyamoya-like vasculopathy are accompanied with NF-1.

The objective of this study is to report on the case of a NF-1 accompanied with

quasi-MMD, which manifested cerebral ischemia at first and fatal intracerebral hemorrhage 20 years later.

### **Case report**

At age 10, she was diagnosed with NF-1 on the basis of physical findings including café-au-lait spots and multiple subcutaneous neurofibromas (Fig. 1A). She had mild mental retardation. At age 35, CT incidentally revealed a low density area in the left parietal lobe (Fig. 1B) and she was referred to our department. MRI revealed old infarction with atrophy in the left parietal lobe (Fig. 1C). Hemorrhagic change was also identified in the left basal ganglia by the T2\* image (Fig. 1D). Hypoperfusion of the infarction area was demonstrated by <sup>123</sup>I- iodoamphetamine (IMP) single photon emission computed tomography (SPECT) (Fig. 1E). Angiography showed steno-occlusive lesion at the terminal portion of the bilateral ICA accompanied with massive moyamoya vessels (Fig. 1F, G). Posterior cerebral arteries were also involved (Fig. 1H). Collateral flow from external carotid arteries (ECA) were developed (Fig. 1I,J). The diagnosis of quasi-MMD associated with NF-1 was made. Since her cerebral hypoperfusion was limited in the infarction area, she has been treated conservatively and followed with MRI annually. Her physical status and radiological finding were stable for 17 years. Thus, her habitual blood pressure was 100-120/80-90 mmHg and any medication was not required. At age 52, MRI incidentally revealed a new microbleed in the right basal ganglia (Fig. 2). At age 53, she was brought to our hospital because of

severe headache. Physical examination showed no focal neurological deficit. CT showed hemorrhage in the left basal ganglia (Fig. 3A). The hypoperfusion of the left basal ganglia was revealed by  $^{123}\text{I}$ -IMP SPECT (Fig. 3B). The cerebral blood flow of the right basal ganglia was 28.5 ml/100g/min and the left side was 25.8 ml/100g/min. The cerebral vascular reserve was 21.3% in the right basal ganglia and 21.7% in the left side. Angiography showed regression of the moyamoya vessels especially in the left side (Fig. 3C-E). During follow-up, the left side lesion was worsened from Suzuki stage 3 to stage 5 [9]. Apparent cause of the hemorrhage such as aneurysm was not observed. Surgical treatment was not performed because of developed collateral flow from ECA as well as risk of ischemic complication injuring the collateral vessels. She returned to her usual life. At age 55, she suddenly died of massive intracerebral hemorrhage.

## Discussion

We have ever conducted nationwide epidemiological survey on MMD, unilateral MMD, and quasi-MMD in 2006 [10]. The annual incidence rate of MMD and quasi-MMD are 1.13/100,000, and 0.11/100,000 respectively, and the prevalence is 5.22/100,000 and 0.34/100,000 respectively. It was revealed that the quasi-MMD is a rare disease. It is reported that the ratio of quasi-MMD is higher in western country [11]. Regarding with clinical manifestation of MMD, it is well known that the pediatric patients present with ischemic attack and adult patients tend to suffer from intracranial hemorrhage [12, 13]. Main cause of intracranial hemorrhage is rupture of dilated, fragile moyamoya vessels

due to hemodynamic stress and hemorrhage occurs in the basal ganglia, thalamus, or periventricular lesion. The ratio of intracranial hemorrhage is approximately 20% of definite MMD patients and approximately 50% of adult MMD patients [14, 15]. On the other hands, data from 109 quasi-MMD patients indicated their imaging study type included ischemic type in 64 patients (63.4%), bleeding type in 7 (6.9%), and normal in 27 (26.7%) [16]. Taken together, intracranial hemorrhage is relatively less in quasi-MMD. Thus, the associated disorders of quasi-MMD were atherosclerosis in 27 patients (29%), Down syndrome in 14 (15.1%), von Recklinghausen disease in 13 (14%), brain tumor/irradiation in 7 (7.5%), autoimmune disease in 7 (7.5%), hyperthyroidism in 7 (7.5%) [16]. NF-1 is the third major disorder of quasi-MMD.

In term of NF-1, eight (2.5%) patients among 316 NF-1 patients were found to have an abnormality of the cerebrovascular system [17]. Seven patients had a vasculopathy diagnosed as an incidental findings on neuroimaging, but a patient presented with ischemic stroke. The main characteristic of vascular lesions in patients with NF-1 is occlusion of the lumen and hyperplasia of the intima wall. Based on microscopic evaluation of the affected vessels, it has been proposed that the vasculopathy of NF-1 patients results from abnormal neurofibromin function that leads to excessive proliferation of vascular smooth muscle cells during normal maintenance of the vessel [18, 19]. In addition to the arterial occlusion, a variety of vascular lesions such as aneurysm, pseudoaneurysm, stenosis, fistulae and ruptures have been observed in patients with NF-1. Koss et al. report that among 32 cases of quasi-MMD associated with NF-1, only one case presented with hemorrhage [20]. Our case suffered from cerebral

ischemia at first and repeated minor hemorrhages later. Finally, she died of massive intracerebral hemorrhage. It is considered that fragile moyamoya vessels and ischemia or hemodynamic change due to the regression of the moyamoya vessels are the cause of the hemorrhage. Thus, vacuolar changes of the myelin sheath are found in 60-90% of NF-1 patients and are typically located in the basal ganglia, thalami, and the cerebral white matter [19]. That might affect the hemorrhagic complication in the bilateral basal ganglia of our case.

According to the Japan adult moyamoya trial, extracranial-intracranial bypass surgery is effective to reduce incidence of rebleeding and improved patient prognosis [21]. Surgical revascularization for NF-1 appears safe and is protective against further ischemic and neurological damage [20]. Vascular reconstruction was discussed in this case. However, collateral flow from ECA had been developed. Bypass surgery for the case with well developed collateral circulation is challenging and the effective blood supply to the basal ganglia has not been established. That is why, she was treated conservatively. Close monitoring of these abnormalities is warranted because the long-term outcome of these vascular lesion is unknown. Early recognition of a disease progression may prevent complications by surgical treatment.

### **Conclusion**

We reported a case of NF-1 complicated with cerebral ischemia and repeated intracerebral bleeding due to the progression of quasi-MMD. A long-term follow-up is

required to detect progression of cerebrovascular disease.

### **Disclosure**

Informed consent was obtained from the patient and the family.

### **Acknowledgement**

no

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No

Conflict of Interest – None

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## Figure legends

Fig. 1 Patient at 35 years old.

A: A photograph of upper extremities shows multiple subcutaneous neurofibromas.

B: CT shows low density area in the left parietal lobe.

C: MRI fluid attenuated inversion recovery image shows old infarction with atrophy in the left parietal lobe.

D: MRI T2\* image reveals hypointensity lesion, indicating microbleed in the left basal ganglia (arrow).

E: Hypoperfusion of the infarction area is demonstrated by  $^{123}\text{I}$ - iodoamphetamine (IMP) single photon emission computed tomography (SPECT).

F, G: Right (F) and left (G) carotid angiography shows steno-occlusive lesion at the terminal portion of the bilateral internal carotid artery accompanied with massive moyamoya vessels.

H: Right vertebral angiography shows involvement of the posterior cerebral arteries.

I, J: Right (I) and left (J) external carotid angiography shows collateral flow from middle meningeal artery (arrow) and superficial temporal artery (arrow head) was developed.

Fig. 2 Patient at 52 years old.

MRI T2\* image reveals microbleed in the right basal ganglia (arrow).

Fig. 3 Patient at 53 years old.

A: CT reveals minor hemorrhage in the left basal ganglia.

B:  $^{123}\text{I}$ -IMP SPECT shows hypoperfusion in the left basal ganglia (arrow).

C: Right carotid angiography shows steno-occlusive lesion at the terminal portion with moyamoya vessels.

D: Left carotid angiography shows steno-occlusive lesion at the terminal portion with a regression of moyamoya vessels.

E: Left vertebral angiography shows involvement of the posterior cerebral arteries with regression of moyamoya vessels.

Fig. 1

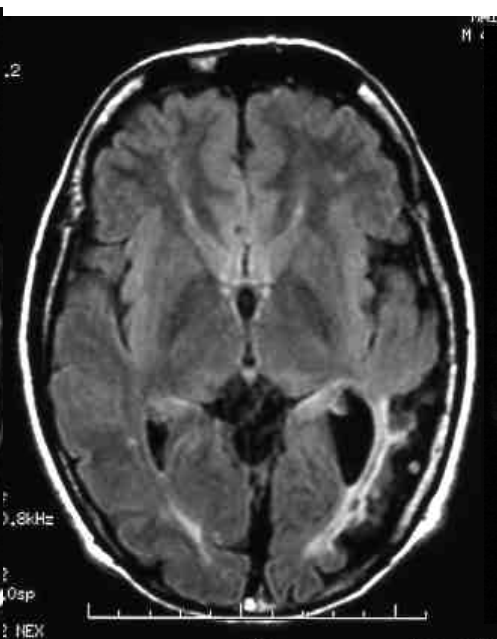
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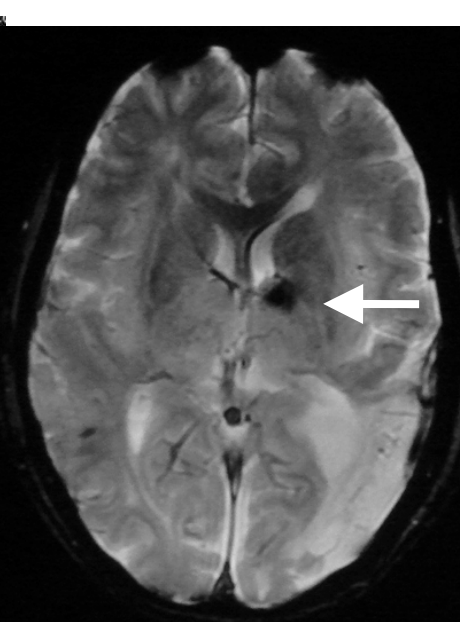
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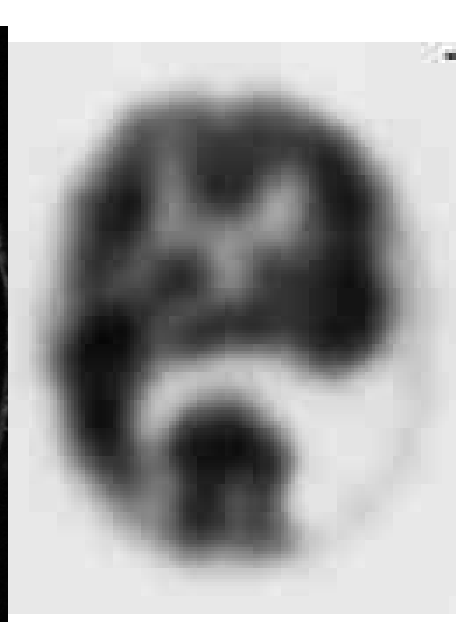
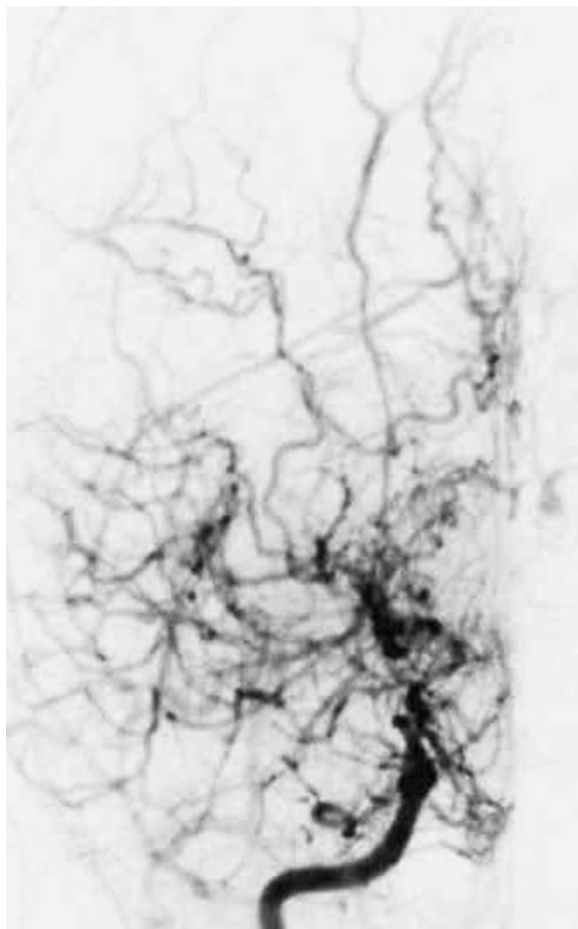
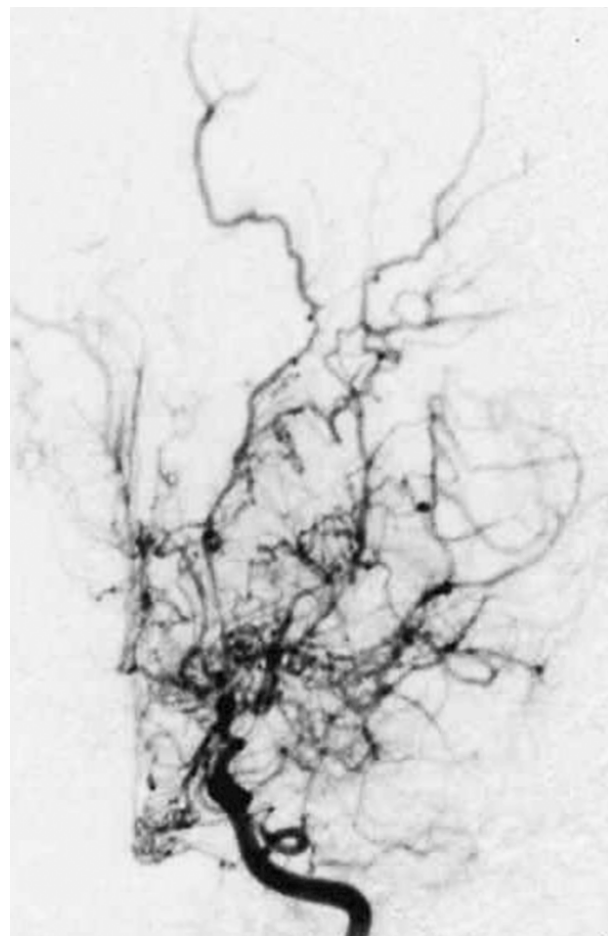


Fig. 1

F



G



H

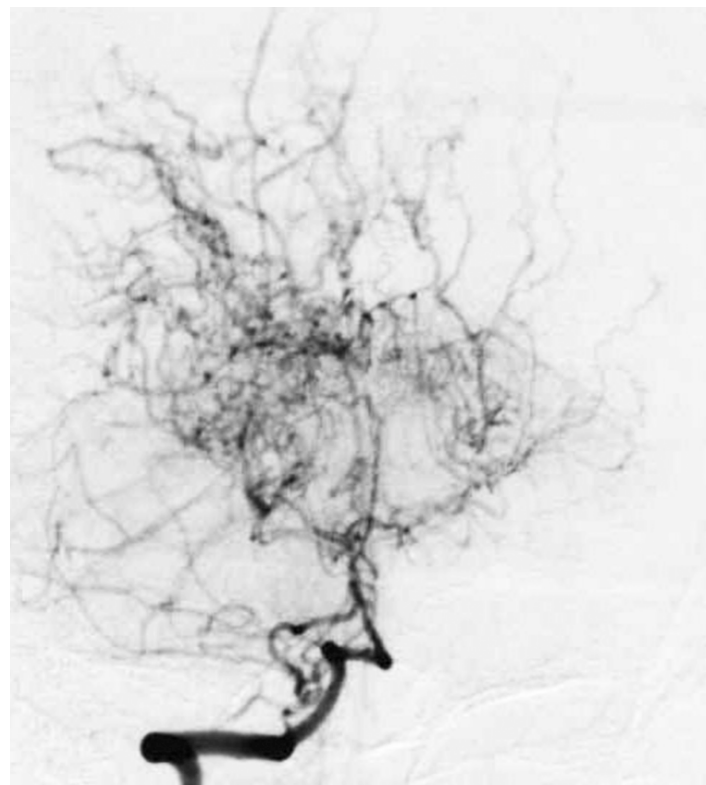


Fig. 1

I



J

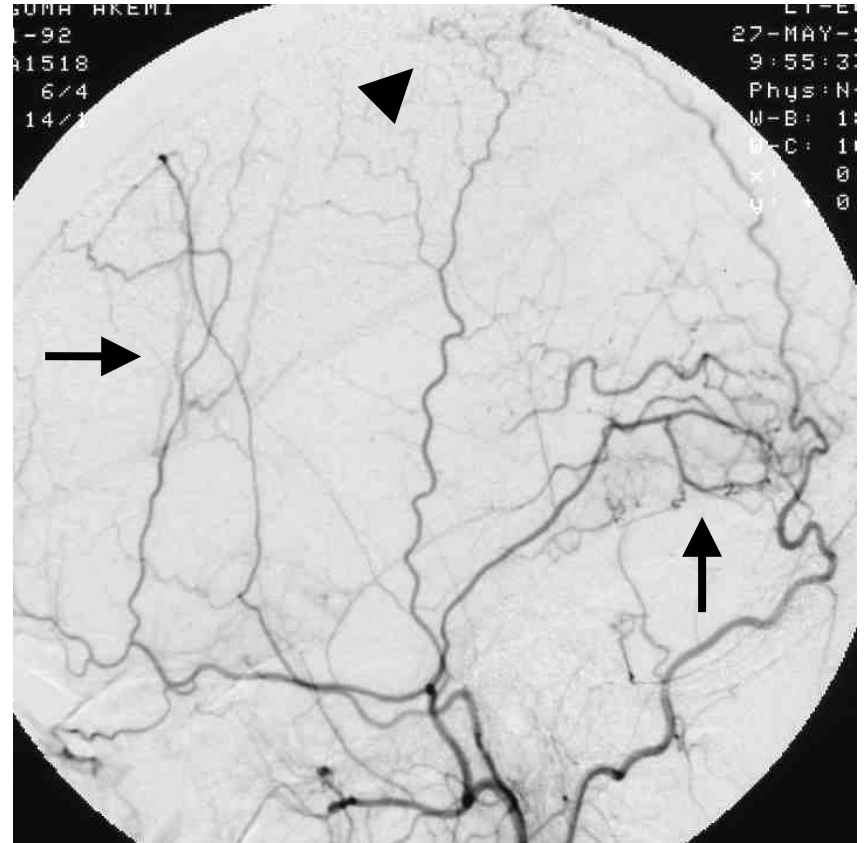




Fig. 2

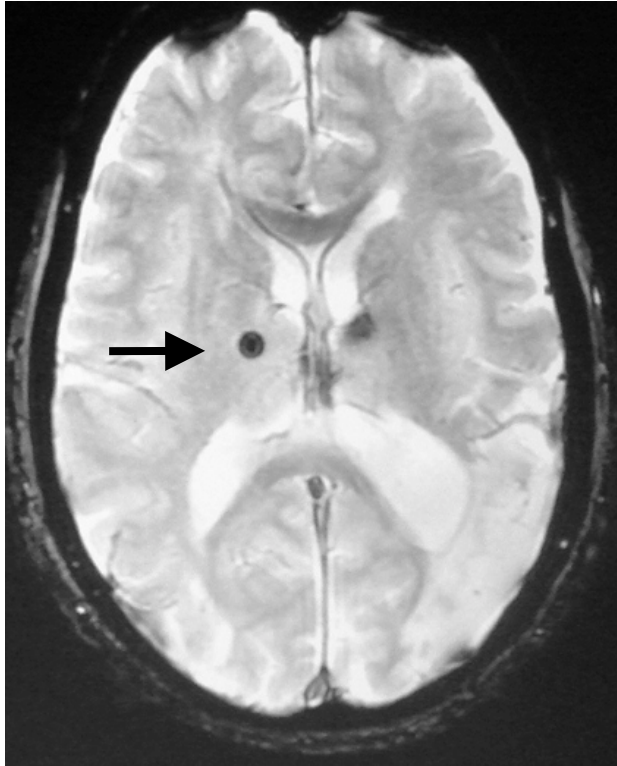


Fig. 3

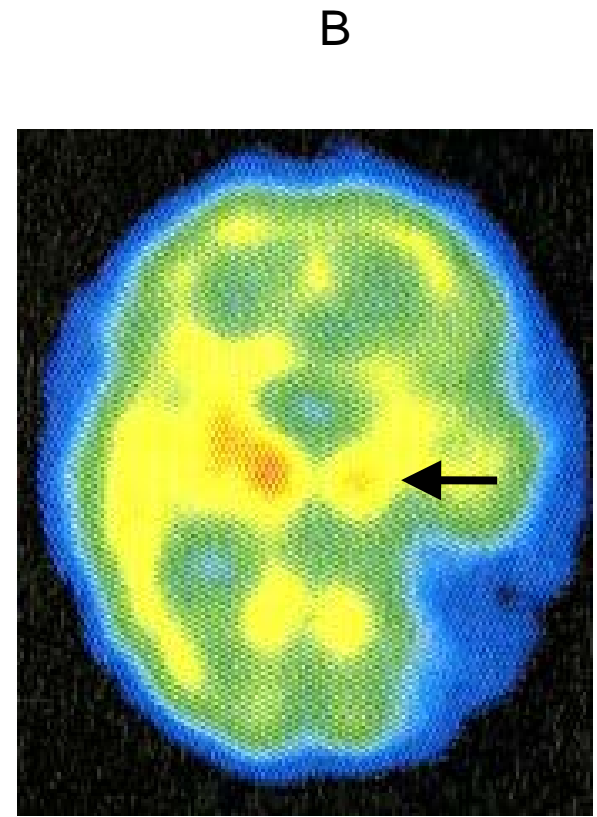
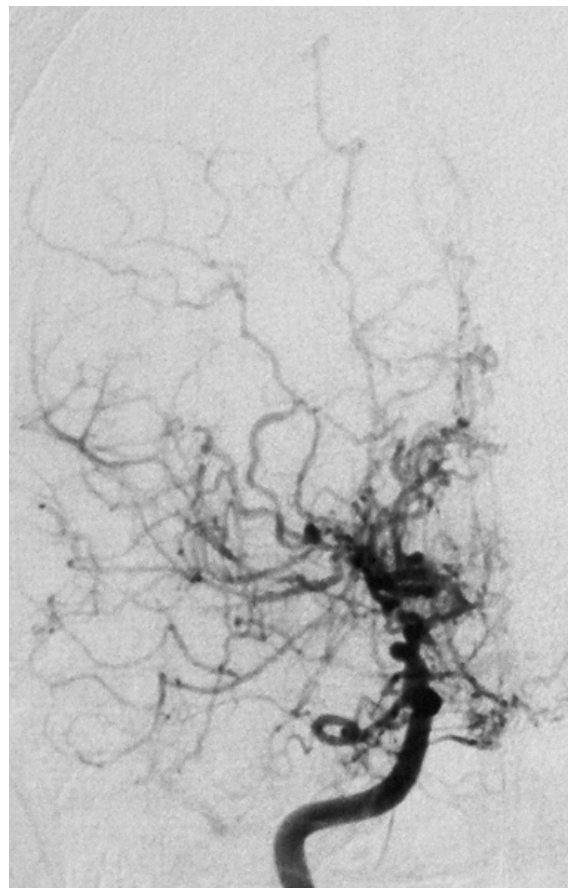
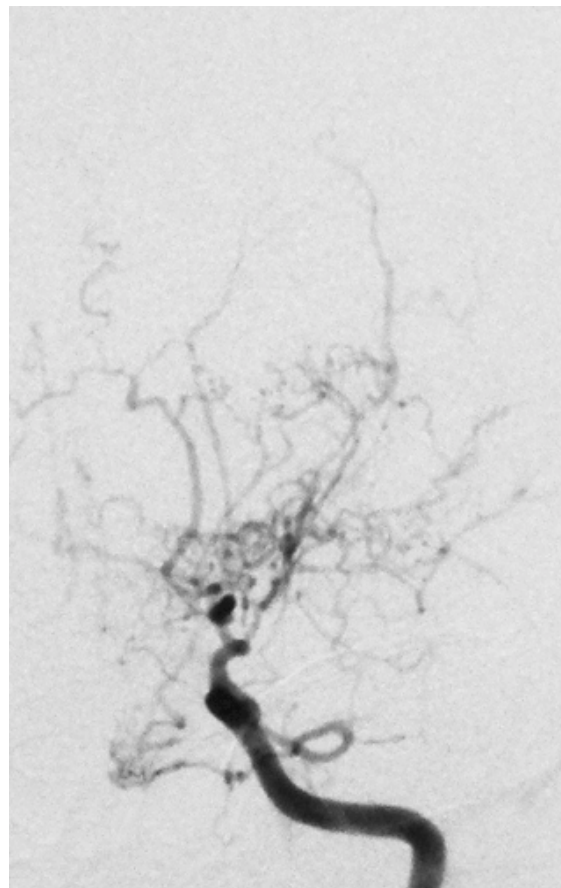


Fig. 3

C



D



E

